Brain Mapping for Cognitive Neuroscience and Neurosurgery

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Introduction

The Unity Principle: Cortical Processes Are Linked to Mental Events—Lesion Studies to Neuroimaging

One of the primary goals of neural science is to understand the biological underpinnings of cognition. This goal is based on the assumption that cognitive events emerge from brain events and that behavior can be explained in terms of neural processes. Francis Crick referred to this as "the Astonishing Hypothesis" [1]. According to this view, the biological principles that underlie cognition link the structure and function of the brain:

> The Astonishing Hypothesis is that 'You,' your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more than the behavior of a vast assembly of nerve cells and their associated molecules. (Francis Crick, 1994, *The Astonishing Hypothesis*, p. 3 [1])

The emergence of functional magnetic resonance imaging (fMRI) has transformed this "hypothesis" into a common assumption. Using neuroimaging methods, it is possible to observe active cortical areas associated with cognitive processes in healthy human volunteers. This capability has stimulated a renewed focus on the physiological bases of mental events. In particular, the implementation of noninvasive, functional imaging techniques such as fMRI offers an unprecedented view of the complexities of the intact working human brain, including local neural circuits (cortical columns), regions, and large-scale systems of interconnected regions. Functional imaging provides a unique view of the cortical activation patterns associated with specific functional processes such as seeing, hearing, feeling, moving, talking, and thinking. Thus, the potential to realize a neural basis for cognition has emerged with the development of neuroimaging.

Conventional definitions of cognition do not directly address the biological components of mental events. For example, *Dorland's Illustrated Medical Dictionary* defines cognition as "operations of the mind by which we become aware of objects of thought or perception; it includes all aspects of perceiving, thinking and remembering" [2]. *The American Heritage Dictionary* offers a similar definition for cognition as "the mental process of knowing, including aspects such as awareness, perception, reasoning and judgment, and that which comes to be known, as through perception, reasoning, or intuition, and knowledge" [3]. However, in his seminal book, *Cognitive Psychology*, Ulrich Neisser defined cognition as "all processes by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used" [4]. This definition could be interpreted to encompass biological processes, although none were specifically proposed by Neisser.

Medical reports of associations between specific brain injuries and functional deficits provided the initial basis for the assumed linkage between specific brain areas and behavior. As early as 1841, Broca reported language production deficits in patients with specific damage to the left frontal lobe, and in 1874, Wernicke reported deficits in language comprehension and expression in patients following specific damage to the left temporal lobe. Since then, Broca's and Wernicke's Areas have become established as regions of cortex associated with aspects of speech production and comprehension, respectively. Around the same time, Harlow reported profound personality changes following an unfortunate frontal-lobe injury in his now well-known patient

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Phineas Gage [5]. Nearly a century later, Penfield pioneered the experimental technique of direct cortical stimulation during neurosurgical procedures. His observations confirmed the functional specializations of the speech-related areas and demonstrated topographical maps associated with sensory and motor functions [6]. Along with the documented associations between lesions and specific functions, Penfield's reports of cortical stimulations that elicited memories, tastes, and other mental events supported the profound link between brain structure and cognitive function widely accepted within the mainstream of clinical neurology and neurosurgery. For example, it had been noted that severing a segment of the optic nerve always resulted in visual field loss (Fig. 31.1), and similarly, severing a primary motor projection always resulted in a contralateral plegia.

One of the key principles that links brain function and mental events is the relationship between neural activity and blood flow. In 1881, Angelo Mosso, a physiologist, studied a patient who had survived an injury to the skull. Due to the nature of the injury, it was possible to observe blood-flow-related pulsations to the left frontal lobe that occurred during certain cognitive events. Mosso concluded that blood flow within the brain was coupled to mental events. Roy and Sherrington [7] subsequently proposed a specific mechanism to couple blood flow and neural activity based on direct measurements on dogs. More recently, using $H_2{}^{15}O$ as a tracer of blood flow in the human brain, Raichle and colleagues [8] confirmed this fundamental relationship between blood flow and local neural activity. This seminal physiology work provided the basis for positron emission tomographic (PET) imaging of active cortical tissue during the execution of a task. The technique was demonstrated by Fox and Raichle [9] with a simple sensory and motor activation paradigm, where hemodynamic variations (as indicated by a radioactive tracer of water molecules) were observed within the pre- and postcentral gyri.

Typically, PET activation studies depend upon subtractive comparisons of images acquired during a task and images acquired during a rest or control condition. The logic of this technique is that the difference in image represents the neural activity present in the task condition and not in the control. For example, activity associated with viewing a flashing checkerboard minus activity associated with viewing a fixation dot presumably reveals the effect of the flashing checkerboard on specialized neural structures. Unfortunately, the PET camera does not provide a detailed image of brain structure; therefore, computational techniques to register the locations of the gamma ray events to brain anatomy obtained by other higher-resolution techniques such as magnetic resonance imaging (MRI) were developed. These procedures also include algorithms to register the anatomical and PET images of multiple subjects based on a standard human brain atlas. When all subject brains are registered to the same atlas, the difference in images of multiple subjects can be averaged to obtain conserved and generalizable results.

These advances in PET techniques enabled the first neuroimaging study of cognitive processes relating to language [10]. The study differentiated cortical patterns of activation associated with four separate word tasks: passively viewing words, listening to words, speaking words, and generating words. These early PET studies firmly established the proof-

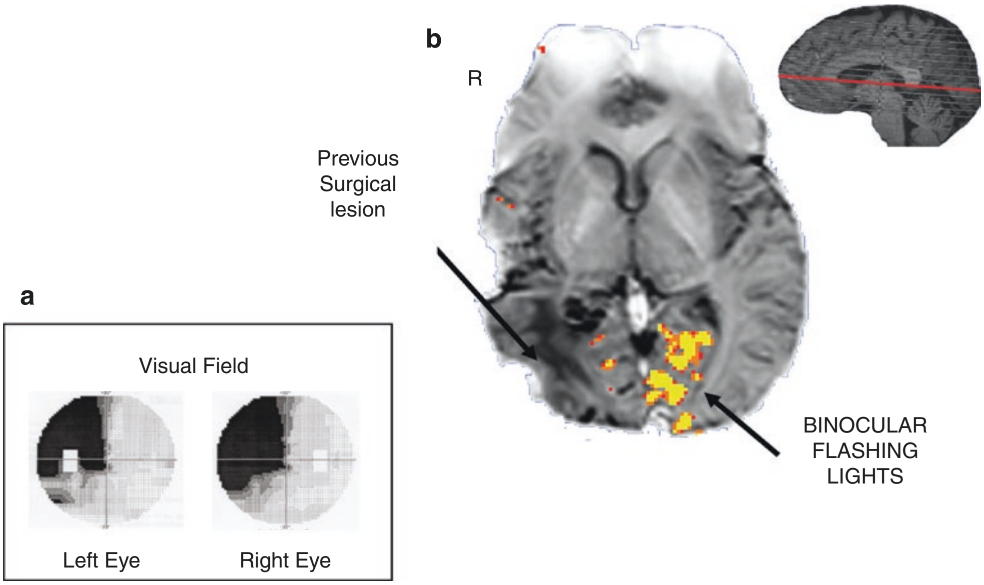


Fig. 31.1 (**a**, **b**) Static visual fields indicate a homonymous quadrantic field defect in the left superior quadrant that is associated with damage to the visual projection fibers within the right occipital lobe following resection of a lesion within the right hemisphere occipital region. Functional magnetic resonance imaging activation during binocular viewing of flashing lights (8 Hz) demonstrates unilateral cortical responses (left hemisphere only), reflecting the loss of visual responses in this topographically mapped area of the visual field

of-principle that activity associated with cognitive events was observable in the living human brain via hemodynamic variations within locally active neural areas. However, due to risks associated with injections of radioactive tracers, limitations to the number of times a subject can be studied, the relatively coarse resolution, and the relatively few PET facilities available for research, the imaging of cortical activity associated with cognitive processes has advanced most rapidly using a newer, noninvasive, higher-resolution, and more available technique: functional magnetic resonance imaging.

Development of Magnetic Resonance Imaging to Visualize Living Brain Structure

Since the invention of the microscope in 1664, imaging technology has guided the mainstream of basic research in biology by revealing structures not visible to the naked eye, including the cell, organelles, molecules, and even atoms. Despite its electronic and computational developments, the microscope is not suited for the imaging of living structures occluded beneath surface tissues such as skin, muscle, and bone. This occlusion problem was solved with the development of MRI, where internal structures within the living body can be resolved at submillimeter scales.

The development of MRI incorporated a long chain of discoveries, beginning with the discovery of molecular beam magnetic resonance in 1936 by Isidor Rabi at Columbia University. Shortly thereafter, in 1945, Edward Purcell and Felix Bloch independently discovered nuclear magnetic resonance (NMR) in condensed matter, followed by Erwin Hahn's observations of nuclear magnetic relaxation and the discovery of spin echo in 1949. A pinnacle event in the development of MRI was made in 1971 by Raymond Damadian who discovered that biological tissues have different relaxation rates. A year later, the first magnetic resonance image of a tube phantom was produced by Paul Lauterbur using a magnetic gradient to produce spatial resolution of the image. The first MRI of a human body part (a finger) was published in 1976 by Peter Mansfield and colleagues. Mansfield and colleagues also developed a key enhancement of a high-speed imaging sequence, echo planar imaging, which enabled three-dimensional (3D) acquisitions of body organs (such as the brain) within seconds. A year later, Damadian produced the first magnetic resonance image of a human whole body (cross-sectional chest) and in 1980 produced the first human whole body commercial MRI scanner.

The Development of Functional Magnetic Resonance Imaging to Visualize Living Brain Function

Advances in MRI have extended imaging of brain structures to include the identification of active neural tissue in the cortex. The chain of discoveries that led to the generation of MR images of the working brain include Michael Faraday's discovery in 1845 that dried blood has magnetic properties, and Linus Pauling's discovery in 1936 that the magnetic properties of hemoglobin change with the state of oxygenation.

The BOLD Response

These discoveries lay dormant with respect to functional neuroimaging until after the development of high-speed MRI of brain structure and PET imaging of active neural tissue based on the coupling of blood flow. The fundamental breakthrough discovery of the blood-oxygen-level-dependent (BOLD) signal in 1990 by Seiji Ogawa and colleagues followed the observation that the MR signal originating from the occipital lobe (the area of the brain specialized for visual processing) in rats had a higher contrast when the room lights were on than when the lights were off. Ogawa reasoned that the increased magnetic resonance signal was related to changes in oxygenated hemoglobin (HGB) resulting from blood flow coupled to neural activity (Table 31.1) [11].

Within a short time, Belliveau and colleagues replicated Ogawa's visual stimulation studies in humans using echo planar MRI, demonstrating the potential to reveal not only brain structure, but also brain function using MRI. This technique, which exploited the fundamental link between the MR signal, blood flow, and neural events, was referred to as functional magnetic resonance imaging (see review by John Gore [12] for a more detailed description of these relationships). Figure 31.2 illustrates a BOLD signal

Table 31.1 The blood-oxygen-level-dependent (BOLD) signal

The BOLD signal	
Physiology	Physics
Neural activation is associated with an increase in blood flow O_2 extraction is relatively unchanged	Deoxy HGB is paramagnetic and distorts the local magnetic field, causing signal loss
Result:	Result:
Reduction in the proportion of deoxy HGB in the local vasculature	Less distortion of the magnetic field results in local signal increase

O_2 oxygen, *Deoxy HGB* deoxyhemoglobin

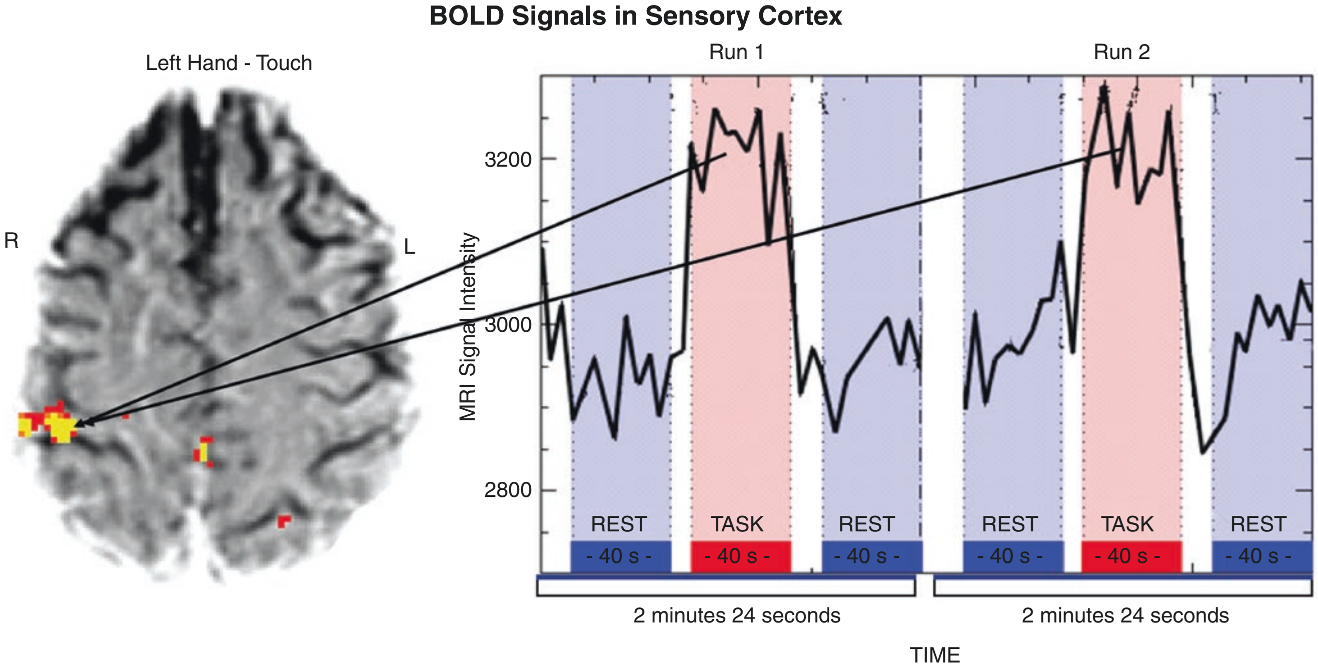


Fig. 31.2 Blood oxygen level-dependent (BOLD) signals associated with tactile stimulation of the left hand. Signals illustrate the changes in MR susceptibility observed in response to passive tactile stimulation of the left hand for a single voxel (1.5 × 1.5 × 4.5 mm) without the benefit of smoothing or "pre-processing." Signals are acquired on two separate short runs. Each run lasted 2 min 24 s, during which 36 images were acquired, including 10 images for each of 3 epochs: initial resting baseline (purple bar), task (left-hand touch) (pink bar), and final resting baseline (purple bar). All voxels in the brain for which the statistical criteria were met (the average amplitude of the signal during the activity epoch was statistically different from the baseline signal) are indicated by either a yellow, or red color superimposed on the T2*-weighted image at the voxel address and signify decreasing levels of statistical confidence. Arrows point to the source voxel, which is centered within a cluster of similar (yellow) voxels and located in the right (R) hemisphere of the brain along the postcentral gyrus. (Reprinted with permission from Hirsch J, Ruge MI, Kim KHS, Correa DD, Victor JD, Relkin NR, Labar DR, Krol G, Bilsky MH, Souweidane MM, DeAngelis LM, Gutin PH. An integrated fMRI procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery. 2000;47(3):711–722 [13])

(right) originating from the right hemisphere (R) region of postcentral gyrus (indicated by the arrow and yellow cluster) in response to touch of the left hand [13]. The active region is contralateral to the stimulation and well established as an area functionally specialized for tactile sensation.

The "Real Estate" Principle: Functional Specialization from "Bottom-Up" and "Top-Down"

One of the central principles that drives clinical applications that link cortical structure and function behavior is that specific brain areas are involved in specific aspects of behavior such as action, perception, cognition, affect, and consciousness. We refer to this as the "Real Estate" principle.

In the case of the well-studied visual system, multiple distinct visual cortical areas are organized into well-defined processing pathways. Visual signals from the retina are transmitted to the lateral geniculate nucleus of the thalamus, and then to primary visual cortex where visual information fans out to the extrastriate visual cortical areas. The extrastriate visual areas serve many different aspects of visual perception and visually guided behavior. Among the dimensions suggested for independent visual analysis are: brightness, texture, color, depth, movement, shape, face recognition, and object recognition. While specializations for these functions are active topics for investigation, Fig. 31.3 illustrates the well-known specialization of primary visual cortex for primitive stimuli such as on/off full-field stimulation. Similar specializations exist for language, sensory, motor, and auditory systems, and provide the focus for recent developments in cortical function mapping that protect these systems during invasive neurosurgical procedures.

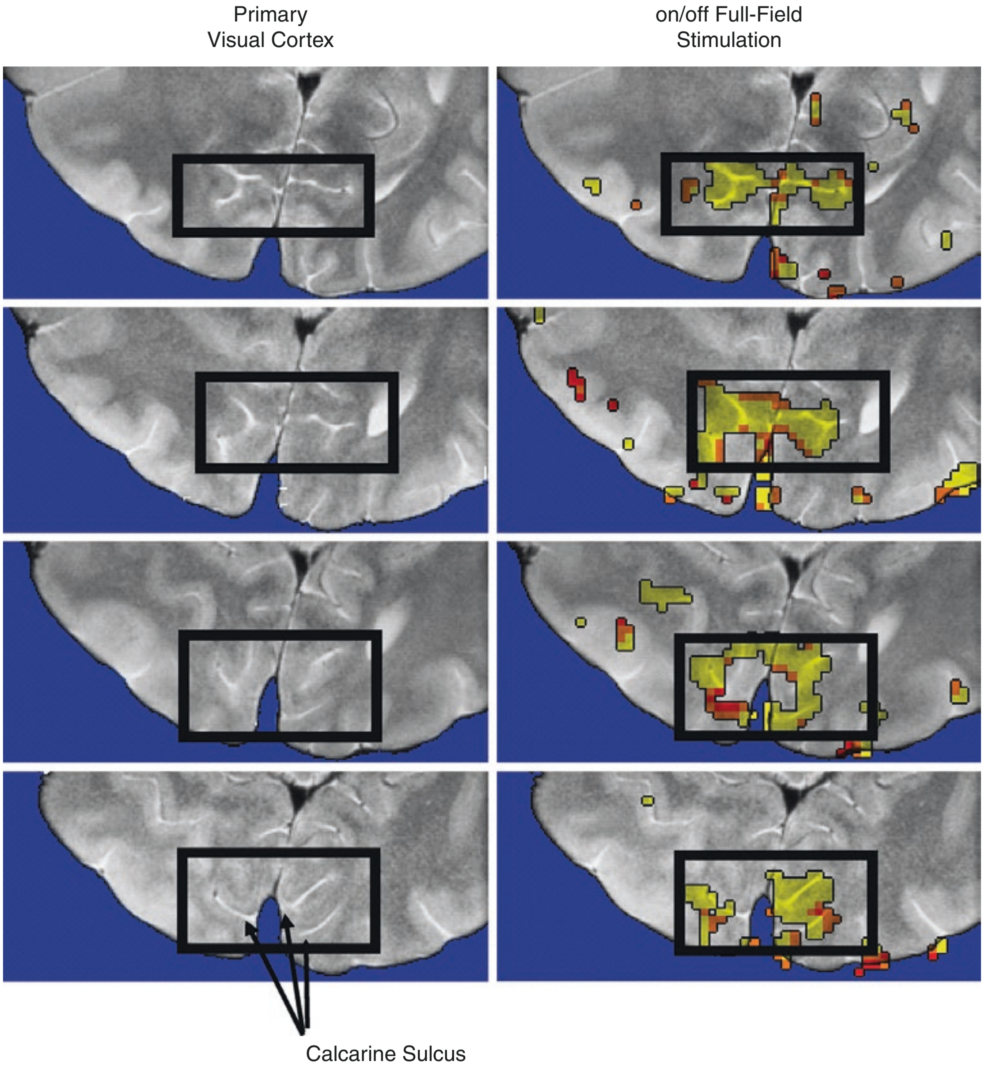


Fig. 31.3 Boxed areas surround the anatomical calcarine sulcus in contiguous 3-mm-thick axial slices (left column). The right column illustrates cortical activity (fMRI) observed during viewing of full-field 8 Hz on-off stimulation. The proximity of the activity patterns and the calcarine sulcus (primary visual cortex) is consistent with the known of functional specificity for this region

Identification and Preservation of Cortical Areas Specialized for Essential Tasks

Functional maps for individual subjects aim to identify functional specializations specific to that particular subject. In the case of functional mapping prior to a surgical procedure, the goal is to identify regions of the individual patient's brain that are employed for functions (such as motor movements, tactile sensation, language functions, vision, and audition) that might be at risk because of the location of the surgical procedures. The presence of a space-occupying lesion or long-term seizure-genic conditions can modify or shift functional foci, and normal assumptions do not necessarily apply. In these cases, functional images are acquired at the highest-possible resolution and integrated into the appropriate treatment plan. Ideally, individual effects are studied by comparisons that occur before and after a therapeutic intervention where functional changes would be expected.

The preservation of function during a resection or other new surgical procedure is an essential goal of neurosurgery, and various intraoperative and preoperative brain mapping techniques are currently employed for this purpose. These techniques aim to identify cortical areas involved in sensory, motor, and language functions and have become standard practice. They include intraoperative electrophysiology with motor and language mapping, preoperative Wada tests, and visual field examinations. However, the added risk, time, and expense of multiple mapping procedures favors a single, noninvasive, preoperative procedure that could prove effective for mapping these functions. Functional MRI has emerged as such a technique. Functional MRI maps of sensory and motor functions, either alone or in combination with other neuronavigation techniques [14–16], have been shown effective in directing brain tumor resection procedures away from cortical regions with residual function [14, 17–23].

Standard of Care and CPT Codes

A series of evaluation/procedural codes were approved to the American Medical Association (AMA) CPT Editorial Panel for use in billing for these procedures by physicians or licensed clinical psychologists. As of January 2007, three CPT codes were approved for use in billing for services provided during an fMRI procedure, grouped as follows:

> **70554**: MRI, brain, fMRI; including test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration (do not report 70554 when 96020 is performed).

And

> **70555**: MRI, brain, fMRI; requiring physician or psychologist administration. This code is intended to be reported with 96020: neurofunctional testing selection and administration during noninvasive imaging functional brain mapping, with test administered entirely by a physician or psychologist, with review of test results and report [24].

These codes and their intended applications are described in Box 31.1 [24, 25].

Box 31.1

Code 70554

This code is to be used by the physician acquiring the images of the brain and interpreting the locations of activations when the neurofunctional tests to be administered are limited to repetitive body part movement and/or simple visual stimulation. These simple motor and visual tasks can be administered by a radiologic technician under the supervision of the physician in charge of the procedure. If the indication for fMRI procedure is the treatment of a brain lesion and for locating it, then in these cases, it requires only an assessment of simple perceptual and/or sensorimotor functions. This procedure may then be appropriate in the judgment of the referring physician.

The preservice work of the physician typically includes reviewing the patient's clinical history and prior imaging studies, and preliminary planning of the neurofunctional tasks to be performed. The typical intraservice work consists of a limited examination to determine if the patient can perform the tasks. The patient is then placed in the scanner, simple motor, and/or visual testing is administered by radiologic technician or physicist during scanning and data acquisition, image data are analyzed, and coregistered fMRI images are interpreted by the physician. Postservice work includes report generation and communication to the neurosurgeon.

Codes 70555 and 96020

In the fMRI studies requiring mapping of neurologic/cognitive functions (e.g., language, memory, cognition, higher-order movements, and perception) beyond simple motor a sensory assessment, both the 70555 and 96020 are reported together. Either the referring physician or physician supervising fMRI procedure have determined that mapping of brain functions in these patients will require more extensive neurofunctional testing than those covered by 70554. The choice to map cognitive functions will be determined in part by the patient status, age, presence of neurologic deficit, specific cognitive expertise, location of the lesion, and/or lesions in brain regions known to affect cognition, language, or other higher-order operations.

Faro 2007, ACR Standards and Guidelines for fMRI [25]

Hart, 2007, Clinical functional magnetic resonance imaging, p. 142 [24]

www.ASFNR.org for more information

Tasks for fMRI and Mapping of Essential Functions

Tasks employed for functional mapping of sensory and motor-sensitive regions have generally been developed by separate research groups in the service of neurosurgical planning. As a consequence, many task variants have been employed. For example, motor tasks are sometimes accomplished by single finger–thumb tapping [20], and in other cases by multiple finger–thumb tapping [18, 26, 27]. Other approaches include self-paced clenching and spreading of the hand [23, 28–30], or sponge squeezing [19, 21]. Tactile stimulation has included palm brushing [19], compressed air puffs to the hand [21], and scratching the ventral surface of the hand [20]. Similarly, functional mapping of language areas has also been accomplished by a range of tasks and procedures including object naming and verb generation [31], production of the names of animals starting with a given letter [18], word generation in alphabetical order [32], or auditory noun presentations with a required category response [33]. It is not known, however, how these various tasks compare with respect to sensitivity or targeted regions of interest. Assessment of cortical activity associated with visual stimulation has been accomplished with intermittent binocular photic stimulation [18, 27, 34], as well as with various projected pattern stimuli [35]. The length of the activity period and the number of epochs in a run are also nonstandard. Additional variation is introduced to the literature by different levels of statistical stringency and multiple data-processing procedures. Although all of these tasks for sensory, motor, language, and visual functions may be individually effective, an integrated and standardized battery of tasks could optimize application for neurosurgical planning.

Within a cohesive task battery, it is desirable to maximize reliability by using multiple tasks to target-related functions. One such battery of fMRI tasks targets cortical regions associated with tactile, motor, language, and visual-sensitive cortical areas [36]. The task battery targets functions selective for regions frequently considered most critical for surgical decisions. All functions are repeated using both active (volitional) and passive (receptive) modes to assure that it is applicable to patients with a range of symptoms and performance capabilities. Any subset of these tasks may be selected for specific clinical objectives while retaining the advantages of the standardized procedures with validations based on responses of both healthy volunteers and patients.

An Example of a Multifunction Task Battery

The specific tasks selected for this task battery are intended to be nearly universally applicable and employ common stimuli and procedures [13]. The tasks consist of four separate procedures (Fig. 31.4 [13]) including:

1. Passive tactile stimulation of a hand (either the dominant hand or the hand relevant to the hemisphere of surgical interest) with a mildly abrasive plastic surface that is gently rubbed on the palm and fingers. Simultaneously, the patient views a reversing checkerboard pattern (8 Hz). This visual stimulation also aids in head stabilization of the patient.
2. Active hand movement (finger–thumb tapping) using either the same hand, as in the passive tactile stimulation, or both hands during a repeat of the simultaneous visual stimulation (reversing checkerboard).
3. Picture naming by internal (silent) speech in response to visually displayed, black-and-white, line drawings [37] presented at 4-s intervals. These drawings are selected from an appropriate range of the Boston Naming Test.
4. Listening to recordings of spoken words (names of objects) presented through headphones designed to reduce scanner noise. A visual fixation cross helps prevent head movement.

fMRI Task Battery for Cortical Mapping of
Sensory, Motor, Language and Vision-Related Areas

1. SENSORY Touch/hand	+	VISION Reversing Checkerboard
2. MOTOR Finger/Thumb tapping	+	VISION Reversing Checkerboard
3. LANGUAGE/active Picture Naming	+	VISION Pictures
4. LANGUAGE/passive Listening to Words	+	AUDITION Spoken words

Fig. 31.4 A summary of the functions mapped by the four conditions in the fMRI task battery. (Reprinted with permission from Hirsch J, Ruge MI, Kim KHS, Correa DD, Victor JD, Relkin NR, Labar DR, Krol G, Bilsky MH, Souweidane MM, DeAngelis LM, Gutin PH. An integrated fMRI procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery. 2000;47(3):711–722 [13])

The aims of these four task conditions include:

1. Localization of sensory and motor cortices, and by inference, location of the central sulcus
2. Localization of language-related activity, and by inference, the locations of Broca's and Wernicke's Areas and the dominant hemisphere for speech
3. Localization of primary and secondary visual and auditory areas

Each of the targeted functions and structures associated with each task is illustrated in Fig. 31.5 for a healthy volunteer [13]. The sensory and motor tasks target post- and precentral gyrus (GPoC and GPrC), respectively, and are illustrated in the left panels. These figures also illustrate the expected overlap along the pre- and postcentral gyrus between activity associated with sensory and motor stimulation. The language tasks target putative Broca's and Wernicke's Areas that are found within inferior frontal gurus (GFi) and superior temporal gyrus (GTs), respectively, on the dominant hemisphere for language (middle panels of Fig. 31.5). Both areas are redundantly targeted by expressive (active) and receptive (passive) language tasks, and by both visual and auditory modalities. Visual and auditory systems also are revealed by the activity in inferior occipital gyrus (GOi) and the transverse temporal gyrus (GTT), respectively, left and right language panels. Vision-related activity elicited by the reversing black-and-white checkerboard stimulations also targets primary visual cortex found along the calcarine sulcus (CaS), illustrated in the far-right panel of Fig. 31.5. Given the high levels of statistical confidence (*p* values from ≤ 0.0001 to ≤ 0.0005), it can be assumed that activity not circled also represents true physiological activations that are task-related and distributed outside the targeted regions of interest.

Healthy Volunteers and Patients

Development of this test battery was based upon a total of 63 healthy volunteers (24 female and 39 male) who participated in the evaluation of the specific set of tasks targeted to iden-

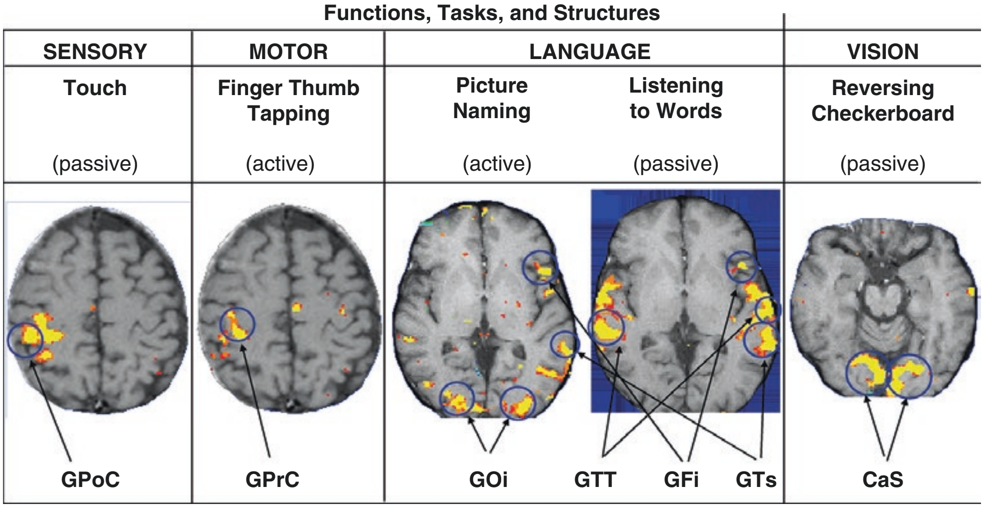


Fig. 31.5 Selected slices for a healthy brain illustrate targeted (circled) structures each of the functions and tasks: sensory, passive touch of the hand (left) using a rough plastic surface targets the postcentral gyrus (GPoC); motor, active finger–thumb tapping targets the precentral gyrus (GPrC); language, picture naming (expressive) and listening to spoken words (receptive) target the inferior frontal gyrus (GFi; Broca's Area) and the superior temporal gyrus (GTs; Wernicke's Area) on the dominant hemisphere; and vision, viewing of the reversing checkerboard and picture naming target the calcarine sulcus (CaS) and the inferior occipital gyrus (GOi). Primary auditory activity expected to be associated with the listening task also is observed bilaterally in the transverse temporal gyrus (GTT), middle panel. (Reprinted with permission from Hirsch J, Ruge MI, Kim KHS, Correa DD, Victor JD, Relkin NR, Labar DR, Krol G, Bilsky MH, Souweidane MM, DeAngelis LM, Gutin PH. An integrated fMRI procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery. 2000;47(3):711–722 [13])

Table 31.2 Evaluation of task sensitivity. Modified with permission from Hirsch J, Ruge MI, Kim KHS, Correa DD, Victor JD, Relkin NR, Labar DR, Krol G, Bilsky MH, Souweidane MM, DeAngelis LM, Gutin PH. An integrated fMRI procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery. 2000;47(3):711–722 [13]

		(A) Healthy subjects				(B) Surgical patients			
		Targeted regions of interest				Surgical regions of interest			
		Central	Broca's	Wernicke's	Visual	Central	Broca's	Wernicke's	Visual
		sulcus	area	area	cortex	sulcus	area	area	cortex
Task	Structure	($n = 30$)	($n = 45$)	($n = 45$)	($n = 15$)	($n = 63$)	($n = 22$)	($n = 34$)	($n = 6$)
Touch	GPoC	100%				94%			
Finger–thumb	GPrC	100%				89%			
Tapping									
Picture	GFi		90%				72%		
Naming	GTs			73%				65%	
Listening to	GFi		93%				54%		
Spoken words	GTs			100%				88%	
Checkerboard	CaS				100%				100%
Pictures	Goi				100%				100%
Composite sensitivity		100%	93%	100%	100%	97%	77%	91%	100%
(Logical OR)									

tify brain regions most likely to be surgical regions of interest for (1) primary brain tumor, (2) brain metastasis, (3) seizure disorder, or (4) cerebral vascular malformation. A total of 125 patients also participated. These patients were surgical candidates and presented with surgical regions of interest that included sensorimotor ($n = 63$), language ($n = 56$), or visual ($n = 6$) functions [13].

Sensitivity of Task Battery: Healthy Volunteers

Each task was associated with the targeted region of interest, and the percentage of cases showing activity in those regions (sensitivity) was determined (Table 31.2a) [13]. This task battery provides two opportunities to observe the targeted region. For example, whereas the superior temporal gyrus (GTs) was activated in only 73% of cases during picture naming, it was activated in 100% of healthy volunteers during listening to spoken words (Table 31.2a, column 5). Overall, the sensitivity of the entire battery to identify language-related cortex in the superior temporal gyrus is 100% for the population of healthy volunteers, as indicated on the bottom row: Composite Sensitivity. Specifically, the composite sensitivity is the result of a logical operating room (OR) decision rule based on two tasks that target a specific region. Central sulcus and visual cortex were identified in 100% of cases and Broca's Area in 93% [13].

Sensitivity of Task Battery: Surgical Population

Following task-sensitivity determinations for healthy volunteers, similar determinations were made for surgical candidates with pathology in the specified cortical regions of interest. This enabled assessment of the fMRI task within the affected pathological cohort. These subgroups served as the basis for evaluation of the respective tasks, although all patients completed all tasks in the battery, regardless of the region of surgical interest. Table 31.2b reports the task sensitivity within each surgical group, thus indicating the sensitivity in the presence of pathology [13]. The tactile stimulation revealed activity in the postcentral gyrus in 94% of patients with lesions in or close to the motor strip, whereas the finger–thumb-tapping task predominantly demonstrated function in the area of the precentral gyrus in 89%. Of the two patients for whom the central sulcus was not identified, one was characterized by excessive (not correctable) head movement and marginal compliance. Neurological deficits were the most likely contributing factor in the second case. Overall, the location of central sulcus, as indicated by either its posterior or anterior margins, was obtained in 97% of the cases with pathology in this region and is indicated as the composite sensitivity (bottom row). This boost in sensitivity is achieved by exploiting the two approaches to locate central sulcus and the employment of a logical OR combination decision rule between the two tasks [13].

With the combined performances of the picture-naming task, as well as the passive listening task, the fMRI signal was observed in Wernicke's Area in 31 of 34 (91%) patients with pathology in superior temporal gyrus and Broca's Area in 17 of the 22 patients (77%) with pathology in inferior frontal gyrus. Explanations for the three unsuccessful Wernicke's area patients included movement artifact (*n* = 1) and probable lack of compliance (*n* = 2). Explanations for the five unsuccessful Broca's Area patients included neurological deficits (*n* = 3), probable marginal compliance (*n* = 1), and head-movement artifact that was not correctable (*n* = 1), although a false-negative finding cannot be ruled out. The fMRI signal was observed in the visual cortex (calcarine sulcus and inferior occipital gyrus) in all six patients with lesions in these cortical areas [13].

Comparison of Task Sensitivity for Patients and Healthy Volunteers

Although the sensory and motor probes of GPoC and GPrC were each 100% effective in healthy volunteers, they were individually 94% and 89% effective in patients with tumors in those regions. These observations include patients with severe symptoms such as hemiparesis and loss of sensory function. However, by combining the two tasks with the either/or decision rule, the central sulcus was identified in 97% of cases. By combining the hit rates of the picture-naming and the listening to spoken words tasks for the healthy volunteers, the targeted Broca's Area (GFi) and Wernicke's Area (GTs) were activated in 93% and 100% of cases, respectively. Correspondingly, for the surgical cases, these areas were activated in 77% and 91% of the cases, respectively [13].

The reduction in patient sensitivity for the language areas presumably reflects tumor-related receptive and expressive aphasias, as well as related cognitive losses. The visual functions within CaS and GOi were 100% effective in both healthy subjects and also for surgical patients where the unaffected hemisphere provided the comparison. Accuracy of the fMRI observations also can be assessed in all surgical patients for whom multiple procedures were included in the treatment plan by comparison of the fMRI maps with conventional techniques such as intraoperative mapping, Wada and visual fields testing methods. This method of comparison serves to establish the concordance of the fMRI technique with other accepted techniques.

Accuracy of Task Battery: Comparison with Intraoperative Electrophysiology

Both fMRI preoperative maps and intraoperative electrophysiology were performed in 16 cases. Intraoperative recording of somatosensory evoked potentials (SSEPs) were performed to localize the central sulcus [38], and successful recordings were obtained in 15 cases. Direct cortical stimulation was performed in 11 of these cases with successful stimulations in nine. The areas of electrophysiological response were referenced to axial images with the use of an intraoperative frameless-based stereotactic navigation device and compared to the preoperative fMRI images. Due to the differences in the orientations of the acquired slices, however, precise measurements of the localizations of the two techniques were not possible. In each case, the surgeon judged the correspondence as consistent. (See case example Fig. 31.8.)

The fMRI maps revealed precentral gyrus activity in 16 of 16 (100%) cases and postcentral gyrus in 13 of 16 (81%) cases. However, the combined maps revealed the location of the central sulcus in all cases. When both methods (fMRI and electrophysiology) reported the central sulcus, the locations concurred in 100% of the cases for the SSEPs (15 of 15), and 100% for the direct cortical stimulation (9 of 9), as determined within the spatial accuracy of both methods, and in accord with previous findings of other investigators [21, 39, 40].

Comparison of fMRI, Wada, and Intraoperative Language Mapping

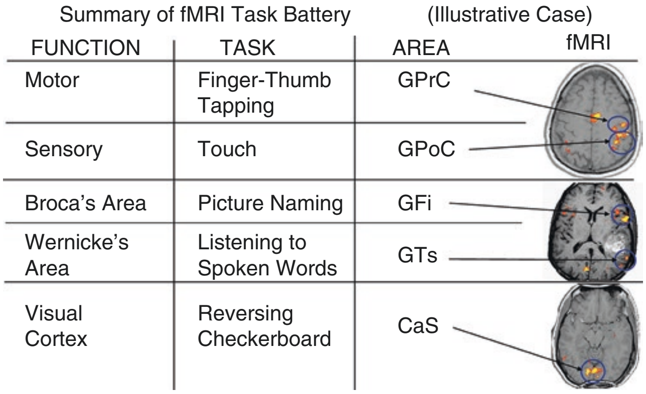
Hemispheric language dominance as predicted by the fMRI language-related maps was compared to preoperative Wada procedures in 13 cases [41]. The dominant hemisphere for language as determined by Wada testing was consistent with fMRI results in all 13 cases (double-blind study), and is consistent with findings of previous investigations [33]. In a subsequent cohort of five patients, this integrated battery of tasks was applied prior to intraoperative language mapping, with consistent findings between the two methods [42].

Comparison of fMRI and Visual Fields

Homonymous visual field defects were compared with fMRI response patterns in primary visual cortex in six cases (illustrated in Fig. 31.1). Visual fields determined by formal static perimetry indicated hemianopic or quadrantanoptic field deficits consistent with known disruptions of visual projection pathways and were consistent with the fMRI cortical maps when compared with activity within the unaffected hemisphere. That is, gross absences of hemispheric symmetry along the calcarine sulcus in regions expected to correspond to the visual field were taken as demonstrations of field and fMRI consistency.

Case Example 31.1 Motor and Language Mapping

In this case, a 43-year-old, right-handed man presented with mild headaches and brief episodes of receptive language disturbance, as well as occasional word-finding difficulties. Preoperative neuropsychological evaluation revealed no language deficits. MRI revealed a rounded, partially hemorrhagic lesion, 4.5 cm in diameter located in the left posterior temporal lobe. To optimize a therapeutic plan, functional maps were obtained using the multifunction task battery (results are summarized in Fig. 31.6 [13]). The central sulcus was identified clearly by the sensory and motor tasks (top rows). The language tasks revealed language-related activity on the left hemisphere adjacent to both the posterior margins and the anterior margins of the mass (GTs and GFi; middle rows). The visual stimulation was reliably associated with signals within and along the primary visual areas (CaS). Due to the proximity of the language-related activity to the tumor, an awake craniotomy with electrophysiological mapping of motor and language functions was performed.



Summary of fMRI Task Battery (Illustrative Case)

FUNCTION	TASK	AREA	fMRI
Motor	Finger-Thumb Tapping	GPrC	
Sensory	Touch	GPoC	
Broca's Area	Picture Naming	GFi	
Wernicke's Area	Listening to Spoken Words	GTs	
Visual Cortex	Reversing Checkerboard	CaS	

Fig. 31.6 Selected slices (right) illustrate cortical responses associated with each of the tasks and the targeted regions of interest for Case Example 31.1. Sensory and motor tasks elicited activity within pre- and postcentral gyri and predicted the location of the central sulcus on multiple contiguous slices. The slice illustrated in the right top row shows a relatively inferior representation. The two language tasks—picture naming and listening to spoken words—elicited activity in the left hemisphere within the inferior frontal gyrus (GFi) and the superior temporal gyrus (GTs; arrows). In this case, the specific locations of the activity within the GFi and GTs were replicated on both tasks and the overlapping regions were taken as the best predictor of Broca's and Wernicke's Areas, respectively. Finally, the reversing checkerboard (bottom row) indicated primary visual cortex, as illustrated by the activity labeled calcarine sulcus (CaS). Similar to the language-related regions, these regions were replicated across the multiple visual tasks and served to increase confidence in these results. (Reprinted with permission from Hirsch J, Ruge MI, Kim KHS, Correa DD, Victor JD, Relkin NR, Labar DR, Krol G, Bilsky MH, Souweidane MM, DeAngelis LM, Gutin PH. An integrated fMRI procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery. 2000;47(3):711–722 [13])

Integrative Mapping of Sensory and Motor Functions

Recording of SSEPs indicated the location of the central sulcus (Fig. 31.7, left columns), which was confirmed by direct cortical stimulation of precentral gyrus (middle columns). Comparison with the location of central sulcus by fMRI (right column) indicates good agreement with both techniques, as illustrated by the arrows [13].

Interoperative Mapping of Language Functions

Direct cortical stimulation of the left inferior frontal gyrus with the Ojemann bipolar stimulator disrupted the patient's ability to count, and a similar stimulation of the superior temporal gyrus produced language disturbances, including literal paraphasic errors and word-finding difficulties, respectively (Fig. 31.8). Sites of observable responses were tagged with numbers, photographically documented, and cross referenced to the fMRI, as illustrated by arrows [13].

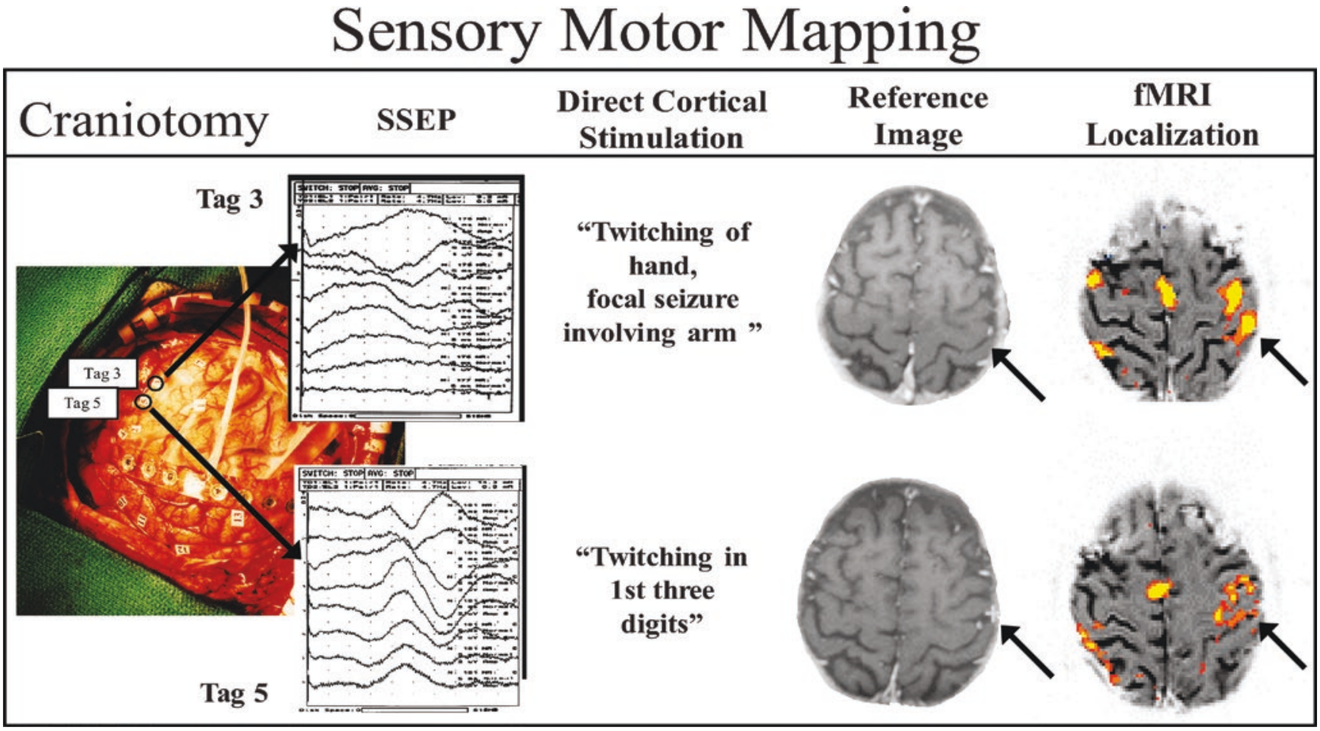


Fig. 31.7 Needle-recording electrodes were placed at Erb's Point and stimulating electrodes were placed over the left or right median nerve at the wrist. Following craniotomy and exposure of cortex, subdural strip electrodes were placed in the operative field. The median nerve was stimulated to elicit epicortical responses measured with the electrodes. A consistent phase reversal between electrode sites (tags 3 and 5, column 2) was taken as the physiological identification of sensorimotor cortex, and therefore, the central sulcus (indicated by arrows on the reference images in column 4). These recordings of somatosensory-evoked potentials (SSEP) were made with an eight-Channel Viking IV7 and standard filter settings (30 Hz to 3 kHz). Direct cortical stimulation of the exposed cortex directed by the SSEP results was performed using the Ojemann bipolar stimulator (1 s trains of 1 ms pulses at 60 Hz) varied from 2 to 18 milliamperes (mA), peak to peak, resulting in hand twitching and a focal seizure of the right arm (top row) and twitching of the first three digits of the hand (bottom row). Using a frameless-based intraoperative navigation system (BrainLAB GmbH, Munich, Germany), the tagged locations were referenced to anatomical axial MR images localized using a viewing wand and subsequently compared with areas of activation on corresponding fMRI images, as illustrated by comparison of the images in columns 4 and 5 (arrows). The T2* images (right column) and the conventional T1 images (reference image) were not acquired at exactly corresponding plane orientations, accounting for the variation in the two structural images and limiting the precision with which the electrophysiological and fMRI locations can be compared. (Reprinted with permission from Hirsch J, Ruge MI, Kim KHS, Correa DD, Victor JD, Relkin NR, Labar DR, Krol G, Bilsky MH, Souweidane MM, DeAngelis LM, Gutin PH. An integrated fMRI procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery. 2000;47(3):711–722 [13])

Postsurgical Status

A total resection was achieved that spared these functional regions. The pathology was consistent with an ependymoma. Immediately postsurgery, no impairments in language function were detected. However, the postoperative recovery of the patient was complicated by a temporary mixed aphasia and seizures. Subsequently, within 10 days, the patient's condition was substantially improved, and no further adjuvant treatment was planned. A 6-month postsurgical fMRI scan was consistent with previous findings, and neuropsychological evaluation revealed residual, mild word-finding difficulties and occasional literal paraphasic errors.

Case Example 31.2 Language Mapping: Late Bilingual Patient

In this case, the patient was a native of Italy who emigrated to the United States as a young adult and then learned English. When she was 44 years old, she began to experience episodes of word-finding difficulty in both Italian and English, as well as slowed speech production. An MRI obtained during a medical evaluation revealed a large tumor in the left inferior posterior frontal region of her brain expected to be associated with speech production (Fig. 31.9a). In order to determine the location of her language areas relative to her tumor, a functional MRI was acquired using the task battery previously described for each language, which revealed: (1) separate locations for her native (Italian) and second language (English), and (2) that both languages were displaced from the expected locations by the tumor. These displacements were confirmed during surgery and the tumor was resected without damage to either language function. Approximately 2 years later, she remained tumor free, with excellent English and Italian language function. A follow-up fMRI scan indicated the language areas associated with each

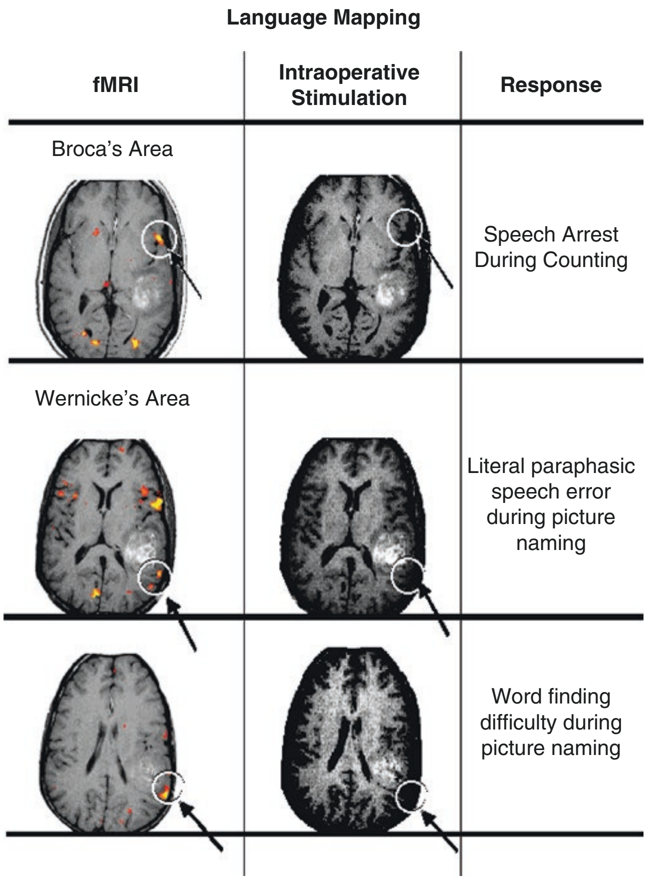


Fig. 31.8 After craniotomy and recording of SSEPs, the patient was awakened and asked to count forward and backward while the cortex in putative Broca's Area was stimulated. Subsequently, the picture-naming paradigm used in the fMRI battery of tasks was administered and stimulation at the site where fMRI maps indicated the location of Broca's Area resulted in speech disruption (top row). Stimulation was systematically repeated and extended to temporal lobe cortex, and sites of activation revealed by the fMRI maps were specifically targeted as indicated by the circles in the middle and bottom column. These stimulations resulted in paraphasic speech errors and word-finding difficulties as indicated, consistent with disruption of Wernicke's Area-related functions that occurred in the two separate locations as indicated. The corresponding preoperative fMRI maps shown on the left column confirm the correspondence of cortical areas (circles and arrows). (Reprinted with permission from Hirsch J, Ruge MI, Kim KHS, Correa DD, Victor JD, Relkin NR, Labar DR, Krol G, Bilsky MH, Souweidane MM, DeAngelis LM, Gutin PH. An integrated fMRI procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery. 2000;47(3):711–722 [13])

language had shifted back to the expected locations within the brain (Fig. 31.9b). The separation of the locations active during the native language and the second language within Broca's Area is consistent with previous findings of separation between L1- and L2-sensitive areas, when L2 was acquired during adulthood [43].

Case Example 31.3 Language Mapping: Early Bilingual Patient

A 23-year-old right-handed bilingual woman who worked as a waitress in her father's Italian restaurant was seen on an emergency basis following the sudden onset of supplementary motor seizures. An MRI revealed the presence of a left posterior frontal cystic lesion suggestive of cystic astrocytoma. Although the patient was born and educated in the United States, she was raised in a household that spoke Italian and became bilingual during her early language development. Functional MRI of her language areas for both languages revealed overlapping clusters in putative Broca's Area (left inferior frontal gyrus) as illustrated in Fig. 31.10a, which was not changed following surgery (Fig. 31.10b), consistent with the absence of postsurgical morbidity.

Individual variations in language maps that depend upon language experience is confirmed by previous reports that compared activity patterns in Broca's Area for L1 and L2 for early and late bilinguals (Fig. 31.11) [43].

Case Examples 31.2 and 31.3 illustrate earlier findings that document different cortical organization with respect to early and late acquisition of a second language. Kim and colleagues showed that the average centroid separation in putative Broca's Area during L1 and L2 production in late bilingual subjects was approximately 7 mm, whereas in early bilingual subjects, the language activations were indistinguishable (Fig. 31.11) [43].

Case Example 31.4 Motor Mapping

An 11-year-old female with a completely unremarkable medical history presented following the occurrence of a grand mal seizure. Imaging revealed a large mass along the lateral margin of right central sulcus (Fig. 31.12a). Due to the risk to sensory and motor functions, a surgical resection was recommended, and recommended treatment consisted of seizure management. Seeking a second opinion, her parents sought a medical center with fMRI mapping capability; the functional map revealed that the tumor had displaced eloquent sensory and motor sensitive cortex medially and posteriorly from the expected positions (Fig. 31.12b). Based on this information, an anterior surgical route resulted in a complete and total resection of a ganglioglioma without functional deficit. Six months postsurgery, she returned for a follow-up map that revealed the expected functional pattern (Fig. 31.12c). She had returned to her normal activities, including soccer, dance, and rock climbing.

A novel feature of this battery of integrated fMRI tasks is the redundancy in the measurements. For example, language-sensitive regions are mapped by both active (expressive) and passive (receptive) tasks, as are the regions sensitive to motor (active tapping) and sensory (passive touching) tasks. Visual areas also are assessed by passive viewing of the reversing checkerboard stimulus (no response required) and active viewing of pictures during a naming task in which a response was required. Advantages to employing more than one task associated with a particular function to isolate eloquent cortical areas include improved confidence when replications are observed, and improved sensitivity when the activity is

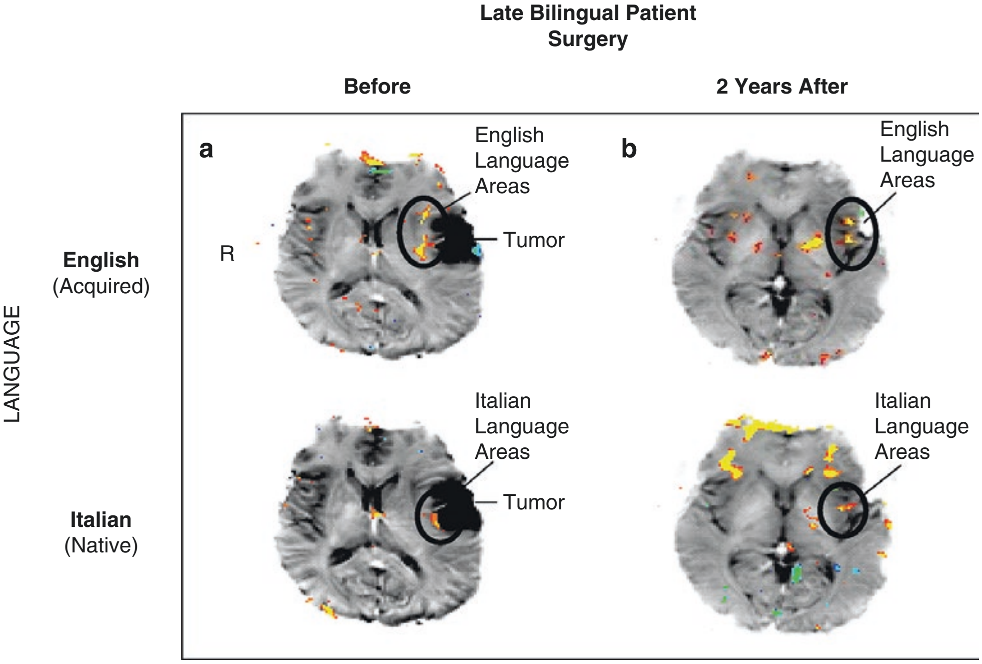


Fig. 31.9 Language mapping of a late bilingual patient. Object naming was performed in the native language (Italian), and also in the acquired language (English). Typical of late bilingual individuals, the languages occupied distinct regions of Broca's Area (**a**). These distinct regions were preserved following surgery and are consistent with her clinical outcome of no deficits in either language (**b**)

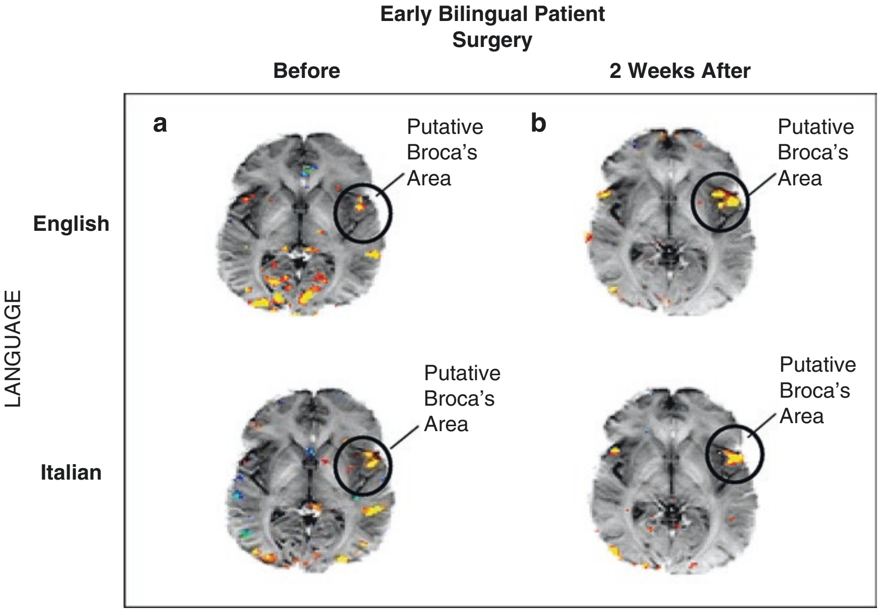


Fig. 31.10 Language mapping of an early bilingual patient. Object naming, as for the late bilingual patient (Fig. 31.9), was performed in both languages: Italian and English. Typical of early bilingual individuals, the activity clusters associated with both languages were largely overlapping within Broca's Area (**a**). This single language area was preserved following resection (**b**), consistent with the absence of postsurgical morbidity

observed during either an active or a passive performance. This feature translates into a greater likelihood of a successful map for patients with neurologic deficits. Together, the task sensitivity and accuracy observed for these fMRI maps suggests that this multifunction task battery yields a reliable estimate of the locations of critical functions potentially at risk during brain surgery, and thus extends the potential of a single preoperative fMRI brain mapping procedure to facilitate optimal outcomes for neurosurgery.

Based on our experience with this fMRI task battery, the images serve both pre- and intraoperative objectives. On the preoperative side, the fMRI maps have contributed to our estimates of the risk–benefit ratio and to the decision whether or not to offer surgery to the patient; although these decisions are based on the entire medical situation taken together, and not on any single factor. Communication between the surgeon and the patient is also facilitated by images that summarize the relevant structure and function issues. On the intraoperative side, as illustrated previously, the fMRI results have also served to direct the intraoperative electrophysiology, and thereby have contributed to the efficiency of the intraoperative procedures. However, it has been observed

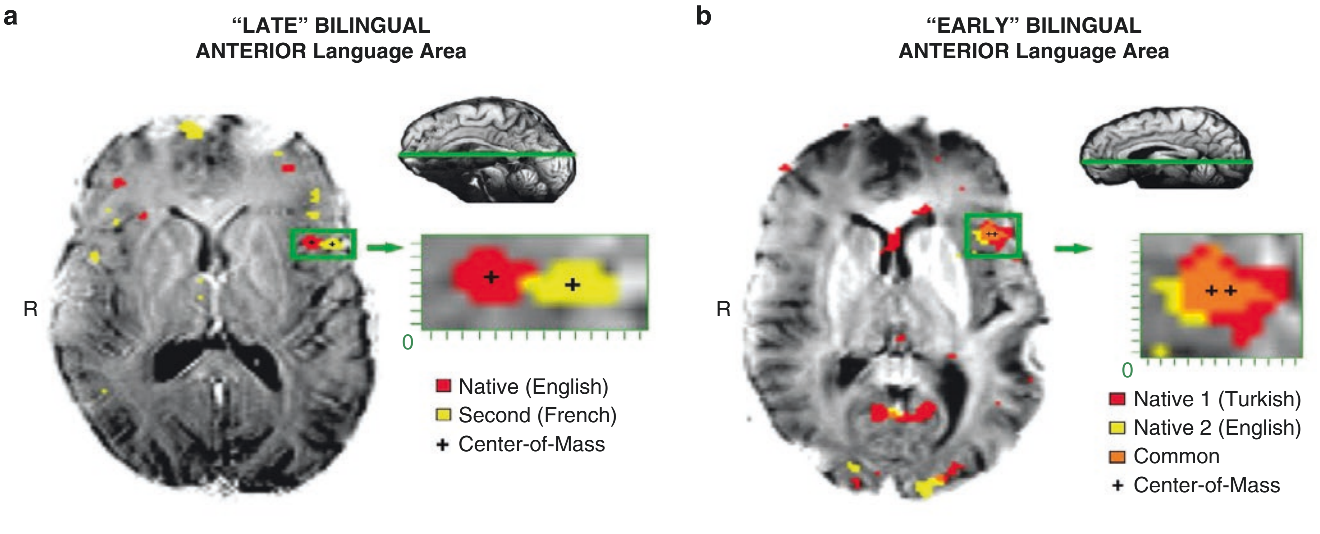
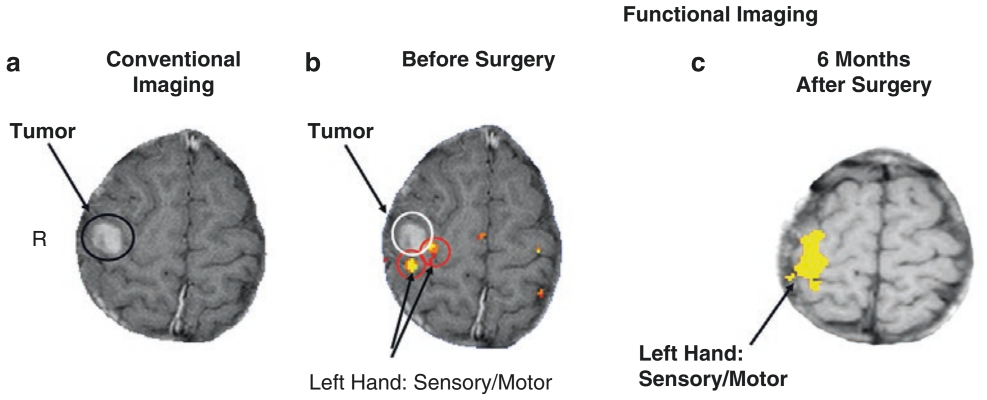


Fig. 31.11 Examples of main findings based on two samples of healthy volunteers who were either late (**a**) or early (**b**) bilinguals. Cluster centroids and variances (spreads) were determined for activity associated with each language. A significant separation between centroids of activity was found for late bilingual subjects and not for the early bilingual subjects in Broca's Area. No differences were observed within Wernicke's Area. (Reprinted with permission from Kim KHS, Relkin NR, Lee K-M, Hirsch J. Distinct cortical areas associated with native and second languages. Nature. 1997;388:171–174 [43])

Fig. 31.12 (**a**) Conventional T1 image reveals right hemisphere mass located on the margins of the central sulcus. (**b**) Functional map of tactile and finger–thumb tapping suggests displacement of eloquent cortex. (**c**) Six months after surgery, the patient was disease-free, without deficits consistent with the sensory and motor activity revealed by fMRI



that the information offered by the preoperative fMRI map is often more distributed than that of the intraoperative map, and the question of which active regions are essential to the function is not directly addressed by fMRI [44]. A false-positive interpretation is therefore possible based on these associated patterns of activity, whereas a false-negative finding is also possible due to sensitivity, compliance, and imaging artifacts. The likelihood of both types of errors is reduced with repetitions and checks for internal consistency, as suggested by this integrated task battery. However, advances to resolve these issues may depend upon additional techniques, such as transcranial magnetic stimulation (TMS) to confirm the essential nature of an area identified by fMRI.

Many future enhancements of this initial task battery are possible using methods that determine task sensitivity and clinical validity, as well as improve confidence by reducing the risk of either false-positive or false-negative findings. The battery could be extended to include memory functions, high-level cognitive tasks, and perhaps even emotion and affect, and continued development could improve the tasks to target the sensory/motor and language areas. Techniques employed for the development of this integrated battery of functions could serve as a basis to develop other similar probes, and thus extend the potential role of fMRI in neurosurgical planning to encompass more precision and diversity in structure and function relationships.

Functional MRI During Loss of Consciousness: A "Voice" for Unresponsive Patients

Applications of functional neuroimaging now extend beyond mapping the primary stages of perception, language, and motor systems to characterize cortical function in patients with disorders of consciousness [45]. At first pass this objective appears paradoxical because conventional investigations of cognitive processes require patient cooperation with a task. For example, to map the location of language-sensitive cortex, a language-related task is performed according to a temporal sequence that alternates the task with rest (no-task) periods. However, another strategy employs the use of *passive stimulations* of patients who are not conscious. Comparisons between patients with altered states of consciousness due to sedation or brain injury and healthy subjects may be employed to map eloquent cortex and to infer readiness and potential to sustain awareness.

As if a "mindscope," fMRI enables a view of occluded neural processes to inform medical practitioners about the health of the neurocircuitry mediating cognitive processes. An underlying point-of-view is that assessment of recovery potential might be enhanced by neuroimaging techniques that reveal the status of residual systems specialized for essential cognitive and volitional tasks for each patient. Thus, development of imaging techniques that assess the functional status of individual unresponsive patients is a primary goal for current investigations.

The structural integrity of injured brains is often compromised depending on the specific traumatic event, and, therefore, images cannot be grouped across patients as is standard practice for investigations of cognitive systems in healthy volunteers. Thus technical adaptations associated with individual patient assessments where there is "zero tolerance for error," as for neurosurgical planning, and confidence in the results must meet the highest standards of care, can be applied to assessments of cognitive capacity in patients with disorders of consciousness. Adaptations that have been developed for the purpose of personalized planning for neurosurgical procedures by mapping the locations of essential functional systems such as language, perception, and sensory-motor for each individual patient give rise to assessment techniques useful for assessments of neuro-cognitive health in patients who are unresponsive.

"Zero-Tolerance" for Error

In contrast to population-based studies where error bars are considered to be variations largely due to individual differences, clinical tests focus on the individual for diagnosis, treatment, and follow-up. Thus, the burden for accuracy for the "*n* of one" case is 100%, and dictates methodological adaptations to meet this standard. These adaptations include an extraordinary standard for high image quality as well as clarity, accuracy, and precision for interpretation.

The "zero-tolerance for error" standard is further complicated by the special circumstances of many patients. Some key factors include functional deficits that challenge execution of the task, high levels of anxiety leading to claustrophobia, inability to remember or perform instructions, excessive head movements, probability of a seizure or other sudden event that interrupts a scan, the effects of therapeutic drugs, and susceptibility artifacts often resulting from a previous surgical bed, implant, or a vascular abnormality. The methodological adaptations developed to accommodate neurosurgical applications are discussed earlier in this chapter and include standardized paradigms and tasks that map most relevant functions, employ short imaging runs, high-resolution grids, and least number-of-assumptions for data analysis. All of these adaptations are relevant to the even more challenging task of imaging unresponsive patients with disorders of consciousness where passive (rather than volitional) responses are required.

Functional Mapping During Sedation

Following the development of the basic standard battery of tasks for neurosurgical planning, we were challenged by the need to provide similar maps for patients who were sedated during the imaging procedure. The population for which this was generally necessary included children under 6 years old. In the face of specific medical needs, the passive tasks (listening, tactile, and visual photic stimulation) were adapted for use under sedation with propofol [46]. One of the adaptations was the use of a familiar speaker for the passive listening, and meaningful narratives were recorded for the purpose of the functional maps. As illustrated for the case of a 15-month-old sedated female (Fig. 31.13), this technique yields a system of regions consistent with known language-related areas. In the case of this patient, the language-dominant hemisphere was on the right side, which is consistent with the absence of morbidity following a complete and total resection on the left hemisphere. These studies confirm that "consciousness" is not a prerequisite to confirming the presence of an active language-related system in the cortex.

The discovery that the neural correlates for language processes could be engaged during sedation raised the possibility that unresponsive patients due to a disorder of

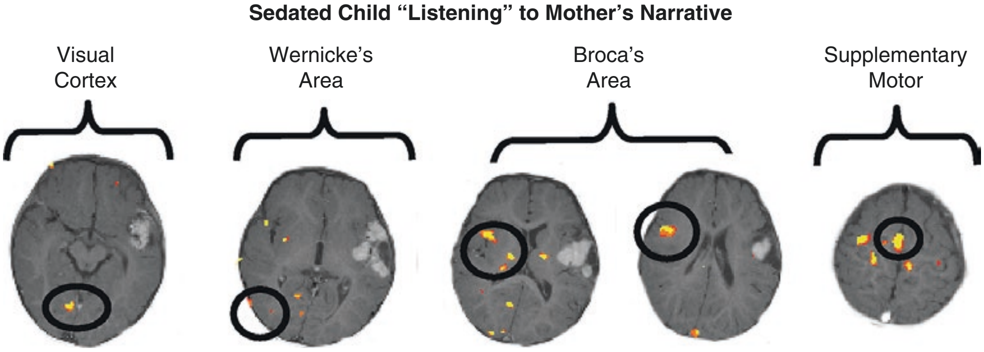


Fig. 31.13 Functional imaging during sedation. Fourteen continuous 4.5 mm slices covering the whole brain of a 15-month-old female with an aggressive tumor (PNET) in the left hemisphere (hyperintense region, slices 1–8 where slice 1, located in the upper left of the figure is the most ventral). In-plane resolution was 1.5 × 1.5 mm and the double-pass paradigm and analysis (see text) was employed. The patient was sedated with propofol and maintained at the lightest level that prevented movement of the head. A recorded passage of the mother talking to the patient was played through earphones worn by the patient while scanning. The circles indicate putative Wernicke's Area, Broca's Area, and supplementary motor area, consistent with the expected language network in preparation for the emerging language function

consciousness could be similarly aroused. The first example of FMRI in patients with disorders of consciousness (DOC) is illustrated as follows.

Functional Mapping of Minimally Conscious Patients

An Illustrative Case

A 33-year-old right-handed male without prior history of neurological disorders suffered severe head trauma secondary to a blow to the right frontal region with a blunt object leading to bilateral subdural hematoma and brainstem compression injury [47]. Bedside examinations were consistent with the diagnosis of MCS [48], and the functional imaging study was performed 24 months after the injury. Neurological examination at the time of the study revealed oculocephalic responses with intact visual tracking and saccades to both stimuli and to commands, marked increased motor tone bilaterally, and frontal release signs. The highest level behavior observed in this patient was his ability to inconsistently follow complex commands including Go, No-Go, countermanding tasks, and occasional verbalization. Right frontal lobe encephalomalacia and paramedian thalamic infarction were present on the structural MRI and on the functional (T2*) scans. Resting fluorodeoxyglucose (FDG) PET demonstrated 40.6% of normal regional cerebral metabolic rate.

Imaging methods were as described previously for neurosurgical patients, and employed passive auditory stimulation by presenting a prerecorded narrative of a family member recalling past experiences that she had shared with the patient. The narrative was also presented as reversed speech including the same content but without linguistic meaning. Passive tactile stimulation was also employed. Single epoch runs each lasting 2 min 24 s and the double-pass short-block paradigm was employed. Single-voxel confidence levels were set at $p \leq 0.0001$ corrected for false positives (Fig. 31.2). Voxel size was 1.5 × 1.5 × 4.5 mm and 21 continuous slices covered the whole brain. The scanner was a 1.5 T GE equipped for echo-planar imaging (EPI) with a standard fMRI sequence (TR = 4000, TE = 60, flip angle = 60).

Figure 31.14 shows the results of activity associated with the forward speech excluding areas associated with the backward speech in order to evaluate the hypothesis that the patient was responsive to the "meaning" of the narrative not just the sound. Most notable is the similarity between the patient and both the group and healthy individuals who performed the same task. In particular, activity observed in the left temporal gyres (GTs) and left inferior frontal gyres (GFi) are consistent with Wernicke's and Broca's Areas, respectively. Of notable interest is the additional activity in the occipital region (calcarine sulcus [SCa] and middle occipital gyres [GOm]) of the patient suggestive of mental imagery and/or top-down information processing in response to the narrative.

The neural activity associated with this stimulation, and the forward-backward narrative comparison is not only remarkably robust for the patient, it is basically indistinguishable from the normals.

These findings and similar cases [49] raise a number of complex questions including "Does this patient have an inner cognitive life that is not reflected by his bedside responses"? If so, what can we do about it? Are any of these findings evidence for "neural preparedness" for emergence? What ethical issues do these findings suggest?[50]. What investigations need to be done to lead us to informed and aggressive thera-

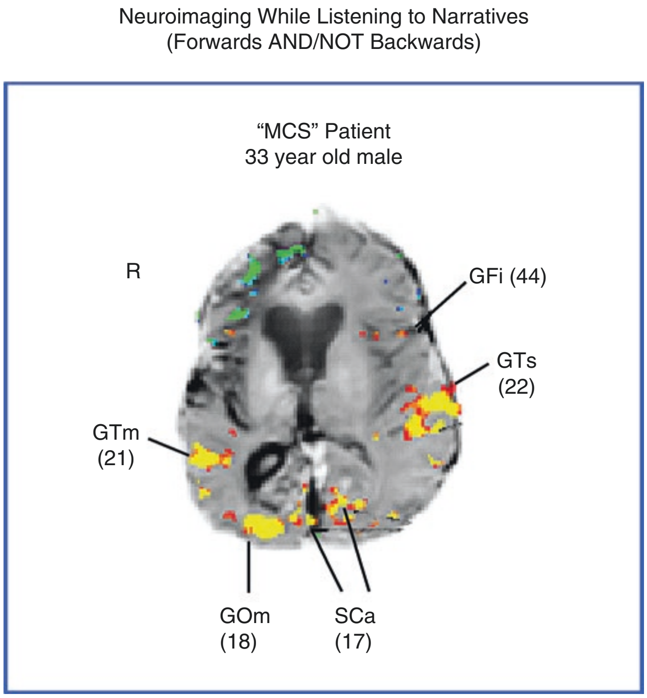


Fig. 31.14 Functional imaging of cognitive processes in minimally conscious states (MCS). Neuroimaging While Listening to Narratives presented as normal speech (Forward) excluding responses elicited when the same speech was presented in reversed time (AND/NOT Backwards). Note the structural abnormalities in the anterior right hemisphere secondary to the injury. Activity in left inferior frontal gyrus (GFi), Brodmann's Area (BA) 44, putative Broca's Area; left hemisphere temporal gyrus (GTs), BA 22, putative Wernicke's Area; and middle temporal gyrus (GTm), BA21, bilaterally, putative auditory-cortex as expected for language tasks is observed. Additionally, the MCS subject shows activity in the extrastriate visual cortex (middle occipital gyrus, GOm, BA18), and in primary visual cortex (calcarine sulcus, SCa, BA17). The levels of statistical stringency and analysis procedures were identical for the patient and a comparison healthy volunteer suggesting that the responses elicited by the patient were (1) more robust as they activated a large volume of cortex (larger number of significant voxels), and (2) more distributed as the global pattern of activity included visual system responses. This was unexpected since there was no visual stimulation (only auditory), and the patient had his eyes closed. We cannot rule out the possibility that this patient was "visualizing" some representation of the narrative that was personalized for him

pies? Can neuroimaging contribute to assessments that will guide and inform therapies for individual patients? Recent investigations suggest that imaging paradigms established to investigate the neural underpinnings of cognition in normals also provide foundations for emerging investigations of the neural underpinnings of consciousness. Both bring neural science closer to the goal of understanding the biological underpinnings of the mind, and perhaps closer to the goal of treating patients with disorders of consciousness.

Objective Assessment of Patient States During a Disorder of Consciousness Based on the Extent of the Network Engaged by a Command to Name Objects

The aforementioned studies document that even during states where consciousness is lost, evidence of cognitive engagement is obtainable using fMRI. More recent advances suggest that the integrity of the long-range networks elicited by an instruction to name pictures can inform the neurophysiology. Patients with disorder of consciousness (DOC) can be stratified by completeness of the neural system engaged by the task [51], suggesting that activity of the language network may serve as a proxy for behavioral evidence of awareness. Command-following paradigms that employ fMRI rather than overt motor responses to assess cognitive capacity in DOC patients have emerged as an important clinical advance.

Awareness of self or environment is considered a prerequisite for conscious processing and it is conventionally assessed by overt motor responses. Subjects in the minimally conscious state (MCS) show fluctuations in awareness and clear, but inconsistent, minimal behavioral signs of conscious awareness [48]. In contrast, subjects in the vegetative state (VS) are awake but not aware, and do not show behavioral response to environmental stimuli indicating lack of conscious processing [52]. Subjects in the locked-in syndrome (LIS) show very limited signs of awareness due to profound sensory and motor deficits but have preserved self-awareness and normal or near-normal cognitive capacities [53]. Impairments of the sensory and motor systems in these patient populations render conventional bedside diagnosis inadequate and it is thought to have contributed to high rates of misdiagnosis of LIS, MCS, and VS patients [54, 55], as well as underestimation of cognitive capacity. It has become evident that assessment of these patients' cognitive abilities requires diagnostic tools that do not rely exclusively on overt motor responses. Studies using passive tasks [47, 55], imagery tasks [56, 57], and covert tasks [55–57] have suggested that a larger number of patients with DOC than previously suspected may retain awareness of self or environment undetected by conventional behavioral response methods. Thus, improved assessments of awareness and cognitive abilities that do not depend upon motor responses provide a significant advance for the assessment, treatment, and care of patients with DOC [58–60].

Internal picture naming was employed to assess conscious awareness in patients who fail to demonstrate clearly discernible evidence of awareness on bedside examination. Areas related to visual processing, language, and executive regions would be expected to be activated in a task-contingent manner and be most and least prominent in LIS and VS, respectively. In particular, this task is known to elicit activity in Broca's and Wernicke's Areas as well as medial frontal gyrus [13, 36].

The Coma Recovery Scale—Revised (CRS-R) [61] consists of 23 items organized in 6 subscales that address arousal, auditory, visual, motor, oromotor/verbal, and communication systems. Each subscale is organized hierarchaly, with lower items representing reflexive activity and higher items representing cognitive based behaviors.

Findings demonstrate variations in the underlying brain activity of the MCS patients for the command-following task that generally correspond to the CRS-R. The comparison of the naming network observed in healthy volunteers with DOC patients allows a functional differentiation of patients into three groups: (1) complete network: patients with activation of all brain areas observed in healthy volunteers; (2) partial network: patients with activation of some brain areas observed in healthy volunteers; and (3) absent network: patients with no activation of any brain areas observed in healthy volunteers. These neural categories are related to behavioral measures of status. As expected, patient with high CRS-R scores, including LIS1, EMCS1, MCS1, and MCS2, showed patterns of activity similar to those of control subjects elicited by Boston Naming task (complete network group). Conversely, patients with low CRS-R scores (i.e., VS1) show a very unresponsive brain as expected for this population (absent network group). Remarkably, patients in the partial network group are characterized by lack of activation in the medial frontal gyrus and lower CRS-R scores; i.e., MCS3 to MCS5 (Fig. 31.15).

To our knowledge, this is the first fMRI study to employ covert picture naming (internal speech) as a command following task in a series of patients with a range of disorders of consciousness and behavioral profiles [51]. Picture naming is considered a complex process that requires access to various representations of the object, including stored knowledge about the structural description (physical properties of the object), semantic (functional and associative properties), and phonological (name) representations of the object [61–64]. Boston Naming is thought to recruit stimulus driven (bottom-up) [65] and purpose-driven (top-down) [63] brain circuits: visual input processing areas, language areas, short-term memory regions, motor areas and executive regions. The initial step of the Boston Naming task is the processing of the visual stimuli. Therefore, the presence of visual cortex activation is taken as a prerequisite for successful performance of the task. All the patients reported showed early visual processing as it was used as an inclusion criteria. It has been shown that picture processing during naming tasks is not automated but rather an effortful process that involves controlled attentional resources [66]. Object recognition involves top-down modulation of early visual cortex by regions on the occipito-temporal associated with semantic knowledge of the object [66, 67]. Previous studies highlight the importance of traditional language areas in object naming. For example, the left BA22 of the superior temporal gyrus, also referred to as Wernicke's area, has been associated to semantic knowledge [68, 69] and to phonological code retrieval [70], the left ventral region of the inferior frontal gyrus, Broca's Area (BA 44/45), has been linked to phonological processing [71], phonetic sequencing [72], selection of competing semantic represen-

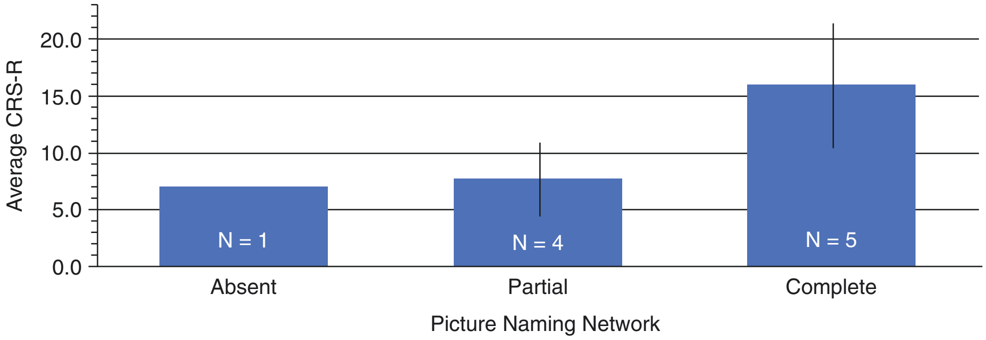


Fig. 31.15 Relationship between Coma Recovery Scale—Revised (CRS-R) scores and preservation of the picture naming network. Disorder of consciousness (DOC) patients are grouped according to preservation of the naming network previously observed in healthy volunteers: (1) complete network: patients with activation of all brain areas observed in healthy volunteers (LGTs, LGFi(v), LGFi(d) and PreSMA); (2) partial network: patients with activation of some brain areas observed in healthy volunteers; and (3) absent network: patients with no activation of any brain areas observed in healthy volunteers. The bars show the average CRS-R score for each group with the corresponding standard deviation

tations [73], and dorsal Broca's area (BA 44/6) associated to executive processes to select a lexical representation and processes related to motor programming and planning of articulation [73–77]. Overt picture naming has a very similar activity pattern relative to covert picture naming [73] although the degree of activation might be higher in inferior frontal regions during overt naming in comparison to covert naming [78]. Although emphasis has been commonly placed in the linguistic aspects of picture naming, it was used as a command following task in this application and expected to engage regions associated in volitional control. Previous imaging reports have associated midline regions (presupplementary motor area [preSMA]) with volitional aspects of cognition and actions [79]. Boly et al. [80] found pre-SMA activation on all subjects performing four different imagery tasks in comparison to rest and interpreted the activation as reflecting cognitive control or the intention to perform the task. A recent study also found medial frontal cortex activation in healthy controls and one MCS patient when subjects counted a target word in comparison to listening to the words [59].

Activity in the superior temporal gyrus BA 22 (including Wernicke's area), inferior frontal gyrus BA44/45 (including Broca's area), and medial frontal gyrus (pre-SMA, BA 6/8) is typically reported during covert picture naming [13, 36]. Similar patterns of activity have also been found to include parietal regions [62, 63, 76]. Observation of this expected functional specificity for the picture naming task can thus be considered as evidence for awareness in these patients, suggesting that conscious, volitional execution of the task may depend on the engagement of visual, temporal, and inferior frontal regions engaged by visual stimuli and linked to activity in the frontal regions to execute cognitive control of the task. This interpretation is in accord with the view that consciousness is characterized by simultaneous activation of multiple brain areas to form a single long-distance network [81]. The comparison of patients' naming networks with that of healthy volunteers allows a classification of patients into three categories: patients that retain all components of the reference network (complete network), patients that engage only some of those brain regions (partial network), and patients that show no activation of any of those components (absent network). For the MCS cohort, activation of neural networks associated with language is counter posed against the lack of consistent verbal expression in these patients. The finding of unresponsiveness at the behavioral level accompanied by extensive preservation of cognitive networks raises challenges to our ability to identify VS by behavioral assessment alone in some patients, as recently shown by Owen et al. [49] using motor imagery.

The functional capacity of these systems can be influenced by anxiety and fluctuations in arousal and awareness. In addition to these caveats, fMRI data acquisition allows for very limited motion; and interpretation of imaging data can be challenged in the presence of structural abnormalities or temporal mismatch between presentation of the target stimulus and the patient's response.

Summarizing, this work provides a framework to identify patients in various levels or states of consciousness that retain neural circuits capable of supporting high-level volitional processes not discerned through conventional behavioral assessment alone. Information provided by fMRI has not yet been sufficiently vetted to justify changing the behaviorally based diagnosis in most cases. However, these findings indicate a clear need to consider the capacity for covert cognitive processing in addition to the overt behaviors when conducting diagnostic assessment, particularly in patients with ambiguous findings or significant sensory and motor impairments. Determining where patients lie on the spectrum of consciousness is key to optimal clinical management, application of available therapies, and maximization of quality of life for this population. These findings indicate that neuroimaging studies provide novel information that may aid in differential diagnosis, identifying patients in DOC with substantially preserved neural circuits that may serve as a marker for retention of high-level cognitive capacities not apparent on bedside examination.

Determination of the Anatomy and Topography of Cortical Areas Specialized for Cognitive Tasks

In contrast to language, sensory/motor, and visual systems, our current understanding of the mechanisms of higher functions is not so closely linked to a specified neurophysiological substrate (Box 31.2 [82]). This is due, in part, to the fact that many aspects of cognition are dynamic processes that involve many working parts, and often cannot be studied in animals. The emergence of neuroimaging provides a new opportunity to test hypotheses and map the underlying mechanisms of cognition in healthy individuals without reliance on lesions or disease processes. However, these investigations remain in their early stages. Determinations of the anatomy and topography of cortical areas specialized for cognitive tasks can contribute to models that integrate multiple functionally specialized areas. These objectives will be discussed later in the context of specific functions, including attention, working memory, executive processes, and consciousness, with an emphasis on the unifying notion that the neurobiological pathways are multiregional with complex covariations. Clinical applications for these maps are currently under development in specialties such as psychiatry, neurology, rehabilitation, and even non-medical specialties such as neuroeconomics and neurolaw.

Box 31.2

> While there has been general agreement that operations performed by the sensory and motor systems are localized, there has been much more dispute about higher-level cognitive processes. It is still undetermined whether higher-level processes have defined locations, and if so, where these locations would be. (Posner and Raichle, *Images of Mind*, 1994, p. 16 [82])

As previously discussed, the functional neuroanatomy of cognitive processes is revealed by comparing the BOLD response elicited by various experimental and control tasks and is typically characterized by a voxel-by-voxel statistical comparison of the signal amplitude during the activity epoch, with the average signal amplitude during a baseline resting or control epoch. The basic assumption is that neuronal activity is increased in a functionally specialized area during the execution of a task that employs that specialization. Locations of active areas, cluster sizes, and dynamic properties of the signal such as covariation can be compared across cognitive conditions. Tasks are designed to either include or exclude the cognitive component of interest and the signals elicited from these tasks are compared.

Conservation of Effects Versus Individual Differences: Generalizing the Results

Investigations of the neural basis for cognitive processes are aimed toward findings generalizable to the population at large. Neuroimaging studies on single subjects can be assumed to include effects that are conserved across all subjects (generalizable), as well as effects that are specific to that individual subject [83]. Results that are present in all or most cases given a sufficiently large sample size can be assumed to reflect a fundamental specialization characteristic of the population, whereas intermittently present results can be assumed to represent other less-conserved (individual) processes. A theoretical basis for inferences to a population based on functional imaging data is currently under development. Based on models using a two-tailed test of significance at a criterion level of $p \leq 0.05$ and a power of 80%, Desmond and Glover [84] suggested that analyses of covariation and connectivity may require sample sizes up to 20 or more subjects.

Inferences to a population based on imaging data generally require registration of individual brains and a standard stereotactic coordinate system. Although registration procedures are an area of active development, the conventional method (originally developed for PET studies) employs the Co-Planar Stereotaxic Atlas of the Human Brain [85]. Acquired brain images are registered to that atlas by reference to the anterior–posterior commissure line and active areas are labeled accordingly and assigned an address in x, y, z stereotactic coordinates. One popular tool for accomplishing this objective is available in Statistical Parametric Mapping (SPM) [86], a software package developed for processing neuroimaging data. Other representations of brain structure and functions include flat maps and inflated brains.

Method of Cognitive Subtraction

The cognitive subtraction paradigm requires two tasks: an experimental task that engages the cognitive component of interest, and a baseline or control task that engages all of the processes included in the cognitive task except for the cognitive component of interest. The neural correlates of the cognitive task of interest are presumed to be revealed by a subtraction of the baseline activity from the activity observed during the experimental task. Examples of the cognitive subtraction design are found in the early PET studies, where, for example, the effect of viewing a fixation dot was subtracted from the effect of viewing a flashing checkerboard to reveal the neural effect of the checkerboard alone. Although the subtractive approach was employed successfully in those early studies, it is limited by the difficulty of selecting tasks that differ only with respect to the cognition of interest. If differences between the experimental task and the comparison baseline task are due to a combinatorial effect not present with either task alone, then the conclusion could be misguided. These assumptions often are referred to as the assumptions of linear additivity or pure insertion, and depend upon the partitioning of complex cognitive tasks into independent subcomponent processes.

Method of Cognitive Conjunction

In contrast to the identification of differences between the elicited activity of two cognitive tasks by subtraction, a conjunction analysis reveals the activity common to multiple tasks. For example, in an investigation to identify the neural substrate specialized for object naming, the same task can be performed using multiple sensory systems—that is, objects that are seen, heard, and felt are named during an imaging

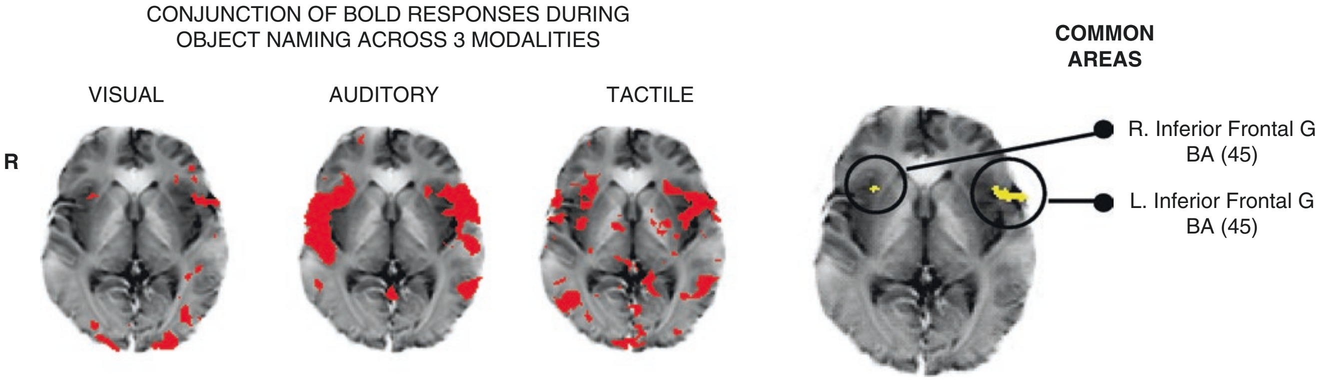


Fig. 31.16 Conjunction of BOLD responses during object naming across three sensory modalities. Voxels active during visual stimulation (left), auditory stimulation (middle), and tactile stimulation (right) are indicated in orange for 1 slice of brain. The conjunction image (yellow) illustrates the supramodal activity common to all three modalities of stimulation following a Boolean AND operation. This activity occurs in left and right inferior frontal gyrus (BA 45) and is taken to represent the aspects of object naming not primarily associated with a specific sensory modality for this single subject. (Reprinted with permission from Hirsch J, Rodriguez-Moreno D, Kim KHS. Interconnected large-scale systems for three fundamental cognitive tasks revealed by functional MRI. J Cogn Neurosci. 2001;13(3):1–16. https://doi.org/10.1162/08989290151137421 [36])

study. The conjunction of neural activity present in all three naming tasks is assumed to represent the neural activity associated with naming alone, and the processes associated with the sensory-related activity are assumed to be excluded by virtue of the fact that such activity is not common to all tasks (as illustrated in Fig. 31.16 [36]).

Some of the same assumptions for the subtractive approach previously described apply. First, it is assumed that the cognitive processes engaged by each task are performed similarly across the sensory modalities. However, there is considerable evidence for intermingling of modality-specific and domain-general mechanisms in some tasks.

For example, mental imagery tasks may draw upon modality-specific subsystems, which would not be observed by this method. Thus, the conjunctive method applied to cross-modal studies identifies a subset of domain-general processes, but may fail to recognize all components critical to task performance.

On the other hand, the conjunctive approach, applied to within-modal studies, can serve to enhance confidence in a result by isolating activity that is repeated on multiple runs of the same task. This strategy is based on the assumption that signals originating from noise sources are distinguished from signals originating from real events by the probability of a repeat occurrence at the same location. Voxels that are reliably activated on multiple separate occasions result in a low false-positive rate that can be empirically determined based on images acquired either during resting states or on images acquired on a spherical container of copper sulfate solution that simulates brain (phantom). For this reason, conjunctions often are employed in clinical and neurosurgical applications to enhance confidence in a result by isolating the activity that is elicited on multiple runs of the same task [13, 42, 43]. However, because repeated stimuli do not usually elicit as robust a response as novel stimuli, all repetitions of a task are optimally performed using equal but different stimuli. Thus, in the case of an object-naming task, all objects would be novel but equated for variables such as familiarity and difficulty, etc., during the multiple runs in order to be optimized for the within-modal conjunction approach.

Integration of Functionally Specialized Areas Associated with Cognitive Tasks: The Network Approach

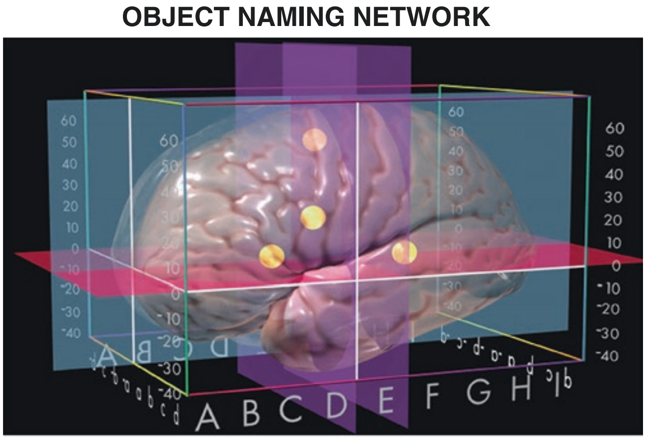
Although functional differentiation of single brain areas is a well-established principle of cortical organization, recent approaches to human cognition have focused on the integration of groups of specialized areas into long-range units that may collectively serve as the comprehensive neural substrate for specific cognitive tasks (Box 31.3 [87]). An early empirical foundation for this view is found in the work of Mishkin and Ungerleider [88], who described ventral and dorsal pathway segmentation during visual tasks that required either object identification or object localization, respectively. More recently, direct interactions between brain regions that participate in specific functions have been proposed as evidence for this systems model; for example, covariations between BOLD responses in separate cortical areas during complex attention tasks have been examined using a statistical approach called structural equation modeling, which can determine whether the covariances between areas are due to direct or indirect interactions [89]. This analysis technique identifies the groups of areas associated with a task, and also characterizes changes in regional activity and interactions between regions over time. Other approaches to identify function-specific long-range systems associated with language and attention processes are illustrated later in this chapter.

Box 31.3

A central feature in the organization of the large-scale network is the absence of one-to-one correspondences among anatomical sites, neural computations and complex behaviors. According to this organization, an individual cognitive or behavioral domain is subserved by several interconnected macroscopic sites, each of which subserves multiple computations, leading to a distributed and interactive but also coarse and degenerate (one-to-many and many-to-one) mapping of anatomical substrate onto neural computation and computation onto behavior. (M.—Marsel Mesulam, 1998 [87])

Functional Neuroanatomy of Language Processes: A Large-Scale Network

Models of the neural correlates for elementary language processes often include left hemisphere regions involved in a variety of language functions, including Broca's and Wernicke's Areas, and are generally consistent with a network model. To demonstrate this network, an object naming task using auditory, visual, and tactile stimuli can be employed. A cross-modality conjunction technique (above) isolates effects not dependent upon sensory processes. Results are consistent with the view that the task of naming objects elicits activity from a set of areas within a neurocognitive system specialized for language-related functions (Fig. 31.17 [36]). The colored circles on the glass brain represent average locations of activity centroids on the standard atlas brain (*x*, *y*, *z* coordinates) as indicated on the table in Fig. 31.17 [36]. There are five regions in this neurocognitive system (all located within the left hemisphere), including putative Broca's Area (inferior frontal gyrus, BA 44 and 45), putative Wernicke's Area (superior temporal gyrus, BA 22), and medial frontal gyrus (BA 6). Thus, these results are consistent with the view that the functional specialization for this elementary language task involves a system of language-related areas rather than a single area.



Anatomical Region	Area	Center of mass x	y	z
Medial Frontal Gyrus (GFd)	6	9	–6	53
Superior Temporal Gyrus (GTs)	22	57	–26	9
Inferior Frontal Gyrus (Gfi)	44	49	10	25
Inferior Frontal Gyrus (Gfi)	45	40	25	8

Fig. 31.17 A fixed large-scale network for object naming. The network of areas that subserve object naming as determined by conjunction across three sensory modalities consists of medial frontal gyrus (GFd, BA 6), superior temporal gyrus (GTs, BA 22; putative Wernicke's Area), and inferior frontal gyrus (Gfi, BA 44,45; putative Broca's Area) in the left hemisphere. These areas are portrayed as colored circles in a three-dimensional glass brain based upon the Talairach and Tournoux Human Brain Atlas45 and stereotactic coordinate system. The table appearing below contains the average group coordinates (*x*, *y*, *z*) of the included regions. (Reprinted with permission from Hirsch J, Rodriguez-Moreno D, Kim KHS. Interconnected large-scale systems for three fundamental cognitive tasks revealed by functional MRI. J Cogn Neurosci. 2001;13(3):1–16. https://doi.org/10.1162/08989290151137421 [36])

Functional Neuroanatomy of Attention Processes: A Large-Scale Network

Like language, the ability to direct attention is involved in a range of cognitive tasks. Functional imaging studies by Mesulam [87] and others suggest that spatial attention is mediated by a large-scale distributed network of interconnected cortical areas within the posterior parietal cortex, the region of frontal eye fields, and the cingulate cortex. Kim and colleagues [90] used a conjunction analysis to compare activity associated with two different types of visuospatial attention shifts: one based on spatial priming and the other based on cues that directed spatial expectancy to test the hypothesis of a fixed area network for both tasks. The activation foci observed for the two tasks were nearly overlapping, indicating that both were subserved by a common network of cortical and subcortical areas. The main findings of this study were consistent with a model of spatial attention that is associated with a fixed large-scale distributed network specialized to coordinate multiple aspects of attention. Alternative hypotheses that predict that task variations are associated with an increase in the number of involved areas can be rejected. However, an observed right-ward bias for the spatial priming task suggested that activation within the system showed variations specific to the attributes of the attentional task (Fig. 31.18) [90].

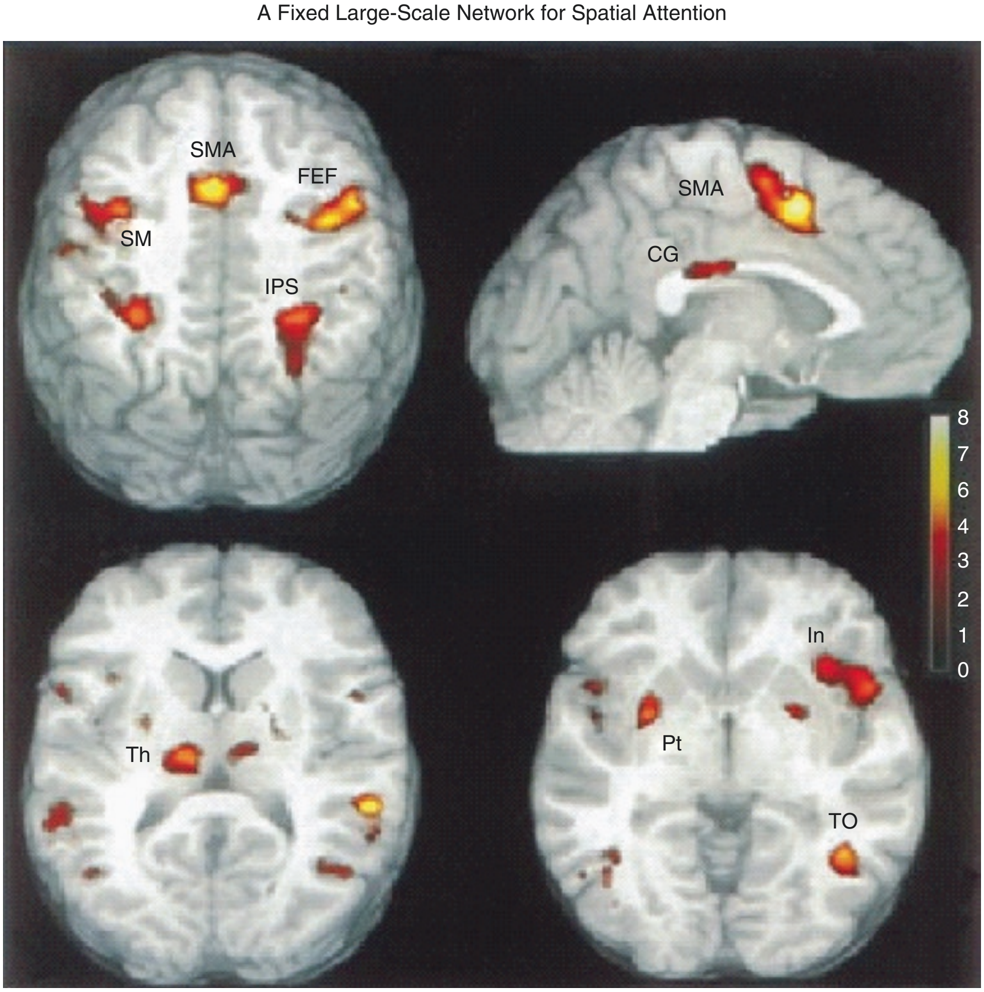


Fig. 31.18 A fixed large-scale network for spatial attention. The network of areas that subserve visuospatial attention shifts consists of supplementary motor area—anterior cingulate cortex (SMA, BA 6), frontal eye fields (FEF, BA 6), and the banks of the intraparietal sulcus (IPS, BA 7,40). This network was determined by a conjunction analysis of activation related to visuospatial attention tasks based on two different types of information: spatial priming and spatial expectancy. Although the same areas are involved in both tasks, a rightward bias in the intraparietal sulcus (IPS) was observed for the spatial priming task and suggests that, within this network, task-related variations are present. (Neurologic coordinates). (Reprinted with permission from Kim Y-H, Gitelman DR, Nobre AC, Parrish TB, LaBar KS, Mesulam M-M. The large-scale neural network for spatial attention displays multifunctional overlap but differential asymmetry. NeuroImage. 1999;9:269–277 [90])

Tests of Cognitive Theory Based on Mapping of Neural Correlates

Advances in our understanding of the biological components of cognition are dependent upon the development of functional tasks that reveal specific cognitive processes; therefore, tasks are selected to target some aspect of cognition that can be varied so that the specific processing requirements are increased or decreased. Current neuroimaging investigations of language, attention, memory, executive processes, and even consciousness generate hypotheses based on theoretical frameworks and behavioral models and develop stimulation paradigms that cause the subject to engage the targeted functions. This section presents a selection of models, hypotheses, cognitive functions, and tasks that have been investigated by neuroimaging techniques.

Although more in-depth coverage of many of these topics is presented elsewhere, the objective here is to illustrate the advantages of neuroimaging for understanding the biological components of various cognitive processes rather than to provide a comprehensive survey of each of these cognitive processes.

Functional Neuroanatomy of Working Memory: A Fixed- or Variable-Area Network

Mechanisms for cognitive functions such as reasoning, problem solving, and language are critically dependent upon working memory processes that briefly maintain a limited amount of information in a mental scratch pad for ongoing processing. To test the hypothesis that a working memory system is subserved by a fixed number of brain areas, Smith and Jonides [91] employed a memory task (*N*-Back) that varied cognitive load. The logic of the experiment follows: If the hypothesis of a fixed number of regions was supported, then increasing the difficulty of the task, and thereby the cognitive load, would increase the amount of activity in each of the component areas. However, if the hypothesis of a variable area network was supported, then increasing the difficulty of the task would activate additional areas.

The N-Back Task and a Test of a Cognitive Theory

The *N*-Back task, illustrated in Fig. 31.19, was developed as a cognitive tool to vary memory task difficulty (load) [91]. The subject views a series of letters separated by fixation points. In the 0-Back condition, the subject responds whenever one of the presented letters matches a standard presented at the beginning of the run. In the 1-Back condition, the subject responds when there is a match to the preceding letter. In the 2-Back condition, the subject responds when there is a match to the letter 2-Back in the series, and similarly for the 3-Back condition.

Results of this study showed a clear increase in the volume of activity, with the increase in difficulty (load) of the task (Fig. 31.20). However, the specific regions involved did not vary with increases in load supporting the fixed-number-of-areas hypothesis for a working memory system [91].

Functional Neuroanatomy of Selective Attention: A Neurological Model of Cognitive Interference

The ability to filter task-related stimuli to guide responses is referred to as selective attention. An experimental task that requires the subject to attend to certain stimulus characteris-

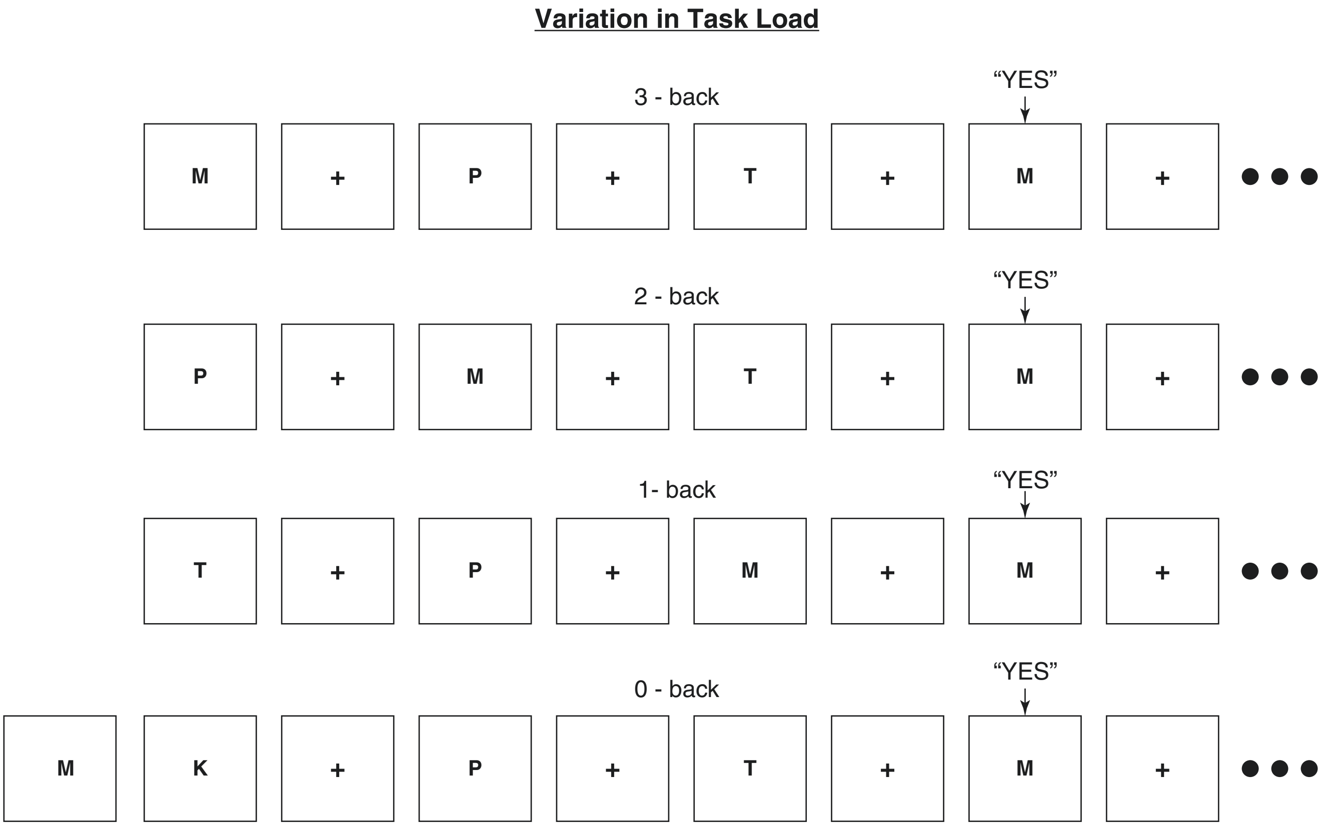


Fig. 31.19 Variation in working memory load based on the *N*-Back task. The *N*-Back task engages working memory by requiring the subject to remember a previous event and respond if a present stimulus (target) is identical to that previously presented stimulus. Task load can be increased by increasing the distance between the target and its match; e.g., 0-, 1-, 2-, 3-Back. (Reprinted with permission from Smith EE, Jonides J. Working memory: A view from neuroimaging. Cogn Psychol. 1997;33;5–42 [91])

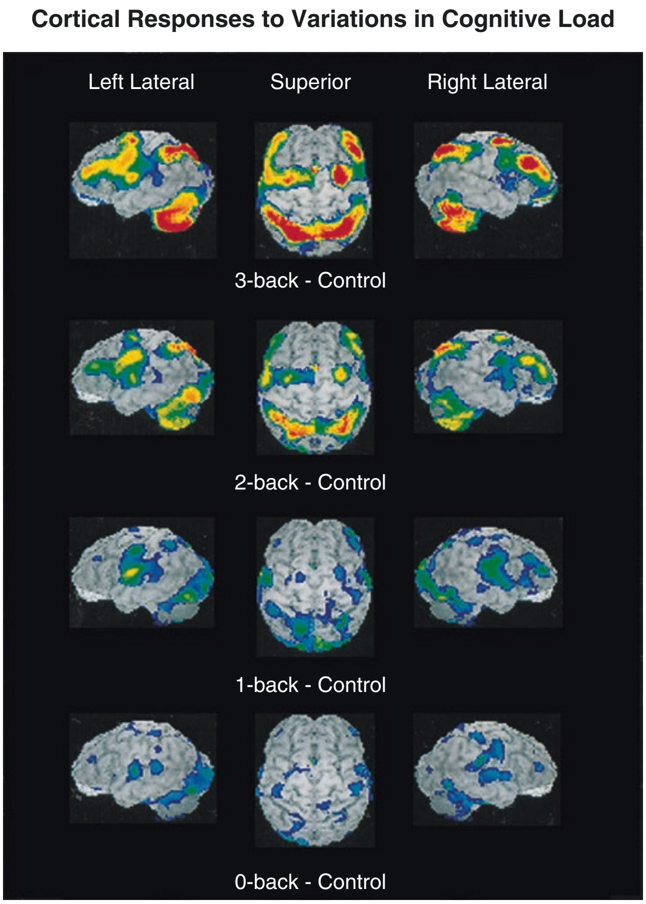


Fig. 31.20 Cortical responses during the *N*-Back task. Left and right lateral, as well as a superior, views of the average PET images are shown. All images are difference images that reflect the subtraction of a control condition in which subjects responded to every stimulus. The different colors reflect the significance of the activation, with red areas being most significant. Robust responses for the 3-Back condition relative to 0-, 1-, and 2-Back conditions are taken as evidence of increased neural activity associated with increased memory load. (Reprinted with permission from Smith EE, Jonides J. Working memory: A view from neuroimaging. Cogn Psychol. 1997;33;5–42 [91])

tics while ignoring others that elicit a competing response engages a system of selective attention. The Stroop task is a classical cognitive task first developed for use in behavioral studies of cognitive interference and is an ideal task for functional imaging studies that seek to identify the neural substrate associated with selective attention mechanisms.

The Stroop Task

In the classical Stroop task, a subject views a series of words in different colored inks. Each word is the name of a color. The subject is instructed to produce the color of the ink. In

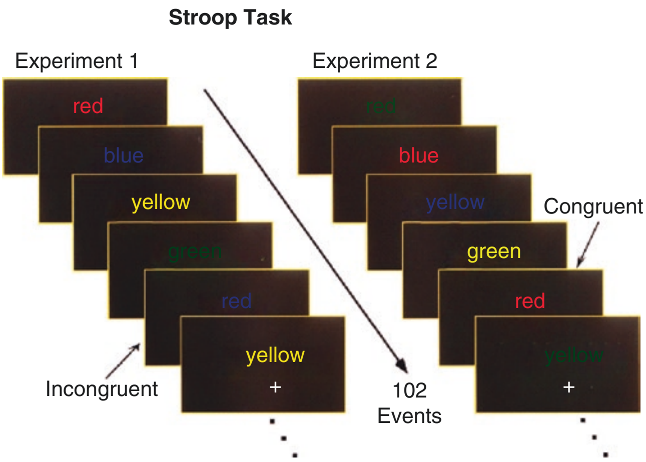


Fig. 31.21 The classical Stroop color word interference task. In congruent cases, the color of the ink matches the color of the word. In incongruent cases, the color of the ink is different from the color of the word. The words are presented sequentially to subjects who respond by indicating the color of the ink for each word. (Reprinted with permission from Leung H-C, Skudlarski P, Gatenby JC, Peterson BS, Gore JC. An event-related functional MRI study of the Stroop color word interference task. Cereb Cortex. 2000;10:552–560. Oxford University Press [92])

the incongruent case, the word and the ink color of the written word are different, resulting in longer reaction times than in the congruent case where the word and ink color match. For example, if the ink color was blue but the word was red (incongruent), the reaction time to report "blue" (the ink color) would be longer than when the word and the ink color were both blue (congruent) (Fig. 31.21) [92].

Cognitive models that account for results obtained by the Stroop task propose that subjects must inhibit the automatic reading response and selectively attend to the color of the letters in order to successfully perform the color-naming task. A neuroimaging study designed to probe the neural basis for this type of cognitive interference, that is, the mechanisms of selective attention [92], compared BOLD responses to congruent and incongruent conditions in an event-related neuroimaging study (see following section on event-related paradigms). The results are shown in Fig. 31.22 for incongruent and congruent conditions, respectively [92]. The incongruent condition is associated with robust distributed responses as compared to the congruent condition, suggesting that a distributed large-scale neural network is employed during selective attention. The results also suggest a possible correspondence between the selective attention mechanisms engaged in this study and visuospatial attention mechanisms.

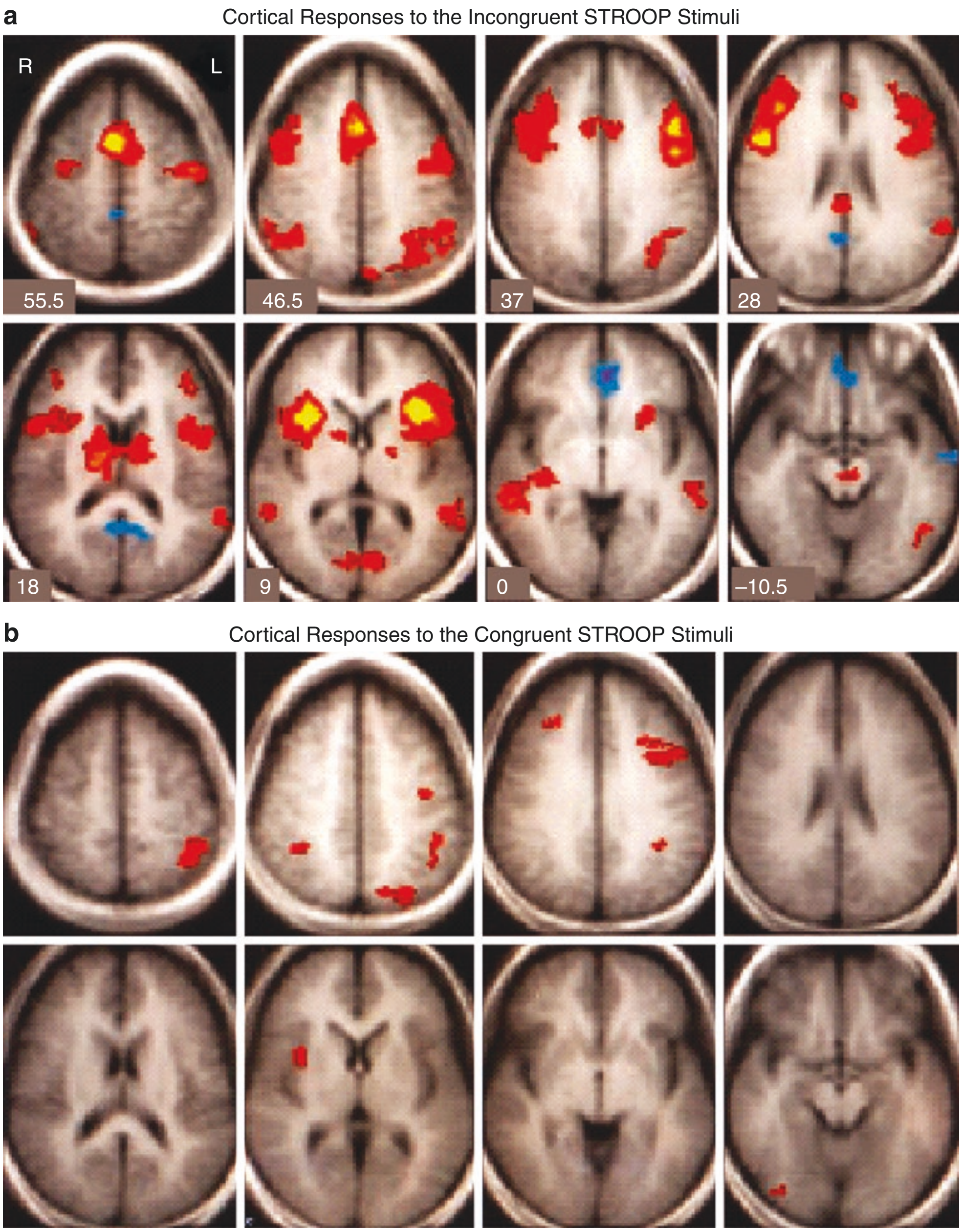


Fig. 31.22 Activation related to the classical Stroop task versus the inverse Stroop task. Images represent composite maps of 13 subjects performing the Stroop task. In Experiment 1, the classical Stroop task was employed, that is, incongruent words appear infrequently whereas congruent words appear frequently (**a**). In Experiment 2 (**b**), an inverse Stroop task was employed; that is, congruent words are infrequent events and incongruent words appear frequently. The robust response for the incongruent condition (**a**) relative to the congruent condition (**b**) is taken as evidence of a neural basis for response inhibition. (Reprinted with permission from Leung H-C, Skudlarski P, Gatenby JC, Peterson BS, Gore JC. An event-related functional MRI study of the Stroop color word interference task. Cereb Cortex 2000;10:552–560. Oxford University Press [92])

Functional Neuroanatomy of Executive Processes: Separate or Combined Systems

Current models of cognition often include undefined mechanisms (frequently referred to as a black box) to account for executive processes such as the allocation of attentional resources among competing tasks. Functional neuroimaging techniques and experimental paradigms, such as the dual performance task and the Go/No-Go task, have been developed to observe the neural correlates of these executive functions and attempt to define the black box in neurophysiological terms.

D'Esposito and colleagues [93] introduced an fMRI task paradigm that required subjects to perform two tasks simultaneously, referred to as a dual performance task. Comparison of the BOLD responses elicited during each task alone and both tasks together enabled tests of hypotheses about the neural system involved in the execution of competing tasks. Specifically, the hypothesis of a modular executive system predicts the recruitment of additional regions during the dual task condition, whereas the fixed-areas hypothesis predicts an increase in volume of the areas activated by a single task. Adcock and colleagues [94] employed this paradigm with paired combinations of spatial rotation tasks (visual), semantic categorization tasks (auditory), and facial identification tasks (visual). Results indicated that the activated areas varied with the sensory modality of component tasks as expected based on these domain-specific functional specializations. However, all of the areas activated during the dual task performance were also activated during the component tasks; that is, there was no evidence for a separate executive system. Increases in activity within a given area during the dual task are related to the additional load of the second task. These results can be interpreted as generally consistent with the hypothesis that these executive processes may be implemented by interactions between anatomically and functionally distinct systems engaged in the performances of component tasks rather than by a specific area or areas dedicated to a modular and separable executive system.

The Go/No-Go Task

Another classical executive function is the ability to inhibit a prepotent or habitual response that has been studied psychophysically using a Go/No-Go task paradigm. Neuroimaging investigations of the neural correlates of response inhibition have employed a version of the task to investigate the neural correlates of response inhibition in children and adults [95]. The hypothesis was that the ability to successfully inhibit a response varies with maturity. This variation could be neurally represented as either the recruitment of different areas in children versus adults or variations in the volumes within a fixed set of areas. During the Go/No-Go task, the subject views a series of letters presented sequentially and presses a button on each successive presentation except when the letter is an *X*. On the *X* trials, the subject must inhibit the response.

The BOLD responses for children (ages 7–12) and adults were compared within five selected areas of the prefrontal cortex using an event-related paradigm and an analysis of variance (ANOVA) where subject age and the task conditions (Go versus No-Go) were taken as factors. The areas demonstrating significant activity related to the No-Go task include anterior cingulate and four frontal gyri, including inferior, middle, orbital, and superior. The areas involved in the response inhibition function did not vary between adults and children. However, during No-Go trials, the amount of activity was higher in children, particularly in the dorsal and lateral prefrontal sites.

This observation is consistent with the hypothesis of a distributed system for response inhibition and further suggests that the elements include anterior cingulate and four frontal gyri, including inferior, middle, orbital, and superior.

Integration of Temporal and Spatial Information to Map Executive Processes

A common theme in the aforementioned neuroimaging studies of cognitive functions is the identification of the underlying cortical networks associated with each function and the question of fixed versus variable areas for related functions. In the case of the language, attention, memory, and cognitive control systems illustrated previously, the results suggest that a fixed number of areas (rather than the recruitment of new areas) are modulated with increased load. This is an active area of research, and new evidence from studies using techniques such as electrophysiological recordings, developing connectivity analyses, and tractography to probe within-system effects may be required to elucidate the modulation of processes both within and across these systems.

Integration of ERP and fMRI

New investigations that focus on within-system processes and the modulation of a specialized system consisting of a fixed set of distributed areas require probes of the computations performed within neural systems. A new class of multi-technique experiments are currently being developed that elucidate the spatial localization of active regions (fMRI), as well as the temporal co-variations between these cortical or subcortical regions, as reflected in event-related potentials (ERP). These techniques may be employed either simultaneously or sequentially and require an adaptation of the blocked fMRI experiments (event-related fMRI) and a task specialized for both fMRI and electrophysiological approaches.

Event-Related fMRI

As in conventional event-related electrophysiology, individual trials (events) are presented separately (rather than in a continuous block), and the signal is selectively averaged across like trials. This acquisition scheme is illustrated in Fig. 31.23 [96], where both block and event-related schemes are shown [97]. Event-related fMRI offers an additional class of task designs that expand and elaborate investigations of cognitive processes. Given that the BOLD response tracks neuronal activity with hemodynamic delays on the order of about 2–4 s, it is possible to reliably identify the activity associated with each successive trial.

There are several advantages to event-related fMRI:

1. By detecting signals that are linked to individual trial events rather than to blocks, the observations can paral-

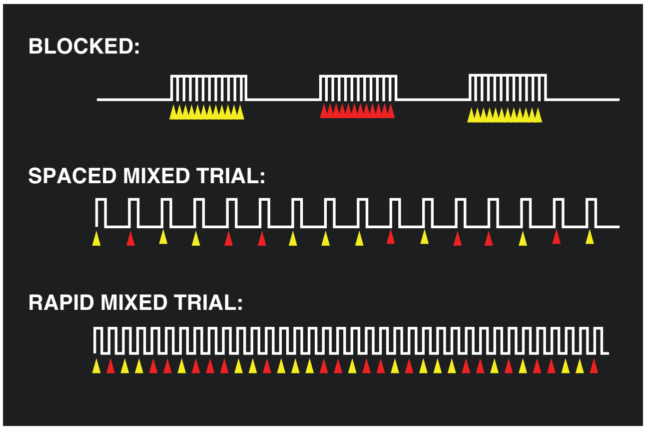


Fig. 31.23 Blocked- versus event-related fMRI paradigms. Schematic diagrams illustrate the difference between two forms of imaging paradigms: blocked trials and event-related trials. Each schematic shows two trial types indicated by either yellow or red arrows. In blocked trial paradigms (labeled Blocked), the trial types are clustered together in succession so that the same trial type or condition occurs for an extended period of time. Event-related trials, by contrast, intermix different trial types either by spacing them widely apart to allow the hemodynamic response from one trial to decay before the next trial occurs (labeled Spaced Mixed Trial), or by presenting them rapidly (labeled Rapid Mixed Trial). (Reprinted with permission from Buckner RL. Event-related fMRI and the hemodynamic response. Hum Brain Mapp. 1998;6:373–377 [96])

lel other behavioral and evoked response potential studies that are also linked to individual events. Thus, the added value of precise temporal data from other integrated methods in combination with the high-resolution data of fMRI extends the range of questions that can be addressed.

2. An event-related approach is particularly useful when subject response is a factor, as in the case where it is necessary to separate trials in which there was a correct response from trials in which the response was not correct, or trials where the stimulus was novel from trials where the stimulus was repeated, or to isolate the acquisitions associated with bistable perspectives of ambiguous figures as reported by the subject during the experiment. Thus, the event-related approach allows trials to be categorized post hoc on the basis of the subject's behavior.
3. Some events cannot be presented in a blocked design, as in cases involving a surprise element or the occurrence of an oddball stimulus that is distinguished from the expected context. In those cases, an event-related approach is required.

The Oddball Task

Cortical mechanisms specialized for novelty oddball detection compare incoming information with relevant memories to register a novel event. Opitz and colleagues [98] reported the spatial and temporal properties of cortical mechanisms involved in the detection of novel tones by combining evoked response potential and fMRI measures. The evoked response potential methods lack precision with respect to the spatial source of the signal as detected by scalp electrodes because these sources must be inferred from two-dimensional scalp topography and using dipole fitting algorithms. Temporal resolution of signals, however, is within milliseconds. By combining evoked response potential and fMRI, both temporal and spatial properties of the cortical responses corresponding to novelty can be investigated. Although registration of these separate data domains remains a challenge, results of the Opitz study relate specific evoked response potential responses to bilateral superior temporal gyrus and right prefrontal cortex, suggesting coordinated activity between areas previously associated with novelty using event-related fMRI techniques.

A similar evoked response potential and fMRI experiment by Kruggel and colleagues [99] employed a visual oddball task using illusory contours that deviated from the prevailing visual stimuli (no illusory contours). Results replicated previous fMRI findings, indicating the activation of extrastriate visual cortex in the appreciation of the illusory contours (perceived between the corner elements of Kanizsa squares) and the lack of this activation during viewing of stimuli in which the corner elements were rotated out of alignment. Additionally, the evoked response potential results confirmed a sequential activation of striate to extra striate visual cortex consistent with hierarchal models of visual processing. Thus, integration of approaches that optimize both spatial and temporal information relating to neural mechanisms and both perceptual and cognitive processes offers new directions and precision to probe the neural basis of mental events.

The Functional Neuroanatomy of Very High Level Cognitive Processes

Guided by *The Astonishing Hypothesis* of Francis Crick [1], it is assumed that the biological components of even very high-level cognitive processes, such as decision-making, moral judgments, altruism, and fairness are observable. As in the neuroimaging of related cognitive processes, including language, attention, working memory, and executive control, an investigation of consciousness is also rigorously investigated.

Dehaene and Naccache [81] have developed one theoretical framework for the investigation of consciousness that consists of a global neuronal work space. This framework postulates that, "at any given time, many modular cerebral networks are active in parallel and process information in an unconscious manner." As information becomes conscious, however, the neural population that represents the information is mobilized by top-down attentional amplification into a state of coherent activity that involves many neurons distributed throughout the brain. The long-distance connectivity of these workspace neurons can, when they are active for a minimal duration, make the information available to a variety of processes, including perceptual categorization, long-term memorization, evaluation, and intentional action. According to this theoretical framework, the global availability of information throughout the workspace is what is subjectively experienced as a conscious state.

A major obstacle to applying neuroimaging techniques to the investigation of consciousness is the inability to establish a task that varies the state of consciousness; that is, consciousness is not started and stopped in synchrony with a particular task, as is assumed in many cognitive tasks (Box 31.4 [100]). The global workspace hypothesis suggests a distributed neural system or workspace with long-distance connectivity that interconnects multiple specialized brain areas in a coordinated, although variable, manner [101]. This framework challenges current neuroimaging paradigms based on conventional experimental paradigms and views of functional specialization.

Box 31.4

> The fact that consciousness is a private, first-person phenomenon makes it more difficult to study than other cognitive phenomena that, although being equally private, also have characteristic behavioral signatures. Nonetheless, by combining cognitive and neurobiological methods, it is possible to approach consciousness, to describe its cognitive nature, its behavioral correlates, its possible evolutionary origin and functional role; last but not least, it is possible to investigate its neuroanatomical and neurophysiological underpinnings. (Antonio R. Damasio, 1998 [100])

One approach to circumvent this obstacle is based on the specific hypothesis that conscious humans are engaged continuously during resting states in "adaptive cognitive processes that involve semantic knowledge retrieval, representation in awareness and directed manipulation of represented knowledge for organization, problem solving and planning" [33]. Thus, comparison of resting activation and task activations during a neuroimaging study might reveal neural processes associated with consciousness. Binder and colleagues [102] used fMRI to measure brain activity during rest and during several contrasting activation paradigms, including a perceptual task (tone-monitoring) designed to interfere with ongoing thought processes and a semantic retrieval task (noun categorization) designed to engage ongoing thought processes similar to those hypothesized to occur during rest. Higher signal values were observed during the resting state than during the tone-monitoring task in a network of left hemisphere cortical regions. These areas were equally active during the semantic task. This finding is consistent with the hypothesis that perceptual tasks interrupt specific ongoing processes during rest that are associated with many of the same brain areas engaged during semantic retrieval. Thus, neuroimaging observations suggest that ongoing processing during a conscious resting state involves an underlying neural substrate similar to that employed in cognitive tasks such as semantic processing.

Another paradigm that employs masked (too brief for cognitive awareness) presentations of emotional facial expressions has been found to modulate BOLD and PET-related hemodynamic responses originating in the amygdale [103, 104]. In these studies, the amygdala was involved in (1) nonconscious responses that reflected the emotional valence of stimuli, and (2) was spatially differentiated depending upon level of awareness. Both findings confirm a neural substrate that is active and responsive without awareness.

Conclusion

The resting-state and masking paradigms, as well as other ongoing neuroimaging investigations of related aspects of consciousness, including perceptual awareness, awareness during varying levels of anesthesia, and awareness in patients in vegetative and minimally conscious states, can be expected to contribute to an emerging understanding of the neural basis of consciousness and the neural basis for related events that occur without awareness. Imaging paradigms that are established to investigate the neural underpinnings of cognition also provide foundations for emerging investigations of the neural underpinnings of consciousness and bring neural science closer to the goal of understanding the biological underpinnings of the mind (see Table 31.3 for summaries of key brain mapping studies).

Table 31.3 Summary of key brain mapping studies

Title	Authors	Year	fMRI paradigm(s)	Summary
The JFK Coma Recovery Scale—Revised: Measurement Characteristics and Diagnostic Utility [61]	Giacino JT, Kalmar K, Whyte J	2004	Behavioral measures.	Defines the current behavioral paradigms to distinguish between minimally conscious and vegetative states.
fMRI reveals large-scale network activation in minimally conscious patients [47]	Schiff ND, Rodriguez Moreno D, Kamal A, et al.	2005	Passive auditory stimulation using personalized narratives.	This is the first study to document that minimally conscious patients can engage neural circuitry associated with cognitive function.
Detecting awareness in the vegetative state [49]	Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD	2006	Passive stimulation and command following (motor and memory).	A case report that documents command following in a vegetative patient using fMRI documenting the need for neural imaging as an assessment tool for awareness.
Clinical functional magnetic resonance imaging [24]	Hart J, Rao SM, Nuwer M	2007	Block design for single patient assessments.	CPT codes for billing of MRI procedures that map active cortex engaged during specific tasks including language, sensory, motor, and perceptual functions.
A network approach to assessing cognition in disorders of consciousness [51]	Rodriguez Moreno D, Schiff ND, Giacino J, Kalmar K, Hirsch J	2010	Passive stimulation and command following (language).	Patients who are unresponsive may be able to communicate awareness, or emerging signs of awareness, using fMRI. The extent to which a canonical language network is engaged can be related to the bedside coma recovery scale.

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