Functional MR Imaging of Language Processing: An Overview of Easy-to-Implement Paradigms for Patient Care and Clinical Research[1]

Marion Smits, MD • Evy Visch-Brink, PhD • Caroline K. Schraa-Tam, MSc, MEng • Peter J. Koudstaal, MD, PhD • Aad van der Lugt, MD, PhD

Functional magnetic resonance (MR) imaging is one of the most commonly used functional neuroimaging techniques for studying the cerebral representation of language processing and is increasingly being used for both patient care and clinical research. In patient care, functional MR imaging is primarily used in the preoperative evaluation of *(a)* the relationship of a lesion to critical language areas and *(b)* hemispheric dominance. In clinical research, this modality is used to study language disorders due to neurologic disease and is generally aimed at language function recovery. A variety of language paradigms (verbal fluency, passive listening, comprehension) have been developed for the study of language processing and its separate components. All of the tasks are easy to implement, analyze, and perform. Silent gap acquisition is preferable for the imaging of specific language processing components because auditory stimuli are not degraded by imager noise. On the other hand, continuous acquisition allows more data to be acquired in less time, thereby increasing statistical power and decreasing the effects of motion artifacts. Although functional MR imaging cannot yet replace intraoperative electrocortical stimulation in patients undergoing neurosurgery, it may be useful for guiding surgical planning and mapping, thereby reducing the extent and duration of craniotomy.

ONLINE-ONLY CME

See www.rsna.org/education/rg_cme.html.

LEARNING OBJECTIVES

After reading this article and taking the test, the reader will be able to:

- Describe the neuroanatomic basis of language processing in general and of its separate components in particular.
- Discuss the validity of functional MR imaging of language processing in clinical practice.
- List various functional MR imaging paradigms used for patient care and clinical research.

TEACHING POINTS

See last page

Abbreviations: BA = Brodmann area, PC = personal computer

RadioGraphics 2006; 26:S145–S158 • **Published online** 10.1148/rg.26si065507 • **Content Codes:** MR NR

[1] From the Departments of Radiology (M.S., C.K.S.T., A.v.d.L.) and Neurology (E.V.B., P.J.K.), Erasmus MC–University Medical Center Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. Presented as an education exhibit at the 2005 RSNA Annual Meeting. Received February 3, 2006; revision requested April 12 and received May 1; accepted May 17. All authors have no financial relationships to disclose. **Address correspondence to** M.S. (e-mail: *marion.smits@erasmusmc.nl*).

Introduction

Functional magnetic resonance (MR) imaging is a valuable technique for the study of the cerebral representation of language processing. This modality is increasingly being used for both *(a)* patient care in persons with language disorders due to neurologic disease (eg, brain tumor, stroke, epilepsy) and *(b)* related clinical research.

In this article, we review the neuroanatomic substrates of language and discuss functional MR imaging as a means of studying language processing. We describe our study in terms of task design, imaging technique, silent gap versus continuous acquisition, stimulus presentation, and statistical analysis and image processing. In addition, we discuss and illustrate functional MR imaging paradigms used in clinical practice and clinical research. We also discuss the validity of this modality in preoperative evaluation and current theories of language function recovery.

Neuroanatomic Substrates of Language

The classic model of language processing consists of a frontal expressive or motor area (Broca area), a posterior receptive language center (Wernicke area), and a white matter fiber tract (arcuate fasciculus) interconnecting the two (Fig 1) (1). This model originated from lesion studies that correlated neuropathologic brain changes with different kinds of speech and language disorders (aphasia). Lesions in Broca area are related to effortful, nonfluent, monotonous, often agrammatic speech with phonemic paraphasias (eg, "mook" instead of "book") and articulatory deficits. Language comprehension is reasonably good, but speech production is impaired. Broca area is classically located in the pars opercularis and the posterior portion of the pars triangularis of the inferior frontal gyrus (BA 44 and posterior part of BA 45) (Fig 1) (2). The classic Wernicke area is less well defined, involving parts of the supramarginal gyrus, the angular gyrus, the bases of the superior and middle temporal gyri, and the planum temporale (BAs 22, 37, 39, and 40) (Fig 1). Patients with aphasia due to a lesion in Wernicke area exhibit fluent, melodious, but empty speech that is often distorted by semantic paraphasias (eg, "chair" when "table" is meant) or neologisms, with poor language comprehension (2). Lesions of the arcuate fasciculus (BA 40) break the connection between Broca area and Wernicke area and result in conduction aphasia. Patients with conduction aphasia have fluent speech with phonemic paraphasias and self-corrections with reasonably good comprehension. In particular, the repetition of long words and sentences is disrupted (2).

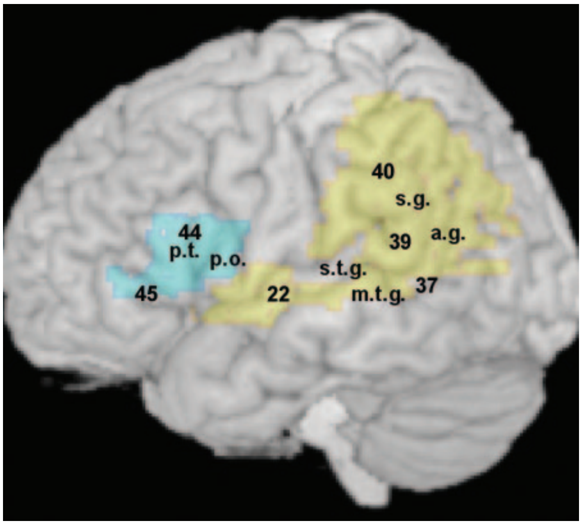


Figure 1. Image shows language processing areas of the brain, including Broca area (blue), located in Brodmann areas (BAs) 44 and 45; and Wernicke area (yellow), located in BAs 22, 37, 39, and 40. *a.g.* = angular gyrus, *m.t.g.* = middle temporal gyrus, *p.o.* = pars opercularis, *p.t.* = pars triangularis, *s.g.* = supramarginal gyrus, *s.t.g.* = superior temporal gyrus. Not shown is the planum temporale, which is located on the dorsal surface of the posterior part of the superior temporal gyrus, inside the sylvian fissure.

Along with a functional distinction between the different language areas, there is also a clear hemispheric dominance in language processing, which is left sided in 95% of right-handed individuals and in 70% of left-handed individuals (3).

Recent neuroimaging studies of language processing indicate that the classic model may be oversimplified. Cerebral anatomy and language representation studied with functional neuroimaging (positron emission tomography and functional MR imaging) appear to be inconstant, and, in a retrospective computed tomographic study of aphasia patients, no unequivocal association was found between the type of aphasia and lesion location (4). The deficits related to lesions in specific regions are not constant, and patients with a lesion in either of the classic language areas may also have symptoms related to the nonaffected language center (2). Moreover, other areas representing language processing in the brain are not included in the classic model. A new approach to language representation in the brain has emerged as the cognitive model, in which language may be described in terms of different levels of organization (5). Whereas the classic subtypes of aphasia are based on superficial language characteristics, the levels of linguistic organization concern the disorders underlying disrupted speech. Within the cognitive model, language is subdivided into related components, including orthography (spelling), phonology (speech sounds), syntax (sentence structure), and lexical semantics (language meaning) (1,6). Functional neuroimaging studies of orthographic processing have shown frontal areas of activation in the anterior inferior frontal gyrus and the posterior parietal cortex (7). In studies of phonologic processing, activation has been observed in the pars opercularis of the classic Broca area as well as in the superior temporal gyrus (1,7). Syntactic processing has been shown to give rise to activation in the inferior tip of the frontal operculum (8). In lexical-semantic processing, activation has been seen in the classic Wernicke area, in the classic Broca area, and in the middle and anterior temporal cortex (7,9). Speech and language disorders are increasingly being classified according to these subcomponents of language, whereas the classic model, although still widely used, has become somewhat outdated because it does not take into account all aspects of language processing. The traditional classification of aphasia is inappropriate for the selection of those patients who should undergo linguistic therapy, since it does not refer to the underlying linguistic deficits (10). Consequently, functional neuroimaging studies are focusing to an increasing extent on imaging of these specific subcomponents of language processing.

Teaching Point

Functional MR Imaging

Functional MR imaging is one of the most commonly used functional neuroimaging techniques for studying the cerebral representation of language processing. Blood oxygenation level dependent functional MR imaging takes advantage of the close relationship between local neuronal activity and blood flow (neurovascular coupling) (11,12). When neuronal activity increases locally, local blood flow also increases, leading to an increase in oxygenated blood that is disproportionate to the increased need for oxygen for neuronal activity. As a result, local susceptibility effects caused by the presence of paramagnetic deoxygenated hemoglobin decrease, leading to a signal intensity increase on T2*-weighted MR images in those brain areas that are active (13,14). Because signal intensity changes are small and occur after a delay, careful design of the task that is performed by the subject during imaging—the paradigm—is necessary.

A paradigm typically consists of active and control conditions. A rough distinction can be made between paradigms that are "blocked" and those that are "event related" (15). Blocked paradigms consist of a sequence of blocks, each of which constitutes an active or control condition and typically lasts 20–40 seconds. Within each block, a series of trial events of one condition is presented, and the signal acquired during one block is then compared with that acquired during the other block or blocks constituting a different condition. Blocked paradigms are statistically robust, since the signal acquired for each condition is high, but are restrained, leaving little room for unexpected or short stimuli. Short, (pseudo)random stimulus presentation is possible within an event-related paradigm design, during which individual trial events, each representing a specific condition, are presented in random order and rapid succession. Therefore, an event-related design allows the presentation of unexpected stimuli as well as many different conditions, rendering the paradigm highly flexible but statistically less robust because the signal that is acquired for each condition is generally low.

Study Parameters

Task Design: General Considerations

We based our paradigms on those described in the literature and used stimuli that are commonly used in neurolinguistic testing to detect those brain regions that are responsible for syntactic, semantic, and phonologic processing. All stimuli were auditorily presented. Each of the paradigms will be described in detail in the following sections.

For clinical studies, either for patient care or for research, one should take into account that subjects will have varying degrees of aphasia, which will influence task performance. Tasks that are too difficult to perform will result in patient underperformance or dropout, yielding suboptimal or even no task-related activation during the study. Tasks should therefore be easy enough to be performed by aphasic patients but challenging enough to invoke language processing.

Teaching Point

For clinical implementation, the task needs to be applicable in the majority of patients, since the procedure can then be standardized and performed by a radiology technologist. Clinical implementation also implies the need for only minimal additional equipment. Most imaging rooms are already equipped with headphones and a sound system that are MR imaging compatible, which makes auditory stimulus presentation preferable to visual stimulus presentation. Auditory stimulus presentation also makes the task easier to perform. Finally, for rapid assessment of all major language areas, the task should involve the major components of language processing.

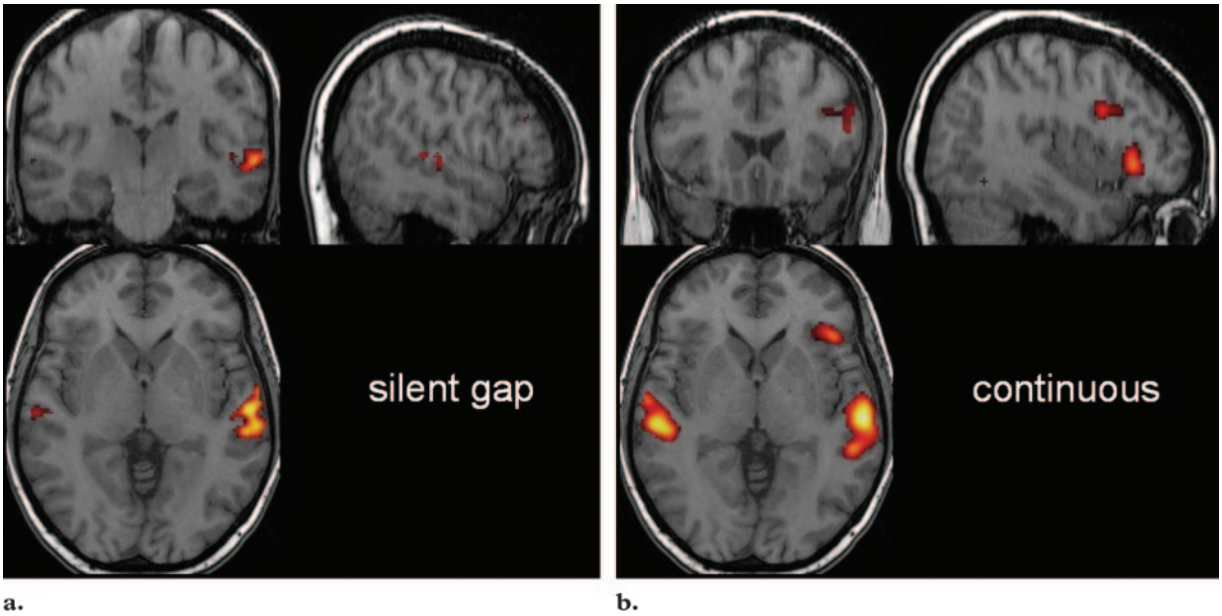


Figure 2. Areas of activation for the semantic paradigm as determined with a fixed-effects group analysis of six right-handed volunteers ($T > 5$, cluster >10 voxels). **(a)** Silent gap acquisition. On high-resolution T1-weighted MR images, superimposed activation is seen only in the posterior language areas, predominantly in the left hemisphere. **(b)** Continuous acquisition. High-resolution T1-weighted MR images show much more widespread (superimposed) activation, with additional activation in the frontal language areas. Although activation is still predominantly left hemispheric, a substantial amount is also seen in the right hemisphere. Presumably, since the words are more difficult to hear with continuous acquisition, the subject will need to concentrate more on the words themselves, not just on the meaning of the words (ie, additional phonologic processing areas of the brain are recruited).

In clinical research, on the other hand, specific components of language processing are typically studied with respect to *(a)* the effects of disease, *(b)* therapy, and *(c)* recovery. Paradigms to be used in clinical research will therefore need to address the specific components of language processing separately rather than all major areas representing language processing as a whole. Tasks still need to be easy enough to be performed by patients with severe neurologic impairment.

For both patient care and clinical research, a blocked design is the paradigm design of choice, since it is easy to implement, interpret, and analyze (possibly even with automation) and gives rise to robust activation patterns.

Imaging Technique

All imaging was performed on a 1.5-T MR imager (CV/I; GE Medical Systems, Milwaukee, Wis). For anatomic reference, a three-dimensional high-resolution fast spoiled gradient-recalled echo inversion recovery T1-weighted sequence was used. Acquisition time was 3 minutes 10 seconds. For functional imaging we used a T2*-weighted gradient-echo echoplanar imaging sequence (echo time, 40 msec; matrix, 64 × 96; voxel size, 3.75 × 2.5 × 3.5 mm). We used repetition times of 3000 msec for continuous acquisition and 6000 msec for silent gap acquisition (see the following section). During the latter, acquisition time was shorter than the repetition time (3000 msec vs 6000 msec), leaving a short period of silence between acquisitions. We used the silent gaps to present our auditory stimuli, which were then clearly audible without any interference from imager noise (16,17). Acquisition times varied between 5½ and 8½ minutes.

Silent Gap Versus Continuous Acquisition

Silent gap acquisition takes advantage of the fact that the hemodynamic response to an increase in neuronal activity is delayed. Therefore, it is possible to acquire data after a delay following stimulus presentation without degradation of the auditory stimuli by imager noise. With continuous data acquisition (ie, without a silent gap), more data can be acquired in the same amount of time or less, thereby increasing statistical power and decreasing the effects of motion artifacts. Obviously, the disadvantage of this procedure is that imager noise interferes with the auditorily presented task (17). The subject will have to extract the stimulus from the background noise and will

Table 1
Equipment for Stimulus Presentation-Synchronization and Response Monitoring

Purpose	Equipment
Stimulus presentation	Common desktop PC (console room) Stimulus presentation software (eg, Presentation, ePrime*) MR imaging–compatible sound system and headphones
Stimulus synchronization (optional)	Cable connection between PC and imager
Response monitoring (optional)	MR imaging–compatible response buttons with connection to PC

*ePrime is a product of Psychology Software Tools, Pittsburgh, Pa.

supposedly need to recruit more areas in the brain than are strictly necessary for performing the task (Fig 2).

Stimulus Presentation

Stimuli were presented binaurally through the imager's headphone system using a common desktop personal computer (PC) running Presentation v9.81 (Neurobehavioral Systems, Albany, Calif) and were synchronized with the imager pulses (Table 1).

Statistical Analysis and Image Processing

All imaging data were analyzed using Statistical Parametric Mapping version 2 software (Wellcome Department, London, England). The functional images were realigned and coregistered with the appropriate high-resolution T1-weighted MR image (18). All images were spatially normalized to the Montreal Neurological Institute (Montreal, Quebec, Canada) brain template. The normalized functional images were spatially smoothed with a three-dimensional gaussian kernel of 6 × 6 × 6 full width half maximum for single-subject and group analysis purposes (19). Single-subject and fixed-effects group analyses consisted of modeling the active and control conditions with a boxcar function convolved with the hemodynamic response function using the general linear model and applying a 128-second high-pass filter (20). Images were created with MRIcro v1.39 (Chris Rorden, PhD, University of South Carolina, Columbia, SC) and WFU Pickatlas (Wake Forest University, Winston-Salem, NC) (21–23).

Imaging in Clinical Practice

Functional MR imaging is increasingly being used as part of the routine preoperative work-up of patients to establish the relationship of the lesion to eloquent areas, such as language representation. Identifying these areas purely on an anatomic basis is inexact owing to considerable interindividual anatomic and functional variability, especially for language representation. Moreover, in the presence of a lesion, functional areas may be displaced due to mass effect, or function may have shifted to other areas in the brain due to plasticity (24). In addition, hemispheric dominance for language processing needs to be established preoperatively in both brain tumor patients and patients with temporal lobe epilepsy. A preoperative functional MR imaging study of language processing provides information on the feasibility of surgery and allows adequate assessment of the risk of postoperative neurologic deficits.

Validity of Functional MR Imaging in Preoperative Evaluation

In brain tumor patients, the aim of neurosurgery is to remove as much pathologic tissue as possible, thereby increasing survival time, while simultaneously minimizing the risk of postoperative neurologic deficits (25). For optimal results, the relationship between the tumor margins and the functionally important brain areas needs to be established as accurately as possible (26). The correlation between functional areas as established with functional MR imaging versus intraoperative electrocortical stimulation has been studied for both motor and, to a lesser extent, language representation brain areas. A high correlation has been shown for motor representation areas, but results from language representation studies are conflicting and disappointing. The sensitivity of functional MR imaging in identifying critical language areas as established with electrocortical mapping varied from 100% to as low as 22% (24,27–30). Specificity was equally variable, ranging from 100% down to 61%. These results depend in part on the kind and number of tasks used, as well as on the statistical thresholds applied to the functional MR images (28,29). Because the aim of surgery is to remove as much pathologic tissue as possible while sparing eloquent areas, both the sensitivity and the specificity of functional MR imaging need to be high for it to replace intraoperative electrocortical stimulation. Unfortunately, such is not yet the case. An additional limitation of functional MR imaging is

Table 2
Overview of Commonly Used Functional MR Imaging Paradigms in Clinical Practice

Paradigm	Task	Presentation	Comments
Verbal fluency	Generate verb from a presented noun or picture	Auditory or visual	Visual stimulation (reading, interpretation of picture) is more (perhaps too) difficult to perform
	Generate word that starts with a presented letter	Auditory or visual	If task is too difficult, subject may be instructed to think of a word starting with the next letter of the alphabet instead
	Generate a complete word from a presented stem	Auditory or visual	. . .
	Generate words in a given category	Auditory or visual	. . .
	Name pictures or line drawings	Visual	Reportedly less reliable than word generation for assessing lateralization (34)
Passive listening	Listen to standard text, story, or sentences	Auditory	Easy to perform (even by children) and implement
	Listen to text from subject's favorite book or magazine	Auditory	Very useful in children; can be performed even when subject is asleep or sedated
Comprehension	Respond to presented clues with a one-word answer	Auditory or visual	. . .
	Read text or sentences	Visual	. . .

that it does not allow the distinction between critical brain regions, which are essential for language processing, and modulatory brain regions, which may be resected without permanent deficit. Thus, functional MR imaging is not yet good enough to replace intraoperative electrocortical stimulation but may be useful for guiding surgical planning and mapping, thereby reducing the duration and extent of craniotomy.

Teaching Point

On the other hand, the validity of functional MR imaging in establishing hemispheric dominance has been proved in a large number of patients and studies, with a greater than 90% agreement between the invasive Wada test and functional MR imaging (3,24,26,30–33). Consequently, functional MR imaging of language processing is currently being used as a substitute for the Wada test, since it is noninvasive and gives additional information on the spatial relationship between language areas and the lesion.

Teaching Point

Commonly Used Paradigms

Multiple-task paradigms have been developed, published, and implemented for the stimulation of language processing. These paradigms include mostly verbal fluency and passive listening tasks (Table 2) (35). In general, verbal fluency paradigms primarily require language expression and secondarily require language comprehension, routinely giving rise to activation in the classic Broca area and often in Wernicke area in the dominant hemisphere, as well as in the premotor cortex, posterior fusiform gyrus, middle temporal gyrus, dorsolateral prefrontal cortex, supplementary motor area, and anterior cingulate gyrus (35). Paradigms of passive listening consistently give rise to activation in the classic Wernicke area and commonly in the expressive speech areas in the inferior frontal gyrus in the dominant hemisphere. This last finding may be due to the subject's covertly repeating or rehearsing the heard text. The use of tasks from different categories may improve reliability for hemispheric dominance assessment, but at the cost of increased examination time (34).

Paradigm for Patient Care

We use a verbal fluency–verb generation task in our preoperative patients, since it produces consistent activation of both the frontal and posterior language areas.

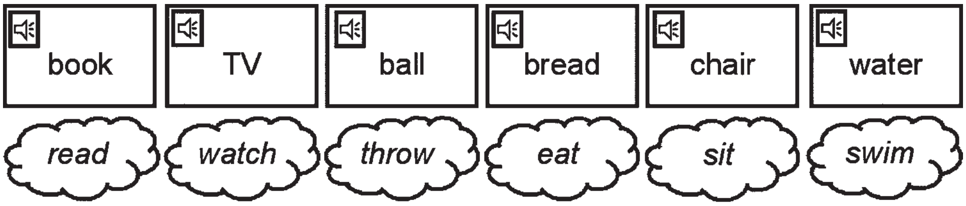


Figure 3. Schematic illustrates the verbal fluency–verb generation paradigm, with suggested responses to the presented nouns shown in text bubbles.

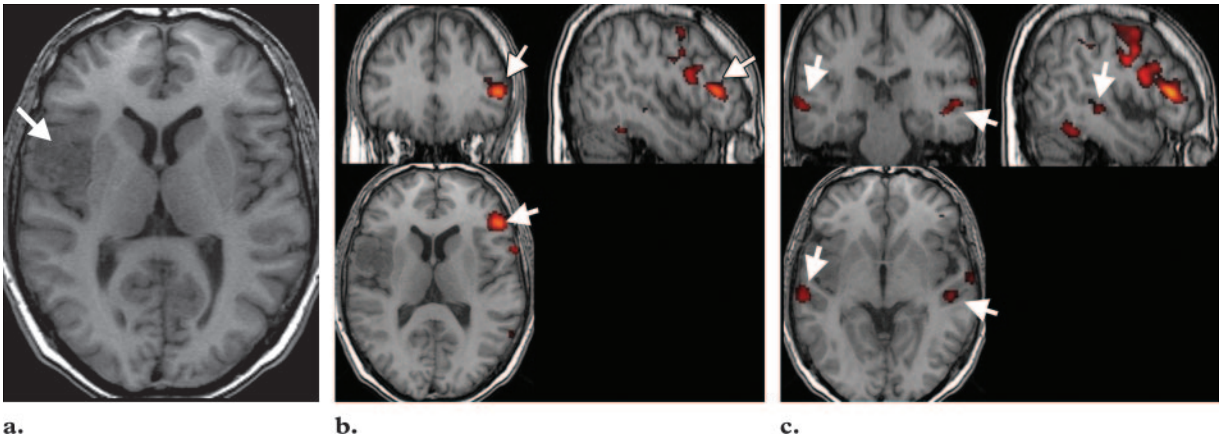


Figure 4. Areas of activation for the verbal fluency–verb generation paradigm. The subject was a left-handed 42-year-old man with a right hemispheric temporal lobe lesion who presented with headache and speech disorders. T1-weighted MR images show a lesion in the right temporal lobe (arrow in **a**), an area of superimposed activation in the left inferior frontal gyrus (classic Broca area) (arrows in **b**), and areas of equal activation bilaterally in the medial temporal gyri (classic Wernicke area) (arrows in **c**). Conclusions: left hemispheric dominance for language; no relationship between the areas of activation and the lesion.

The task consists of 10 alternating blocks of 30 seconds each (total duration, 5 minutes), in which the active and the control condition stimuli are presented binaurally (Fig 3). A stimulus is presented every 3 seconds. Stimuli in the control condition consist of high and low tones to engage auditory processing and attention. The patient is instructed to listen to the tones attentively. During the active condition, a noun is presented every 3 seconds. The patient is instructed to think of a verb that is semantically related to (ie, indicates "what to do with") the presented noun. Silent word production reduces the amount of motion artifacts significantly compared with overt word production, although a clear disadvantage is that task performance cannot be monitored (36). Language components that are involved in this task include both *(a)* language production, since a word is heard and a verb needs to be produced; and *(b)* language comprehension. The three main linguistic levels involved in performing this task are syntax (the patient has to combine two word classes, ie, a noun and a verb), semantics (the verb needs to be related to the noun), and phonology (ie, phonemic encoding of the heard word and production of a phonemic string). These processes invoke activation in the inferior frontal region (classic Broca area) and posterior parietotemporal region (classic Wernicke area). Activation is also seen in other areas related to language processing and speech production, namely, the superior and middle temporal gyri (language association areas), the medial part of the superior frontal gyrus (supplementary motor area), the anterior cingulate gyrus (cingulate motor area), the middle frontal gyrus, and the cerebellum (1,37).

With this paradigm, the proximity of the lesion to the functional language areas can be assessed, and the images can be used by the neurosurgeon for pre- and intraoperative surgical planning (Figs 4–6). In addition, hemispheric dominance can be evaluated. The most common approach to quantifying hemispheric dominance is to calculate a

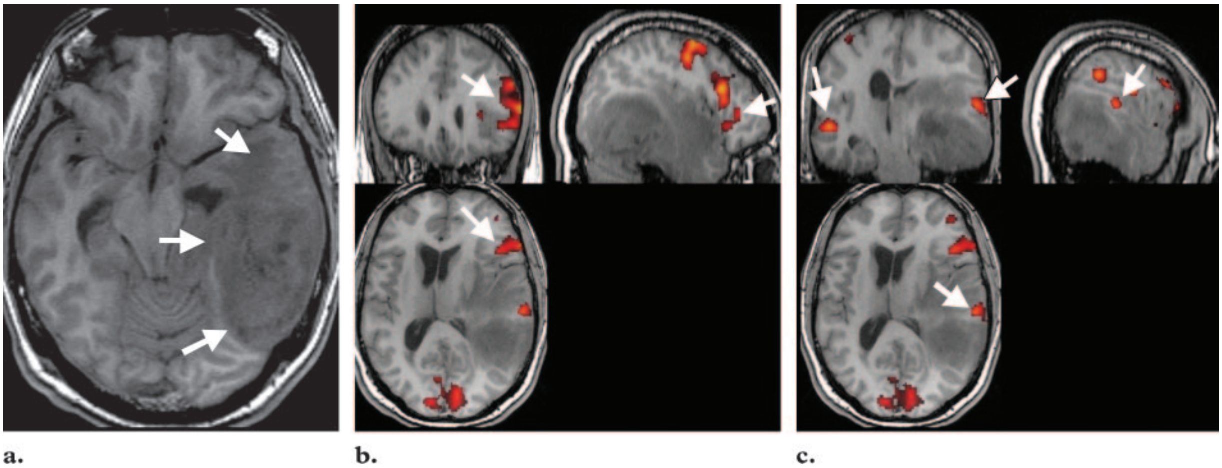


Figure 5. Areas of activation for the verbal fluency–verb generation paradigm. The subject was a left-handed 34-year-old man with a left hemispheric temporal lobe lesion who presented with speech disorders and seizures. T1-weighted MR images show a very large lesion in the left temporal lobe (arrows in **a**), an area of superimposed activation in the left inferior frontal gyrus (classic Broca area) (arrows in **b**), and areas of equal activation bilaterally in the medial temporal gyri (classic Wernicke area) (arrows in **c**). Conclusions: left hemispheric dominance for language; classic Wernicke area activation adjacent to lesion.

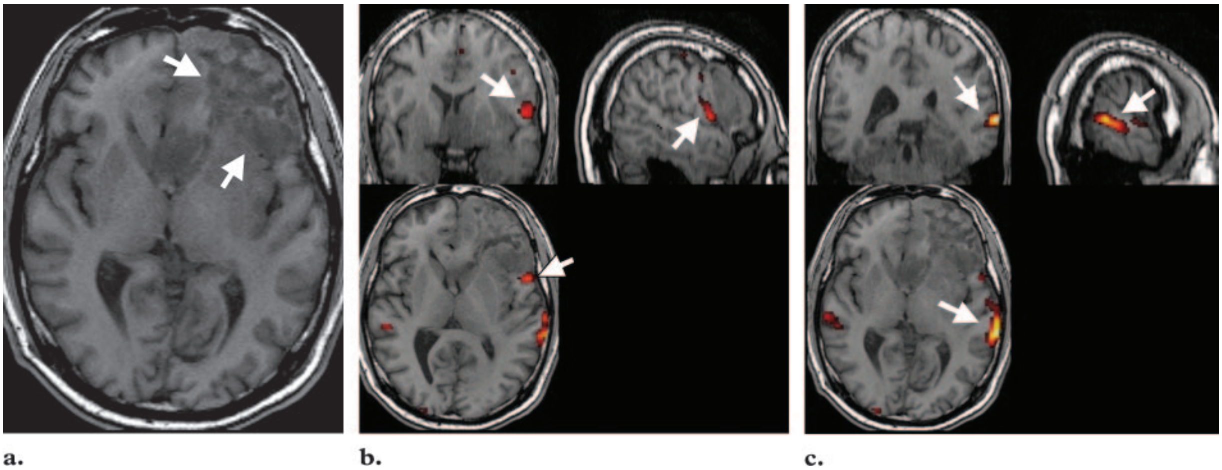


Figure 6. Areas of activation for the verbal fluency–verb generation paradigm. The subject was a left-handed 49-year-old man with a left hemispheric temporal lobe lesion. T1-weighted MR images show a lesion in the left frontal lobe (arrows in **a**); an area of superimposed activation in the left inferior frontal gyrus (classic Broca area) (arrows in **b**); and areas of activation bilaterally in the medial temporal gyri (classic Wernicke area) (arrows in **c**), with greater activation on the left side than on the right. Conclusions: left hemispheric dominance for language; classic Broca area activation adjacent to lesion.

laterality index in both the frontal and posterior language processing regions (3). For routine clinical practice, however, visual inspection is more commonly used, having demonstrated a strong correlation with the laterality indexes (31).

Imaging in Clinical Research

In addition to being used for evaluating language processing for patient care, functional MR imaging can be used in clinical research to study language processing in patients with aphasia due to stroke or other neurologic disorders, such as primary progressive aphasia, an unusual form of dementia (38). Functional MR imaging may also be used to study language function recovery and the effects of therapy (eg, after aphasic stroke).

Language Function Recovery

Recovery of language function commonly occurs, even with extensive damage to dominant hemispheric language areas. Clinical studies have given rise to two main hypotheses about the mechanisms of language function recovery. The fact that even patients with large lesions in dominant hemispheric language areas show recovery has fostered the idea that homologous language

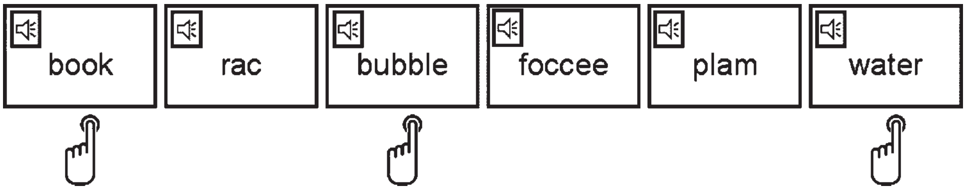


Figure 7. Schematic illustrates the lexical decision paradigm, with the correct responses indicated by the button-press symbol.

areas in the nondominant hemisphere take over part of language function. Another hypothesis is that language function recovery is achieved by recruiting perilesional and other undamaged language areas in the dominant hemisphere (39).

Teaching Point

Functional neuroimaging studies have provided some evidence supporting both theories, even suggesting that in the early stages of recovery the contralateral hemisphere is involved, whereas perilesional regions take over later on (40). Unfortunately, studies are limited in number, usually involve few subjects, and show a large variation in tasks and in time elapsed since the onset of aphasia (39,41). Perilesional activation is often observed in incomplete lesions of the classic Broca and Wernicke areas, where activation is seen in the rim of the lesion or infarct (42). Increased activation of other language areas in the dominant hemisphere has also been seen—for example, an increase of activation in the classic Broca area in the presence of a lesion in the posterior language area, as well as increased activation in the homologous areas in the nondominant hemisphere (41). In general, increases of activation after stroke are seen in areas that are also commonly activated in certain groups of healthy subjects during the performance of a language task.

It has been postulated that good recovery of language function is correlated with the recruitment of the homologous language areas in the nondominant hemisphere, but this finding may well be due to preexistent extensive and bilateral recruitment of language areas rather than to reorganizational processes in the brain (42). Assessment is difficult, since the pattern of activation before the event (eg, stroke) is not known, whereas reporting on recovery by comparing patients with healthy subjects is strongly biased. Reports of patients showing good recovery after stroke far outnumber those of patients showing poor or no recovery (42). Recent reports indicate that right hemispheric changes seem to occur after left hemispheric damage irrespective of the amount of recovery. Therefore, it has been postulated that many of the right hemispheric activation changes observed after a stroke can be attributed to transcallosal disinhibition rather than functional reorganization (41).

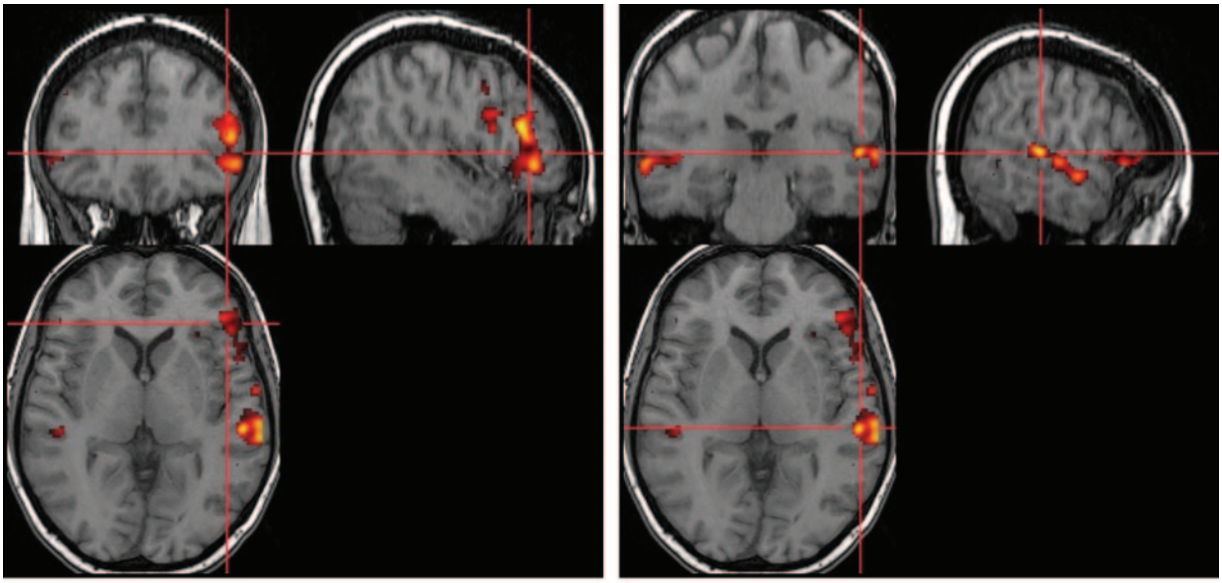
The effect of treatment on language function recovery is neurobehaviorally well established; again, however, studies examining the neural bases of treatment-induced recovery are limited in number and are nonuniform (10,39). In a study of the direct effects of training in aphasic patients, changes in activation similar to those seen in spontaneous recovery were observed, but the number of patients was limited (43). Also, very little is known about the time course of changes in activation patterns in poststroke recovery (40). In summary, functional neuroimaging studies of language processing in specific patient populations, performed at specific stages after stroke and after spontaneous or therapy-induced recovery, are badly needed to gain more insight into the reorganizational processes that occur either spontaneously or due to therapy after aphasic stroke.

Paradigms for Clinical Research

For our clinical research studies of language function recovery and patient treatment, we use three different paradigms, addressing phonologic processing and semantic processing separately. Each task consists of 12 blocks, with each block consisting of six stimuli and one instruction. Silent gap acquisition is used, with a repetition time of 6 seconds and an acquisition time of 3 seconds; the stimuli and instructions are presented every 6 seconds during the 3-second silent gap between acquisitions. Total imaging time per task is 8½ minutes. Binaurally presented stimuli are counterbalanced within tasks. Performance is monitored with a "button-press" response device held in the subject's left hand.

The control condition is the same in each of the three tasks and consists of either a high (2000-Hz) or low (400-Hz) tone, each presented for 1.5 seconds, 0.5 seconds after the onset of the silent gap. The subject is instructed to press the response button upon hearing a high tone.

The first task is a lexical decision task, in which mainly phonologic language processing is engaged (Fig 7) (44). The stimuli consist of single



a. b.

Figure 8. Areas of activation for the phonologic paradigm as determined with a fixed-effects group analysis of six right-handed volunteers ($T > 5$, cluster > 10 voxels). High-resolution T1-weighted MR images show superimposed activation in the frontal **(a)** and posterior parietotemporal **(b)** language areas, predominantly in the left hemisphere.

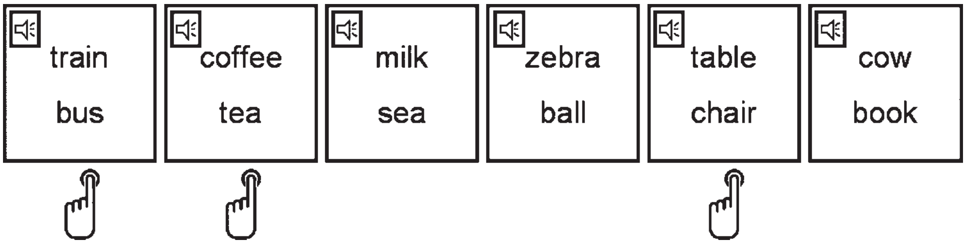


Figure 9. Schematic illustrates the semantic paradigm, with the correct responses indicated by the button-press symbol.

nouns that are either normal (correct) or nonexistent (incorrect) words. The subject is instructed to press the response button upon hearing a correct noun.

Activation with this task is seen mainly in the inferior frontal gyrus as well as in the posterior parietotemporal language area, predominantly in the left hemisphere (Fig 8).

The second task is a semantic language processing task (Fig 9) (45). The stimuli consist of pairs of nouns that are either semantically related or unrelated. The subject is instructed to press the response button upon hearing a pair of words that are semantically related.

Activation with this task is seen exclusively in the posterior parietotemporal language area in the left hemisphere; no activation is seen in the frontal language areas (Fig 10).

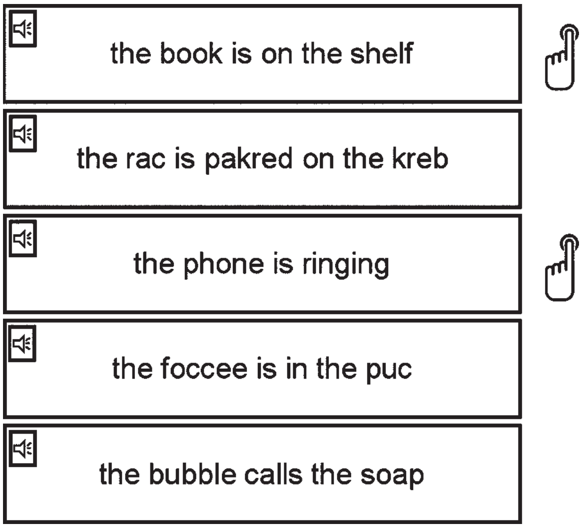
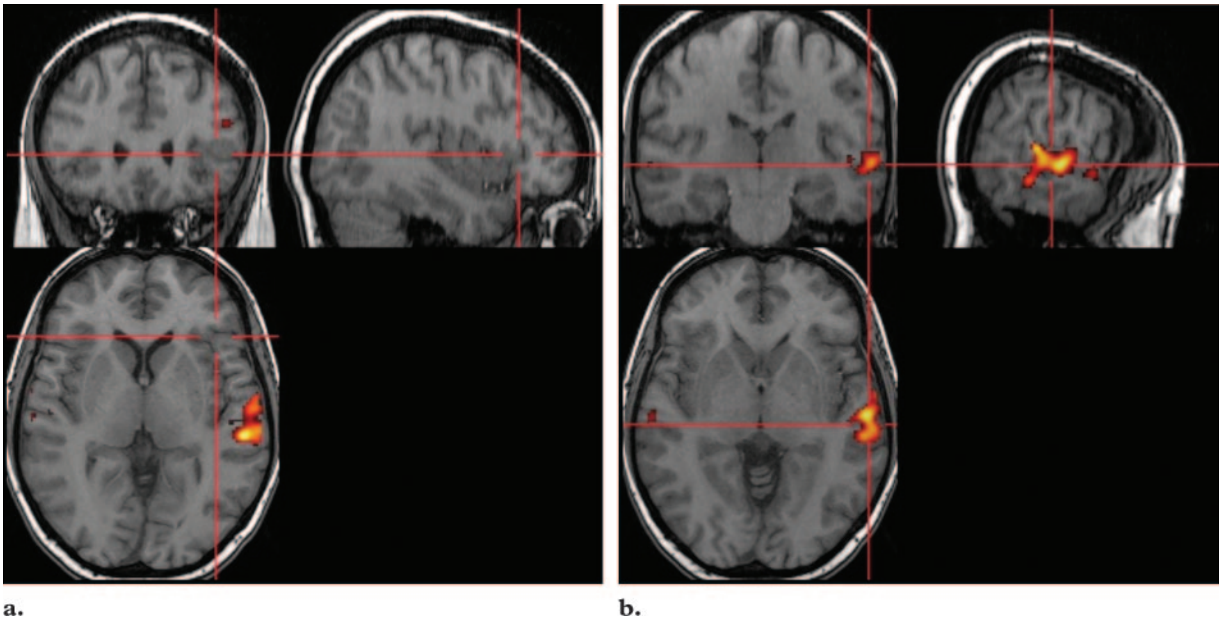
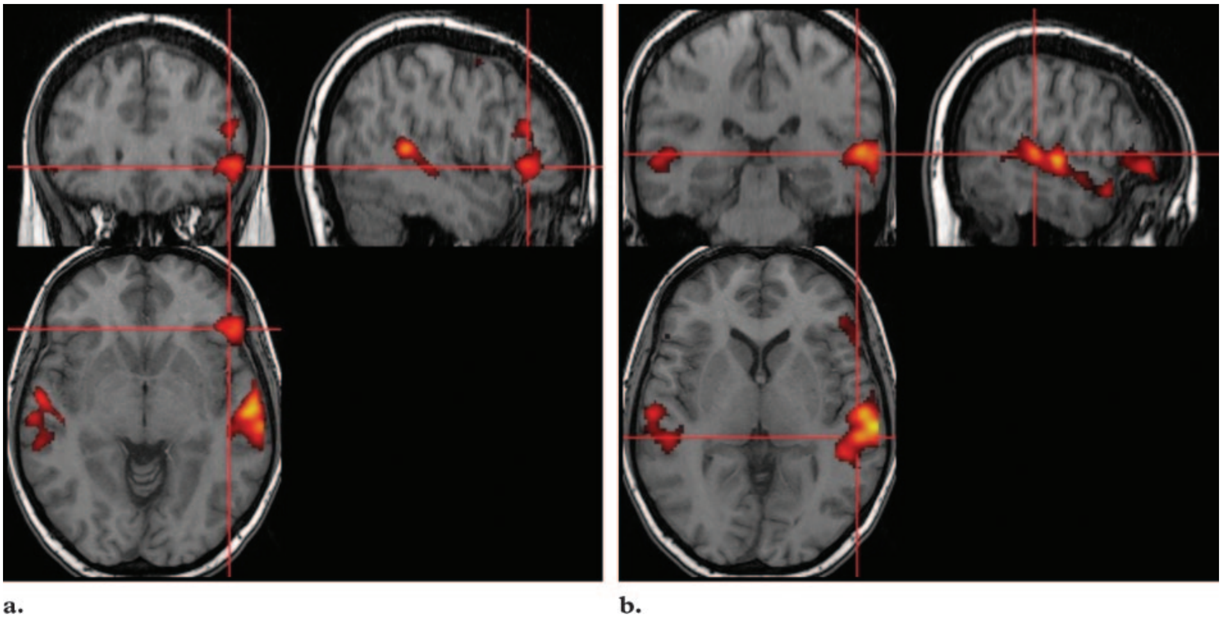


Figure 11. Schematic illustrates the combined phonologic-semantic paradigm, with the correct responses indicated by the button-press symbol.



a. b.

Figure 10. Areas of activation for the semantic paradigm as determined with a fixed-effects group analysis of six right-handed volunteers ($T > 5$, cluster >10 voxels). High-resolution T1-weighted MR images show superimposed activation in the posterior parietotemporal language area in the left hemisphere **(b)**. No activation is seen in the frontal language area **(a)**.



a. b.

Figure 12. Areas of activation for the combined phonologic-semantic paradigm as determined with a fixed-effects group analysis of six right-handed volunteers ($T > 5$, cluster >10 voxels). High-resolution T1-weighted MR images show superimposed activation in the frontal **(a)** and posterior parietotemporal **(b)** language areas, predominantly in the left hemisphere.

In the final task, stimuli are presented that involve both phonologic and semantic processing (Fig 11). Sentences are presented that are either phonologically incorrect, semantically incorrect, or neither (ie, both phonologically and semantically correct). The subject is instructed to press the response button upon hearing an entirely correct sentence. Strong activation is seen in both the frontal and posterior parietotemporal language areas, most pronounced in the left hemisphere (Fig 12).

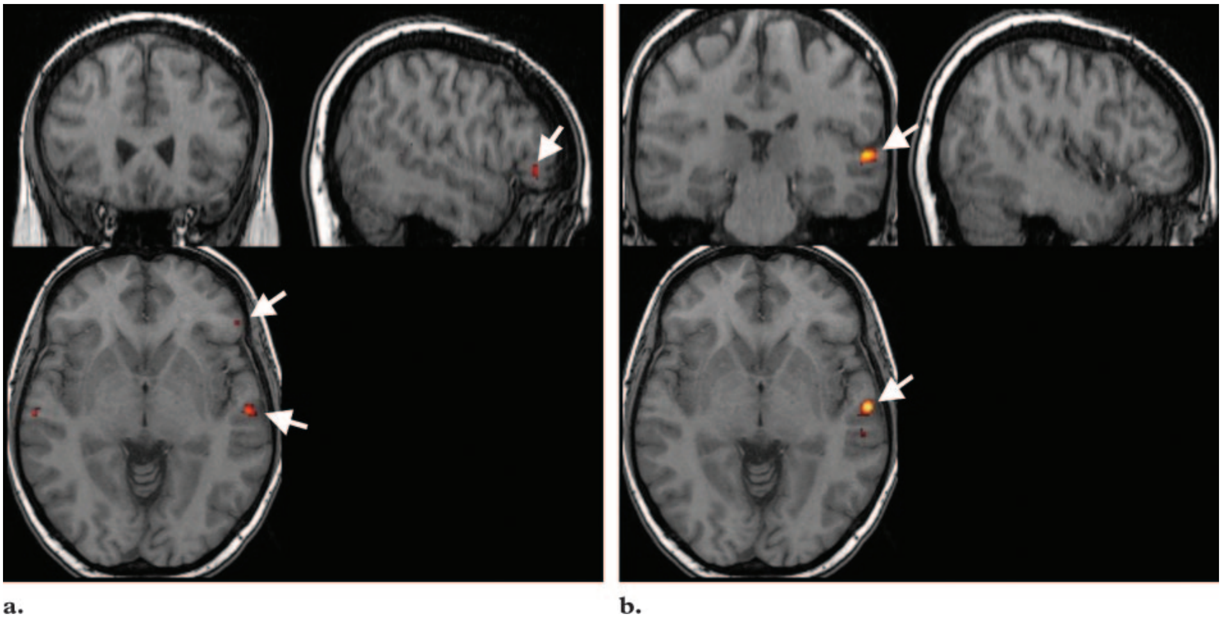
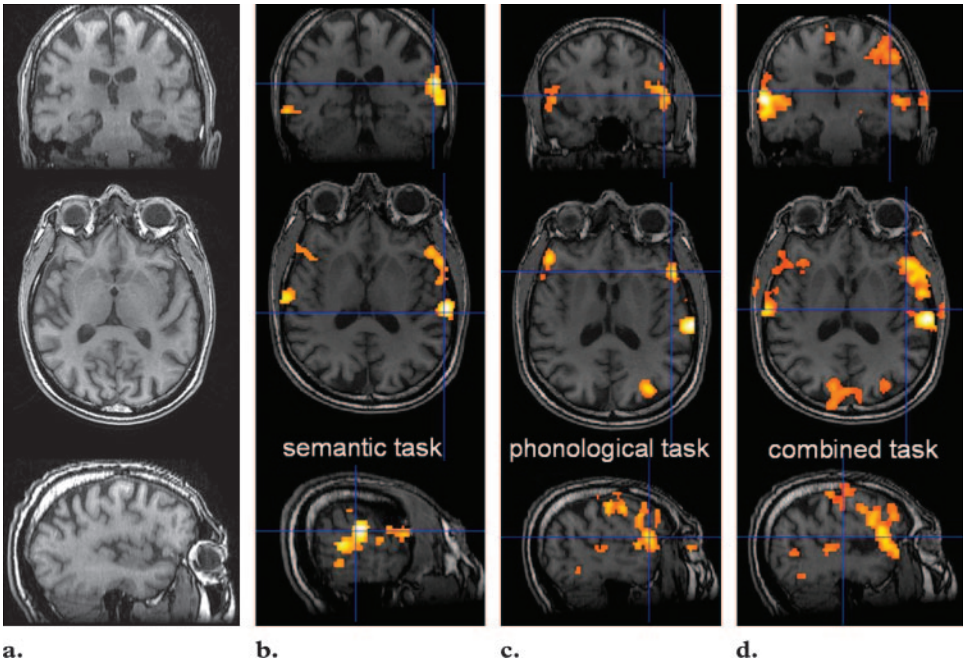

a. b.

Figure 13. Areas of activation for the combined phonologic-semantic paradigm as determined with a fixed-effects group analysis of six right-handed volunteers ($T > 5$, cluster > 10 voxels). High-resolution T1-weighted MR images show superimposed activation in the frontal and posterior parietotemporal language areas (arrows in **a**) for phonologically incorrect sentences and in the posterior parietotemporal language areas only (arrows in **b**) for semantically incorrect sentences.



a. b. c. d.

Figure 14. Areas of activation for the semantic, phonologic, and combined phonologic-semantic paradigms. The patient was a right-handed 59-year-old man with primary progressive aphasia. **(a)** T1-weighted MR images show cerebral atrophy, including atrophy of the temporal lobes. **(b–d)** T1-weighted MR images show superimposed activation in the frontal and posterior parietotemporal language areas for both the semantic **(b)** and phonologic **(c)** tasks, as well as widespread bilateral activation in these areas for the combined task **(d)**.

In addition, it is possible to analyze phonologic and semantic processing separately within this task by using an event-related model and considering either the phonologically incorrect sentences or the semantically incorrect sentences as events. Only posterior parietotemporal language area activation is seen for semantically incorrect sentences, predominantly in the left hemisphere, whereas inferior frontal and posterior activation is seen for phonologically incorrect sentences (Fig 13).

Figure 14 shows the imaging findings in a 59-year-old man with primary progressive aphasia who performed all three tasks. In this stage of the disease, the patient had mainly fluency disorders and was able to perform the tasks.

Conclusions

In this article, we have described several tasks for the imaging and study of language processing and its separate components. All tasks are easy to implement, analyze, and perform, which is essential for clinical care as well as patient-based clinical research. For the imaging of specific components of language processing, silent gap acquisition is preferable to continuous acquisition because stimuli are not degraded by imager noise, giving rise to more specific activation, even though statistical power is lower than when continuous acquisition is used.

References

1. Naidich TP, Hof PR, Gannon PJ, Yousry TA, Yousry I. Anatomic substrates of language: emphasizing speech. Neuroimaging Clin N Am 2001; 11:305–341, ix.
2. Demonet JF, Thierry G, Cardebat D. Renewal of the neurophysiology of language: functional neuroimaging. Physiol Rev 2005;85:49–95.
3. Lurito JT, Dzemidzic M. Determination of cerebral hemisphere language dominance with functional magnetic resonance imaging. Neuroimaging Clin N Am 2001;11:355–363, x.
4. Willmes K, Poeck K. To what extent can aphasic syndromes be localized? Brain 1993;116(pt 6): 1527–1540.
5. Lesser R. Linguistic investigations of aphasia. London, England: Whurr, 1995.
6. Price CJ. The anatomy of language: contributions from functional neuroimaging. J Anat 2000;197(pt 3):335–359.
7. Gitelman DR, Nobre AC, Sonty S, Parrish TB, Mesulam MM. Language network specializations: an analysis with parallel task designs and functional magnetic resonance imaging. Neuroimage 2005;26:975–985.
8. Friederici AD, Opitz B, von Cramon DY. Segregating semantic and syntactic aspects of processing in the human brain: an fMRI investigation of different word types. Cereb Cortex 2000;10:698–705.
9. Binder JR. Neuroanatomy of language processing studied with functional MRI. Clin Neurosci 1997; 4:87–94.
10. Doesborgh SJ, van de Sandt-Koenderman MW, Dippel DW, van Harskamp F, Koudstaal PJ, Visch-Brink EG. Effects of semantic treatment on verbal communication and linguistic processing in aphasia after stroke: a randomized controlled trial. Stroke 2004;35:141–146.
11. Gjedde A. Brain energy metabolism and the physiological basis of the haemodynamic response. In: Jezzard P, Matthews P, Smith S, eds. Functional MRI: an introduction to methods. Oxford, England: Oxford University Press, 2002; 37–66.
12. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 1990;87:9868–9872.
13. Thulborn KR, Waterton JC, Matthews PM, Radda GK. Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. Biochim Biophys Acta 1982; 714:265–270.
14. Matthews P. An introduction to functional magnetic resonance imaging of the brain. In: Jezzard P, Matthews P, Smith S, eds. Functional MRI: an introduction to methods. Oxford, England: Oxford University Press, 2002; 3–34.
15. Donaldson D, Buckner R. Effective paradigm design. In: Jezzard P, Matthews PM, Smith S, eds. Functional MRI: an introduction to methods. Oxford, England: Oxford University Press, 2002; 177–195.
16. Hall DA, Haggard MP, Akeroyd MA, et al. “Sparse” temporal sampling in auditory fMRI. Hum Brain Mapp 1999;7:213–223.
17. Cho ZH, Chung SC, Lim DW, Wong EK. Effects of the acoustic noise of the gradient systems on fMRI: a study on auditory, motor, and visual cortices. Magn Reson Med 1998;39:331–335.
18. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med 1996;35:346–355.
19. Friston KJ, Josephs O, Zarahn E, Holmes AP, Rouquette S, Poline J. To smooth or not to smooth? bias and efficiency in fMRI time-series analysis. Neuroimage 2000;12:196–208.
20. Worsley KJ, Friston KJ. Analysis of fMRI time-series revisited—again. Neuroimage 1995;2:173–181.
21. Rorden C, Brett M. Stereotaxic display of brain lesions. Behav Neurol 2000;12:191–200.
22. Maldjian JA, Laurienti PJ, Burdette JH. Precentral gyrus discrepancy in electronic versions of the Talairach atlas. Neuroimage 2004;21:450–455.
23. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 2003;19:1233–1239.
24. Sunaert S, Yousry TA. Clinical applications of functional magnetic resonance imaging. Neuroimaging Clin N Am 2001;11:221–236, viii.
25. Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. Lancet Neurol 2005;4:476–486.
26. Moritz C, Haughton V. Functional MR imaging: paradigms for clinical preoperative mapping. Magn Reson Imaging Clin N Am 2003;11:529–542, v.
27. Yetkin FZ, Mueller WM, Morris GL, et al. Functional MR activation correlated with intraoperative cortical mapping. AJNR Am J Neuroradiol 1997; 18:1311–1315.
28. Rutten GJ, Ramsey NF, van Rijen PC, Noordmans HJ, van Veelen CW. Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. Ann Neurol 2002;51:350–360.

29. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. Neurosurgery 2003;52:1335–1347.
30. Fernandez G, Specht K, Weis S, et al. Intrasubject reproducibility of presurgical language lateralization and mapping using fMRI. Neurology 2003; 60:969–975.
31. Fernandez G, de Greiff A, von Oertzen J, et al. Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. Neuroimage 2001;14:585–594.
32. Kloppel S, Buchel C. Alternatives to the Wada test: a critical view of functional magnetic resonance imaging in preoperative use. Curr Opin Neurol 2005;18:418–423.
33. Trenerry MR, Loring DW. Intracarotid amobarbital procedure: the Wada test. Neuroimaging Clin N Am 1995;5:721–728.
34. Gaillard WD, Balsamo L, Xu B, et al. fMRI language task panel improves determination of language dominance. Neurology 2004;63:1403–1408.
35. McGraw P, Mathews VP, Wang Y, Phillips MD. Approach to functional magnetic resonance imaging of language based on models of language organization. Neuroimaging Clin N Am 2001;11:343–353, x.
36. Yetkin FZ, Hammeke TA, Swanson SJ, et al. A comparison of functional MR activation patterns during silent and audible language tasks. AJNR Am J Neuroradiol 1995;16:1087–1092.
37. Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T. Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 1997;17:353–362.
38. Snowden J, Neary D, Mann D. Fronto-temporal lobar degeneration: fronto-temporal dementia, progressive aphasia, semantic dementia (CNNM). New York, NY: Churchill Livingstone, 1996.
39. Thompson C. Functional neuroimaging: applications for studying aphasia. In: LaPointe L, ed. Aphasia and related neurogenic language disorders. 3rd ed. New York, NY: Thieme, 2005; 19–38.
40. Fernandez B, Cardebat D, Demonet JF, et al. Functional MRI follow-up study of language processes in healthy subjects and during recovery in a case of aphasia. Stroke 2004;35:2171–2176.
41. Price CJ, Crinion J. The latest on functional imaging studies of aphasic stroke. Curr Opin Neurol 2005;18:429–434.
42. Rijntjes M, Weiller C. Recovery of motor and language abilities after stroke: the contribution of functional imaging. Prog Neurobiol 2002;66:109–122.
43. Musso M, Weiller C, Kiebel S, Muller SP, Bulau P, Rijntjes M. Training-induced brain plasticity in aphasia. Brain 1999;122(pt 9):1781–1790.
44. Behne N, Wendt B, Scheich H, Brechmann A. Contralateral white noise selectively changes left human auditory cortex activity in a lexical decision task. J Neurophysiol 2006;95(4):2630–2637.
45. Prince SE, Daselaar SM, Cabeza R. Neural correlates of relational memory: successful encoding and retrieval of semantic and perceptual associations. J Neurosci 2005;25:1203–1210.

This article meets the criteria for 1.0 AMA PRA Category 1 Credit™. To obtain credit, see www.rsna.org/education/rg_cme.html.

Functional MR Imaging of Language Processing: An Overview of Easy-to-Implement Paradigms for Patient Care and Clinical Research

Marion Smits, MD, et al

RadioGraphics 2006; 26:S145–S158 • **Published online** 10.1148/rg.26si065507 • **Content Codes:** MR NR

Page S147
Speech and language disorders are increasingly being classified according to these subcomponents of language, whereas the classic model, although still widely used, has become somewhat outdated because it does not take into account all aspects of language processing. The traditional classification of aphasia is inappropriate for the selection of those patients who should undergo linguistic therapy, since it does not refer to the underlying linguistic deficits (10). Consequently, functional neuroimaging studies are focusing to an increasing extent on imaging of these specific subcomponents of language processing.

Page S147
For clinical studies, either for patient care or for research, one should take into account that subjects will have varying degrees of aphasia, which will influence task performance. Tasks that are too difficult to perform will result in patient underperformance or dropout, yielding suboptimal or even no task-related activation during the study. Tasks should therefore be easy enough to be performed by aphasic patients but challenging enough to invoke language processing.

Page S150
Functional MR imaging is not yet good enough to replace intraoperative electrocortical stimulation but may be useful for guiding surgical planning and mapping, thereby reducing the duration and extent of craniotomy.

Page S150
Functional MR imaging of language processing is currently being used as a substitute for the Wada test, since it is noninvasive and gives additional information on the spatial relationship between language areas and the lesion.

Pages S153
Functional neuroimaging studies have provided some evidence supporting both theories, even suggesting that in the early stages of recovery the contralateral hemisphere is involved, whereas perilesional regions take over later on (40).