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

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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.

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Abbreviations: BA = Brodmann area, PC = personal computer

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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 (e.g., 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 (e.g., “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). Patients with aphasia due to a lesion in Wernicke area exhibit fluent, melodious, but empty speech that is often distorted by semantic paraphasias (e.g., “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).

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.

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 deoxyhemoglobin 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.

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.
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 (CVI; 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...
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 $6 \times 6 \times 6$ 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 electrophotical 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>
<thead>
<tr>
<th>Purpose</th>
<th>Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus presentation</td>
<td>Common desktop PC (console room)</td>
</tr>
<tr>
<td></td>
<td>Stimulus presentation software (eg, Presentation, ePrime*)</td>
</tr>
<tr>
<td></td>
<td>MR imaging–compatible sound system and headphones</td>
</tr>
<tr>
<td>Stimulus synchronization (optional)</td>
<td>Cable connection between PC and imager</td>
</tr>
<tr>
<td>Response monitoring (optional)</td>
<td>MR imaging–compatible response buttons with connection to PC</td>
</tr>
</tbody>
</table>

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

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.

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.

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

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

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.
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 gyrus (classic Broca area) and posterior parieto-temporal 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...
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
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).

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
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 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.

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

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