An Update on Determination of Language Domiance in Screening for Epilepsy Surgery: The Wada Test and Newer Noninvasive Alternatives

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Summary: The intracarotid amobarbital procedure or Wada test has been the gold standard for lateralization of language dominance before epilepsy surgery. It is based on deactivation of language cortex with intracarotid anesthesia. However, it is an invasive test with risks and discomforts, and it also has limitations. There has been great interest in replacing the Wada test with a noninvasive procedure. One alternative, repetitive magnetic stimulation works by deactivating language cortex, but most other promising alternatives are based on brain activation. Functional magnetic resonance imaging (fMRI), 15O-water positron emission tomography, single photon emission computerized tomography, transcranial Doppler, and near infrared spectroscopy detect hemodynamic responses to language cortex activation, while magnetoencephalography more directly measures event-related physiological activation. Some of the techniques also provide localization of language functions, whereas the Wada test is strictly a lateralization method. Based on widespread availability, fMRI will likely be the most widely used alternative. Key Words: Wada test—Cerebral dominance—Language dominance—Functional MRI—Magnetoencephalography.

The Wada test or the intracarotid amobarbital procedure was initially introduced more than 50 years ago as a method to determine cerebral dominance for language functions prior to surgical resection (Wada, 1949). It was later modified to also evaluate memory function and predict the risk of amnesia following temporal resection (Milner et al., 1962). At the present time, the Wada test is most often used to evaluate lateralized distribution of language and memory functions, in the presurgical evaluation of epilepsy. The finding of impaired memory function in one hemisphere also predicts hippocampal pathology on that side and thus has some value in the localization of the epileptogenic temporal lobe and prediction of surgical success (Loring et al., 1994). This review focuses particularly on the issue of language lateralization; memory lateralization is not addressed here inasmuch as it is a complex issue requiring a separate, in-depth discussion.

THE WADA TEST

Wada test procedure

The procedure involves injection of an anesthetic agent into the internal carotid artery, as a standard component, but other specific components have varied greatly among centers (Abou-Khalil, 1995). This variability encompasses the type of anesthesia, the exact dose used, the choice of which side is injected first, the period of time between one injection and the other, the material used for testing language or memory, and the method of scoring the results. The Wada test starts with a carotid angiogram in order to visualize the cerebral vascular pattern and thus predict how the anesthetic will be distributed in the brain. One important vascular variation, a persistent trigeminal artery, precludes the Wada test for concern of anesthetizing the brain stem. Other variations such as filling of both anterior cerebral arteries from one side or filling of the posterior cerebral artery through the posterior communicating artery are of lesser impact, but may possibly influence the results. After the cerebral angiogram, the patient is prepared for the intracarotid injection of anesthetic, most commonly amobarbital. The anesthetic injection is usually preceded by baseline testing of speech and memory. For example, the patient is asked to name common objects, read single words aloud, count, and recite the days of the week, spell single words, and follow simple commands. It is fairly standard that patients are asked to extend their arms in the air and wiggle their fingers and toes while counting aloud prior to the anesthetic injection. The paralysis of the contralateral arm with arrest of the wiggling of the fingers usually indicates to the neuropsychologist that the hemisphere has been anesthetized and that language...
and memory testing can begin. In general, language testing is performed first. The patient is asked to name objects, follow simple commands, repeat sentences, and count or name the days of the week. Next, memory items are presented for testing memory reserves in the nonanesthetized hemisphere. Following complete recovery of neurological function, memory for presented items is tested. The catheter is then repositioned in the carotid artery of the other side and the same procedures are repeated. It is generally agreed that there should be at least 30 min between the two injections, to avoid residual amobarbital effect on the other side and the same procedures are repeated. It is generally agreed that there should be at least 30 min between the two injections, to avoid residual amobarbital effect in the hemisphere whose functions are to be tested next.

**Determination of language dominance from the Wada test**

Most often, global aphasia develops after dominant hemisphere injection, lasting a few minutes. When speech reappears, it is generally characterized by paraphasic errors and perseverations. After nondominant hemisphere injection, patients most often will continue counting and will demonstrate no change in speech other than dysarthria. However, it is possible to observe a brief period of speech arrest for 10–15 s, with no aphasia once speech returns. Inference of bilateral language representation from the Wada test can be problematic. Bilateral language representation is usually concluded if some language functions are preserved after anesthesia of each hemisphere or if there is language disturbance with injection on each side. Occasionally, there may be dissociation of language functions, with specific functions represented in each hemisphere, for example, comprehension in one hemisphere and automatic speech or naming in the other hemisphere (Risse et al., 1997).

**Risks and limitations of the intracarotid amobarbital procedure**

The Wada test is an invasive test that involves an arteriogram and the risks associated with an arteriogram. In one study, the risk of carotid artery dissection was 0.7% (Loddenkemper et al., 2002). These risks are greater for older individuals. Patients with dissection had a mean age of 51.3 years versus 31.7 years of those without dissection. Other potential complications of the Wada test include cerebral infarction, transient femoral neuropathy, and arterial spasm with potential transient deficits. The invasive nature of the Wada test makes it unsuitable to study language dominance in normal volunteers or in any group where the results are not essential for treatment.

Aside from risks, there are many limitations for the Wada test. An important limitation is that the Wada test is not standardized across centers (Rausch et al., 1993). This is more of an issue with testing of memory. With respect to language, the thoroughness of the language testing and the method of scoring the results have been quite variable. In addition, it is possible that for some patients the amount of amobarbital injected is not sufficient to produce anesthesia of all language areas, or for some individuals there may be language areas outside of the middle cerebral artery distribution. Recently, there has been evidence of failure of anesthetization with amobarbital in patients taking carbonic anhydrase inhibitors such as the antiepileptic drugs topiramate and zonisamide (Bookheimer et al., 2005).

Another important limitation is that the Wada test is strictly a test of lateralization and does not allow further localization of language functions in each hemisphere. If there is concern that surgery may put language cortex at risk in the dominant hemisphere, then further localization of language with electrical stimulation mapping (ESM) is usually indicated. This makes an alternative technique that can offer both lateralization and localization highly desirable.

Finally, amobarbital availability has been an issue, with frequent shortages worldwide, leading to exploration of the Wada procedure with different anesthetics, including propofol (Takayama et al., 2004), methylmercaptal (Buchtel et al., 2002), and etomidate (Jones-Gotman et al., 2005). All three agents have half-lives that are shorter than amobarbital. In the case of etomidate, the half-life is so short that an initial bolus has to be followed by an infusion. This could be advantageous, allowing the procedure to continue until language and memory functions have been satisfactorily tested. The alternative anesthetic techniques seem to be equal to the amobarbital Wada test in their ability to lateralize language. However, these alternative procedures still include the risks of carotid angiography, and there are additional safety concerns related to the specific anesthetics. For example, propofol use was reported to have associated adverse effects in about one-third of patients, the most common being increased tone with twitching or rhythmic movements or tonic posturing (Mikuni et al., 2005). Etomidate has risks in critically ill patients, but their relevance to epilepsy patients is unknown (Grote and Meador, 2005).

The remainder of the article will focus on alternative methods for language dominance that do not involve intracarotid injection of an anesthetic (Table 1). Alternative methods can be divided into those that involve deactivation of language cortex, those that look for structural asymmetries associated with language lateralization, those that detect directly the physiological brain activation by language tasks, and those that detect the hemodynamic response to activation of language cortex (Table 1).

**ALTERNATIVE METHODS USING DEACTIVATION**

**Repetitive transcranial magnetic stimulation (RTMS)**

Transcranial magnetic stimulation can be used to activate primary motor or sensory cortex or deactivate association cortex. In this respect, it has a lot of similarity to deactivation using electrical cortical stimulation either

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directly intraoperatively or through implanted subdural electrodes. The first published study used a stimulation coil held flat on the scalp in six adult volunteers with intractable epilepsy pursuing surgical treatment (Pascual-Leone et al., 1991). Ten second stimulation trains were applied at 15 different positions while the patient counted aloud. When the stimulation was applied to the left side, counting errors or speech arrest resulted in all six patients. The arrest was limited to a single stimulation coil position, but was reproduced at least three times in each subject. When applied to the right side, magnetic stimulation did not lead to speech arrest or counting errors at any stimulation position in any of the patients. However, there was a change in voice quality, namely, tremulous and dysarthric speech. All six subjects had left hemisphere dominance by the Wada test, but one patient had limited language comprehension in the right hemisphere, without expressive language representation. The main complication of magnetic stimulation was a simple partial seizure induced in one patient with stimulation at the maximal output intensity.

Several subsequent studies supported the ability of RTMS to lateralize language in some patients, but also reported limiting adverse experiences from the technique. Jennum et al. (1994) compared the results of RTMS with the Wada test in 8 men and 14 women undergoing surgery for intractable temporal lobe epilepsy. One-second stimulation trains at 30 Hz were applied at left and right frontal, posterior temporal, midtemporal, and pretemporal areas (the latter corresponded to electrode positions F7 and F8). A list of words and forward and backward counting were used to test speech. The stimulus intensity was increased until speech arrest occurred. The Wada test was performed unilaterally, injecting the hemisphere of proposed surgery. Only one patient had a bilateral Wada test. With RTMS, speech arrest was observed in 14 of the 21 patients, whereas in 7 patients there was only slowing of speech or a partial speech arrest in only some of the test procedures. In these seven patients, the intensity was increased to the maximum level or the patient could not tolerate the stimulations. Speech inhibition was most pronounced with stimulation of the pretemporal region. Fifteen patients were left hemisphere dominant by both tests and the rest had atypical representation. Complete or nearly complete concordance was obtained between RTMS and the Wada test in 20 of the 21 patients. The one patient with poor correlation between RTMS and the Wada test had bilateral language representation with right dominance by magnetic stimulation and left dominance with a unilateral Wada test. The complications of the magnetic stimulation were stimulation of the facial and laryngeal muscles during stimulation of the pretemporal and frontal areas, and of the facial nerve with stimulation of posterior temporal area. The facial and laryngeal muscle contractions interfered with the interpretation of the findings. No seizures were provoked. Only two patients felt that the contractions were unpleasant and induced a sensation similar to the initial symptoms of a seizure. Five patients reported a transient headache. Michelucci et al. reported lateralized speech arrest concordant with the site of manual preference in only 7 of the 14 patients studied (Michelucci et al., 1994). The remaining patients did not have a speech arrest. The stimulation was not well tolerated because of pain and discomfort at the stimulation site in 10 patients at intensity values of >75% of maximum output. There was an emotional reaction in three individuals who burst out crying (presumably because of their inability to speak), and two individuals had jerking of one arm persisting for a few seconds after the end of the stimulus, suggesting simple partial seizure activity. One patient had a visual field defect that subsided in 5 min.

The reports of poor tolerability of RTMS stimulated an investigation into improved stimulators and more favorable stimulation parameters. Epstein et al. (1996) used a more powerful and more focal magnetic coil to evaluate

### TABLE 1. Methods of determining cerebral dominance

<table>
<thead>
<tr>
<th>Method</th>
<th>Physiological basis</th>
<th>Directness of measurement</th>
<th>Reliability relative to Wada test</th>
<th>Individual determination of language dominance</th>
<th>Ability to provide localization</th>
<th>Potential to provide Wada memory component</th>
<th>Availability</th>
<th>Complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wada test</td>
<td>Deactivation by anesthesia</td>
<td>Direct</td>
<td>N.A.</td>
<td>Yes</td>
<td>No</td>
<td>N.A.</td>
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<td>+</td>
</tr>
<tr>
<td>RTMS</td>
<td>Deactivation by electrical interference</td>
<td>Direct</td>
<td>++</td>
<td>Possibly</td>
<td>No</td>
<td>--</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>sMRI</td>
<td>Association with dominance</td>
<td>Very indirect</td>
<td>+</td>
<td>No</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>ERP</td>
<td>Electrophysiological expression of activation</td>
<td>Direct</td>
<td>+</td>
<td>No</td>
<td>No</td>
<td>±</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>MEG</td>
<td>Magnetic flux directly associated with activation</td>
<td>Direct</td>
<td>+++</td>
<td>Yes</td>
<td>Yes</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>fTCD</td>
<td>Hemodynamic response to activation</td>
<td>Indirect</td>
<td>+++</td>
<td>Yes</td>
<td>No</td>
<td>--</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>NIRS</td>
<td>Hemodynamic response to activation</td>
<td>Indirect</td>
<td>+++</td>
<td>Yes</td>
<td>Partially</td>
<td>--</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>PET</td>
<td>Hemodynamic response to activation</td>
<td>Indirect</td>
<td>+++</td>
<td>Yes</td>
<td>Yes</td>
<td>±</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>SPECT</td>
<td>Hemodynamic response to activation</td>
<td>Indirect</td>
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<td>Yes</td>
<td>Yes</td>
<td>±</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>fMRI</td>
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<td>Indirect</td>
<td>+++</td>
<td>Yes</td>
<td>Yes</td>
<td>+++</td>
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</tbody>
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the effectiveness and the adverse effects of stimulation at different intensities, orientations, and repetition rates in six normal volunteers. They found that the best ratio of efficacy to pain was at slower repetition rates of 4–8 Hz with a horizontal alignment of the induced electric field. A lower stimulation frequency also allowed clearer distinction between speech arrest and dysarthria from tonic contraction of cranial muscles. They further refined the technique with more comprehensive language tasks than previously described, and moved the coil across the presumed dominant frontotemporal region, increasing the intensity as needed. Complete speech arrest and impaired speaking and reading aloud were obtained in all 10 normal subjects with a latency of 1–3 s. However, when the authors used RTMS in 17 patients undergoing epilepsy surgery evaluation, the findings did not fully agree with the Wada test (Epstein et al., 2000). Sixteen of the 17 patients had complete arrest of counting over one or both hemispheres. The remaining patient had dysarthria with left but not right stimulation. However, only 12 of the 17 patients appeared left dominant, whereas all patients were left hemisphere dominant by the Wada test. Three patients had speech arrest at the same RTMS intensity bilaterally, and one patient appeared entirely right dominant with RTMS while being left dominant by the Wada test. Thus, RTMS appeared to give an excessive yield of apparent bilateral or right hemisphere lateralization using the technique of Epstein et al. The authors suggested that the failure might relate to activation of motor rather than language cortex, and that stimulation over Wernicke’s area may have been more productive. However, its effects were not sufficiently robust in all subjects.

It is possible that RTMS may still be developed as a useful clinical method for confirming cerebral dominance for language, if its accuracy can be improved. A recent study used RTMS in conjunction with functional imaging (Andoh et al., 2006), for therapeutic purposes. After the posterior language areas were determined by functional magnetic resonance imaging (fMRI) while listening to sentences in native or foreign languages, the magnetic stimulator was guided to that posterior temporal area with a frameless stereotactic system. It may seem that the use of fMRI to localize the language area may make diagnostic RTMS redundant. However, areas activated by fMRI may or may not be essential, and a deactivating technique such as RTMS may be useful to make that determination.

**STRUCTURAL IMAGING METHODS FOR LANGUAGE DOMINANCE**

A number of structural MRI measurements have been investigated for relationship to language dominance and compared to the Wada test. Charles et al. (1994, 1997) performed linear measurements of frontal and occipital lobe length and found that asymmetry of the occipital lobe length as well as occipital area on MRI scan 10 mm above the tentorium significantly related to language dominance. Despite these group relationships, both linear and surface area occipital measurements do not reliably identify dominance in individual patients.

A more promising anatomical method required threedimensional MRI analysis to evaluate asymmetries in the perisylvian region. An asymmetry of the planum temporale (the superior surface of the temporal lobe, deep to the Sylvian fissure) was long noted in anatomical studies, with a characteristic pattern in which the right sylvian fissure is shorter and also angulates upward into the parietal region while the left continues posteriorly. This asymmetry was suspected to reflect language lateralization. Using structural MRI, Foundas et al. (1994) found that 11 patients with left hemisphere dominance by the Wada test showed a longer planum temporale on the left and one with right hemisphere dominance a longer planum temporale on the right. The same group also found asymmetries of the pars triangularis convolutions (a triangular part of the inferior frontal gyrus, between the anterior horizontal and anterior ascending ramus). Nine of the 10 patients with left hemisphere dominance for language had leftward asymmetry of the pars triangularis whereas that with right hemisphere dominance had a rightward asymmetry (Foundas et al., 1996).

These promising findings required confirmation with a larger group of patients, including a reasonable number with atypical language representation by Wada testing. Dorsaint-Pierre et al. (2006) investigated various anatomic asymmetries in three patient groups, 20 with left language dominance, 11 with right language dominance, and 13 with bilateral representation. They found leftward structural asymmetries in the planum temporale consistent with the literature, but these did not relate to language lateralization. However, the presence of more grey matter in the region of Broca’s area correlated with dominance, with more grey matter on the left for the left speech group and on the right for the right speech group. Once more, these group differences were not reliable to identify individual language dominance.

**ALTERNATIVE METHODS DIRECTLY MEASURING PHYSIOLOGICAL ACTIVATION**

Two methods have been investigated, event-related potentials measuring the electrical potential from activation and magnetoencephalography/magnetic source imaging localizing the magnetic flux associated with activation.

**Event-related brain potentials (ERP)**

ERPs are electrical potential changes reflecting the cognitive processing of stimuli. Because they are of small amplitude in comparison with background activity, they are difficult to see after the presentation of a single
stimulus, and require averaging of responses after multiple repetitions of the stimulus. The averaging cancels out random background activity, allowing only the response to the stimulus to stand out clearly. The technique has a high temporal resolution that allows independent analysis of ERP components by latency.

ERPs have been tested for determination of hemispheric asymmetries in language processing, using tasks of word fluency and semantic memory encoding. Task performance was found to be associated with a surface negative sustained brain potential, larger on the left. Gerschlager et al. (1998) studied 24 healthy controls and 20 patients undergoing presurgical evaluation for epilepsy. Twelve of the patients also had the Wada tests for comparison. In the event-related potential paradigm, subjects viewed a series of items including readable verbal material and spatial patterns. Verbal and nonverbal items were presented alternately. Subjects were instructed to lift the two index fingers once for new items or twice for old items. With verbal material, ERPs were usually more negative going in recordings of the left hemisphere as compared to corresponding recordings of the right hemisphere (20/24 subjects). With figures, ERPs were usually more negative going in recordings of the right hemisphere. Among the 12 patients who had a Wada test, eight were left hemisphere dominant; ERPs were significantly more negative over the left hemisphere in four, symmetrical in three but conflicting in one patient with left temporal lobe epilepsy. In four patients with bilateral language by Wada, ERP showed left hemisphere dominance in three and no lateralization in one. It appears therefore that ERP asymmetry is not reliable for determining language dominance in individual patients. It is possible that the side of epileptic lesion interferes with ERP asymmetry.

Magnetoencephalography (MEG)

MEG can record the magnetic flux associated with event-related brain activity with excellent time resolution to identify the activity specifically related to activation of language association cortex. The magnetic counterpart to ERP is termed event-related field (ERF). The early portions of the ERF waveform, up to 150–200 ms after stimulus onset, reflect activity in primary sensory cortex, with later portions reflecting activation of association cortex including language cortex. Brain areas responsible for language functions are detected by estimating the regions that contribute to the late portion of the ERF waveform. Several studies have reported excellent concordance with results of the Wada test in adults and in children. Papanicolaou et al. (2004) studied 100 patients with intractable seizures evaluated for epilepsy surgery. The patients underwent both MEG and Wada test. As part of the MEG language processing, patients were exposed to spoken words. The patient’s task involved recognizing the word and determining if it had been presented earlier. Magnetic activity was measured from 148 sensors that covered the surface of the head. The recordings from several consecutive word stimuli were averaged. The resulting ERF consisted of early (30–200 ms) and late (200–800 ms) components. A mathematical model was applied considering the intracranial generators of the observed ERFs as single equivalent current dipoles. The location and the strength of the source were estimated. Using coregistration, the precise location of the dipolar source was marked on the MRI image. A minimum of 140 artifact-free event-related field epochs were used to calculate two averaged waveforms. All patients presented with activity sources in the posterior portion of the superior temporal gyrus. Fewer patients had sources in the middle temporal gyrus (71%), mesial temporal region (79%), and inferior frontal area (45%). MEG activity sources were often found bilaterally in these areas, even for those patients who were left hemisphere dominant. A neurophysiologist blinded to the Wada results made a judgment as to cerebral dominance for language based on the MEG-derived maps. First the sources computed during the late portion of the ERF waveform were selected, then the number of clustered activity sources in the perisylvian region was determined for each hemisphere in each testing session, and then finally a laterality index was created (laterality index = [R−L]/[R + L]). A laterality index between −0.1 and 0.1 was considered to indicate bilateral symmetric activation whereas values greater than 0.1 or smaller than −0.1 indicated right or left hemisphere dominance. There was a strong concordance between the Wada test and the MEG. There was complete agreement in 74 of 85 cases with 11 discordant cases. In the majority of these discordant cases, the MEG showed bilateral language whereas the Wada test showed left hemisphere dominance (7 of 11). When comparing the Wada and MEG for whether language was present or absent in a hemisphere, there was disagreement in only six cases. In five of these cases, MEG indicated that language was present, but the Wada indicated that it was not. In one case, it was the reverse. The MEG judgments showed a sensitivity of 98%, positive predictive value of 91%, negative predictive value of 96%, and a specificity of 83%.

The authors argued that MEG has a distinct advantage of being noninvasive, relatively fast (about 30 min), and free of risk or discomfort.

The task used in the above study seemed more effective at activating temporal than frontal language cortex. Bowyer et al. (2004) used two tasks, silent verb generation in response to visually presented printed nouns and picture naming. They tested 18 normal volunteers and 24 patients with a 148-channel neuromagnetometer. With the verb generation modality, the left supramarginal gyrus, superior temporal gyrus, and angular gyrus areas were activated in all subjects, 184–382 ms after the onset of the stimulus. There was also activity over the left
inferior frontal gyrus in all subjects during the same task, later at 350–450 ms. Using the same language task, the authors also compared MEG and Wada test in 27 patients with localization-related epilepsy (Bowyer et al., 2005). The MEG lateralization was based on the previous findings of a shorter latency for activation of Wernicke’s area and longer latency for Broca’s area. A laterality index was applied to determine language dominance. Laterality index values were calculated for each of the language tasks and for different latency intervals. The Wada testing was successful in 24 of the 27 subjects. The MEG result that was most consistent with the Wada test was the laterality index for Broca’s area activation with the picture-naming task. This was consistent with the Wada laterality in 23 of the 24 patients. Of note is that the method of determining dominance by Wada test in this study was very qualitative, and it is possible that Broca’s area was a stronger determinant of language dominance on the Wada test and that for some patients there may have been dissociation of receptive and expressive language representation not identified by the Wada analysis.

In summary, MEG can identify both frontal and temporal language area activations (Fig. 1), and can identify language dominance in agreement with the Wada test. However, the MEG analysis methods may need to be further refined.

**ALTERNATIVE METHODS BASED ON HEMODYNAMIC RESPONSES TO ACTIVATION OF LANGUAGE AREAS—DIRECT ASSESSMENT OF BLOOD FLOW CHANGES**

Most methods for determining language dominance are based on the hemodynamic response to cerebral activation. Activation of a region of the brain and the associated increase in synaptic activity results in increased glucose metabolism, followed by increased blood flow. The techniques of transcranial Doppler, single photon emission computerized tomography, and $^{15}$O-water positron emission tomography are directly based on this increased regional blood flow.

**Functional transcranial Doppler (fTCD)**

fTCD involves the continuous measurement of blood flow velocities in both middle cerebral arteries during repeated performance of a task. Activation of language functions is expected to increase blood flow in the hemisphere involved in language. The event-related changes in blood flow can be measured and averaged for each hemisphere and the differences between the two sides could potentially identify the hemisphere most activated with language. Knecht et al. (1998) compared functional TCD with the Wada test in 19 patients undergoing epilepsy surgery evaluation. The language task used involved word generation by letter. fTCD could be performed in 15 of the 19

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**FIG. 1.** Localized magnetic sources from two consecutive trials of a word recognition task, recorded using a whole head magnetometer system containing 148 detector channels. A high degree of asymmetry in the number of localized magnetic sources indicated left hemisphere dominance for receptive language. The image shows a sample of the sources coregistered on a structural MRI.
patients who had a successful Wada test. The remaining four patients did not have an adequate acoustic temporal bone window for insonation of the middle cerebral artery. During the word generation, there was a relative predominance in cerebral blood flow increase in the left hemisphere in 11 patients and in the right hemisphere in four patients. In every case, the determination of language lateralization by functional TCD was concordant with the Wada test. The laterality index for language determined by the Wada test revealed a highly significant correlation with the laterality index for functional TCD.

In another study, Knake et al. performed both Wada test and functional TCD with the same word generation task in 13 patients with temporal lobe epilepsy (Knake et al., 2003). fTCD could not be performed in two patients. Among the remaining 11 patients, 9 had left, 1 right, and 1 bilateral language representation. In all patients, the fTCD was in agreement with the Wada test, and the laterality indices for both techniques were highly correlated.

The main limitation of fTCD in both studies presented above is that some (15–21%) subjects lack an acoustic temporal bone window for insonation of the middle cerebral artery. In addition, the two fTCD studies had a relatively small number of patients with atypical representation. The fTCD method may be limited in individuals with bilateral language representation.

**Single photon emission computed tomography (SPECT)**

SPECT assesses regional changes in cerebral blood flow by imaging the brain distribution of a radioligand injected intravenously. The most commonly used radioligand is 99mTc-HMPAO (hexamethylpropylene amine oxime). By comparing activation and baseline regional blood flow, changes associated with activation can be localized and lateralized. Borbely et al. (2003) evaluated SPECT in 17 patients with epilepsy or arteriovenous malformations, all undergoing presurgical evaluation. Patients also had simultaneous fTCD. At baseline the patients were placed in a quiet room with eyes covered for 15 min prior to the administration of HMPAO. For the speech activation study the patients were also placed in a quiet room with eyes covered, but also started to speak continuously about a chosen topic. Following 20 s of spontaneous speech, HMPAO was administered intravenously. The SPECT images were analyzed visually and with special regions of interest placed over the frontal, temporal, parietal, and occipital cortex. Changes in the asymmetry index in the posterior inferior frontal cortex identified the dominant hemisphere. fTCD and SPECT agreed in every case and there were no inconclusive results. Two patients had right hemisphere dominance and 15 appeared left hemisphere dominant. The Wada test was not used or not reported in this series of patients. Thus SPECT has not been directly compared with the Wada test. Another limitation of SPECT is that the baseline and activation studies have to be performed on separate days due to persistence of HMPAO in the brain.

**Positron emission tomography (PET)**

PET using 15O-water, which identifies regional changes in cerebral blood flow, has been used extensively for functional mapping of cognitive processes. Two studies specifically compared language activation PET with the Wada test. Hunter et al. (1999) studied 12 right-handed patients with intractable seizures using visual responsive naming and auditory responsive naming. The tasks began 1 min before the ligand injection and continued during 1 min of data acquisition. The PET analysis used visual assessment as well as circular regions of interest centered on the highest intensity pixel within each of the angular gyrus, the inferior frontal gyrus, the superior temporal gyrus, and the calcarine cortex. Three raters who assessed the studies visually identified activation as left, right, or indeterminate. The two cognitive tasks were equally effective as activating stimuli. The inferior frontal gyrus was activated with both tasks, but during visual responsive naming there was a greater tendency to activate the dominant angular gyrus than the inferior frontal gyrus. By the Wada test, 10 patients had left hemisphere language dominance and two had right dominance. With the PET region of interest analysis, seven patients had left, one had right, one had bilateral, and three had no activation. There were no complete discrepancies between the visual and region of interest analyses, but not all three raters were able to identify one dominant hemisphere. Three raters lateralized language in eight cases, two raters in two cases, one rater in two cases. One patient had total disagreement between PET and the Wada test, PET suggesting left hemisphere dominance, while the Wada test suggested right hemisphere dominance. After a left anterior temporal lobectomy, the patient had difficulties with object naming, word finding, reading, and auditory comprehension, suggesting that PET may have been correct.

Tatlidil et al. (2000) evaluated blood flow PET in 24 patients and compared the results with the Wada test. The PET activation task was verb generation from words and/or pictures. The lateralization of language was determined with the language lateralization index using activation volumes for each hemisphere in the regions of the inferior frontal cortex, the supramarginal gyrus, and the superior temporal gyrus. The two tests were discordant in only one of the 24 patients. This patient who had left hemisphere dominance on Wada test and right hemisphere dominance on PET underwent a right temporal lobectomy and experienced a decline in verbal functions, suggesting that the PET determination of language dominance may have been more accurate.

The evidence above suggests that PET using 15O-water can be used to lateralize and localize language functions.
However, PET is not available in all medical centers and \(^{15}\text{O}\)-water availability depends on access to a cyclotron for ligand generation. In addition, radioactivity limits the number of times that a PET scan can be repeated.

**ALTERNATIVE METHODS BASED ON HEMODYNAMIC RESPONSES TO ACTIVATION OF LANGUAGE AREAS—ASSESSMENT OF INCREASED BLOOD OXYGENATION**

When a region of the brain is activated, resulting in increased regional blood flow, the increased supply of oxygenated hemoglobin exceeds the demand for oxygen, resulting in increased concentration of oxyhemoglobin compared to deoxyhemoglobin. This relative change is the basis for near infrared spectroscopy and fMRI.

**Near infrared spectroscopic (NIRS) mapping**

NIRS is a noninvasive method that utilizes the near infrared light absorption characteristics of hemoglobin to estimate real time changes in cerebral blood flow a few centimeters below the scalp. The method makes use of the fact that light in the near infrared range can pass through skin, bone, and other tissues and has characteristic absorption bands for oxygenated and deoxygenated hemoglobin. The measuring instrument consists of fiber optic bundles. Light enters the head through one bundle and a fraction of the photons are captured by a second bundle and conveyed to a measuring device. Multiple light emitters and detectors can be used. Cerebral activation usually results in an increase in blood flow that is disproportionate to the metabolic rate for oxygen. Regions that are activated will have a greater oxygenation and a greater ratio of oxyhemoglobin to deoxyhemoglobin. Therefore, NIRS can be used to evaluate superficial changes in blood flow with language tasks.

Watanabe et al. (1998) studied 11 healthy volunteers and 6 patients with intractable epilepsy using a word generation task in which the subjects were instructed to generate as many words as possible beginning with a letter presented on a computer screen, and to write down the words on a sheet of paper. Then they were told to stop and switch to copying a picture of a landscape presented on the computer screen using similar hand movements. A laterality index was calculated. The highest ratio of activation was in the inferior frontal region. Healthy volunteers showed activation of the inferior frontal region opposite the side of handedness. Patients with epilepsy had a predominant activation that agreed with dominance determined by the Wada test.

Watson et al. (2004) studied 16 patients and 8 healthy right-handed individuals using a word generation paradigm. Patients had both NIRS and the Wada test, but the NIRS was performed postoperatively in 10 patients. Subjects were given 10 opportunities to write down as many words as possible beginning with a randomly presented letter on a computer monitor. In between presentations, subjects were instructed to focus on copying a picture of a European city for 60 s during which the baseline was established. An asymmetry index was used to evaluate the inferior frontal region. NIRS identified the cerebral hemisphere dominant for language in agreement with the Wada test in 11 of the 16 patients, including 2 of the 3 with atypical speech. Four of the 5 patients that were incorrectly lateralized had testing after epilepsy surgery, 5 of the 6 tested preoperatively were accurately lateralized as opposed to 6 of the 10 tested after surgery.

NIRS studies have included only a limited number of patients and in particular a limited number of individuals with atypical language distribution. It is also limited to detection of blood flow changes in the superficial cortex. Nevertheless, it has attractive features, including portability of equipment, lower expense, and some potential for regional localization, that justify exploring it further.

**Functional magnetic resonance imaging (fMRI)**

The fMRI technique has received the most attention as a replacement for the Wada test. It is based on blood oxygenation level dependent (BOLD) contrast. The increase in cerebral blood flow in activated brain areas surpasses the increase in metabolic rate for oxygen, which produces an overall increase in capillary and venous oxygenation level and a decrease in the relative concentration of deoxyhemoglobin. Deoxyhemoglobin is paramagnetic. A relative reduction in deoxyhemoglobin concentration and increase in oxygenated hemoglobin results in increased BOLD signal. The fMRI technique requires considerable mathematical statistical processing, but the MRI technology is widely available and fMRI is likely to be the method that is most accessible in medical centers around the world. Since language activation tasks are also likely to activate visual, auditory, or other nonlanguage areas, language activation maps usually require controlled tasks that activate nonlanguage cortex equally. A variety of language paradigms have been used in this process, with variable results (Table 2). The regions activated vary, as does the consistency with which this activation occurs. There have been numerous fMRI studies of language, and more than 25 publications that have compared the fMRI with the Wada test. Only some of the studies that compared fMRI with the Wada test can be considered here. These studies have varied in the fMRI language tasks, the fMRI analysis, fMRI scoring, and fMRI classification of language dominance, as well as in the Wada test technique and scoring. For quantitative analysis, the most common measurements of activation were measurement of total activation in a defined region of interest or measurement of activated volume after application of a threshold. A laterality index was then usually applied based on the difference between left and right activation divided by the sum of the two activations.
TABLE 2. Selected single activation tasks used for determination in cerebral dominance with fMRI

<table>
<thead>
<tr>
<th>Task</th>
<th>Control</th>
<th>Region(s) with predominant (relevant) activation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squeeze a ball according to the abstract or concrete nature of</td>
<td>Squeeze a ball depending on whether word is in upper- or lowercase</td>
<td>Inferior frontal</td>
<td>Desmond et al., 1995</td>
</tr>
<tr>
<td>visually presented words</td>
<td>letters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Press button when a heard noun belonged to an animal native and</td>
<td>Press button when sequence of tones contained two high-pitched tones</td>
<td>Lateral frontal and tempo-parieto-occipital junction</td>
<td>Binder et al., 1996</td>
</tr>
<tr>
<td>commonly used by humans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generate words that begin with a specific letter, silently</td>
<td>None</td>
<td>Inferior frontal gyrus and precentral gyrus</td>
<td>Yetkin et al., 1998</td>
</tr>
<tr>
<td>Generate semantically related verb to a concrete noun, silently</td>
<td>Fixation on a cross hair</td>
<td>Multiple foci, predominantly frontal</td>
<td>Benson et al., 1999</td>
</tr>
<tr>
<td>Generate words from a given semantic category, silently</td>
<td>None</td>
<td>Frontal lobe, particularly inferior frontal gyrus and sulcus (only 50% had posterior temporal activation)</td>
<td>Lehericy et al., 2000</td>
</tr>
<tr>
<td>Repeat short sentences mentally</td>
<td>None</td>
<td>Bilateral superior temporal gyrus/inferior parietal area (only 50% had frontal activation)</td>
<td>Lehericy et al., 2000</td>
</tr>
<tr>
<td>Listen to a story</td>
<td>Listen to same story played backwards</td>
<td>Temporal and inferior parietal areas, 60% had frontal activation</td>
<td>Lehericy et al., 2000</td>
</tr>
<tr>
<td>Press button for sentences correct or incorrect (visual or auditory</td>
<td>Press button for sentence pitch similarity to tones or length</td>
<td>Inferior frontal</td>
<td>Carpentier et al., 2001</td>
</tr>
<tr>
<td>presentation)</td>
<td>similarity to lines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Push button if word pairs were synonyms</td>
<td>Push button if pairs of unpronounceable consonant strings had identical letters</td>
<td>Inferior and middle frontal, temporoparietal junction</td>
<td>Fernandez et al., 2001</td>
</tr>
<tr>
<td>Name in response to definition presented visually, covertly</td>
<td>See patterns of dots</td>
<td>Posterior temporal, inferior frontal</td>
<td>Gaillard et al., 2002</td>
</tr>
<tr>
<td>Find a pair of synonyms out of a set of five words presented</td>
<td>Find an identical color out of a set of five colors presented simultaneously (answer by pressing one of four keys)</td>
<td>Lateral frontolateral, temporoparietal</td>
<td>Spreer et al., 2002</td>
</tr>
<tr>
<td>simultaneously (answer by pressing one of four keys)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

One study suggested statistical analysis and measurement of regions in which left and right activations are statistically different. Some studies investigated the adequacy of qualitative review by an experienced investigator. Despite the differences between studies, it is remarkable that most studies lateralized language by fMRI in agreement with the Wada test in most individuals. Select studies are described, chosen based on specific testing paradigms and fMRI analysis methods.

The first published study from Desmond et al. (1995) used a task of visually presented words, half of which were abstract and half concrete. Half of the words appeared in uppercase letters and the other half in lowercase letters. The patient’s task was to press a squeeze ball with the right hand according to the abstract or concrete nature of the word. The control task was to squeeze the ball depending on whether the word was in uppercase or lowercase letters. The task activated inferior frontal regions predominantly. Frontal activation was measured in inferior frontal regions of interest (ROI), and the magnitude of activation in the left and right ROIs was used for a lateralization index (R−L)/(R+L). There was a perfect agreement between the Wada test and the fMRI: four patients who were left hemisphere dominant for language by Wada test had negative fMRI laterality index and three who were right hemisphere dominant by Wada test had a positive index.

Binder et al. (1996) investigated 22 patients undergoing evaluation for epilepsy surgery with a different fMRI language task. The subjects heard spoken English nouns designating animals and had to pick animals native to the United States and commonly used by humans. The control task was hearing brief sequences of tones, with low or high pitch and picking a sequence that contained two high-pitched tones. An fMRI laterality index was calculated using the activation volumes for left and right hemispheres. The Wada and the fMRI were concordant in all cases. Eighteen patients had strong left hemisphere dominance for language by the Wada test and the same 18 also showed clear left hemisphere dominance by fMRI. The four remaining patients had atypical language distributions by both Wada and fMRI and were clearly separated from the left dominant group in the laterality index. Correlation between the laterality index of the Wada and the laterality index of the fMRI was very high. The main foci of language activation were in the lateral frontal lobe and tempo-parieto-occipital junction in all subjects. The validity of the fMRI in defining language dominance may be best tested practically by its prediction of language disturbance following dominant hemisphere resections. Using
the same fMRI paradigm above, Sabsevitz et al. (2003) investigated the prediction of language deficits by both the Wada test and the fMRI in 24 patients undergoing left anterior temporal lobectomy. Both tests were predictive of naming outcome, but fMRI showed greater sensitivity and specificity in predicting >2 standard deviation drop in naming 6 months postoperatively.

Word generation tasks have been frequently used in studies comparing the fMRI and the Wada test, and appeared superior to reading, naming, or repetition tasks. Yetkin et al. (1998) studied 13 patients with a word generation task and used the number of activated pixels in each hemisphere as the basis for a laterality index. The fMRI activation was in the frontal lobe. It was concordant with the Wada lateralization in all 13 cases. Benson and colleagues (1999) studied volunteers and patients with brain lesions using three language tasks including object naming, single word reading, and verb generation. In right-handed volunteers, the verb generation task was left hemisphere lateralized in all 10 patients while the reading task was left lateralized in 7 of 10 and the naming task in 5 of 7. As a result, the word generation task (generating a semantically related verb to a concrete noun) was used in patients. In 12 patients who had both Wada test and fMRI, there was a concordance in all 12. Three of these had atypical language representation. Woermann et al. (2003) compared the fMRI during covert word generation and the Wada test in 100 patients with a variety of partial epilepsies. The determination of fMRI language dominance was based on visual assessment of frontal and temporal activation maps. Frontal activation was noted in all, but 17% had no posterior language activation. The authors found 91% concordance between the two tests. The highest rate of false categorization by fMRI was 25% in left-sided extratemporal epilepsy. The authors concluded that fMRI with the word generation task may be more useful as a replacement for the Wada test in patients with temporal lobe epilepsy. Lehericy et al. (2000) studied 10 patients with temporal lobe epilepsy using three tasks, semantic verb fluency, covert sentence repetition, and story listening. A laterality index was based on the number of activated voxels in the left and right hemispheres. The asymmetry of frontal (not temporal) activation with semantic verb fluency and story listening was correlated with Wada laterality, while covert sentence repetition showed no correlation. Of note is that with the semantic fluency test, activation was observed in the posterior temporal parietal areas in only five patients. The covert sentence repetition and the story listening activated superior temporal and inferior parietal cortex in all 10 patients studied, but temporal asymmetry did not correlate with Wada laterality. In a subsequent study of patients with arteriovenous malformations, the authors found that flow abnormalities may interfere with lateralization of language by fMRI (Lehericy et al., 2002).

The word generation task most reliably activates frontal cortex (Fig. 2A). Since epilepsy surgery most often involves the temporal lobe, it is important to find tasks that reliably activate temporal language sites. Gaillard et al. (2002) succeeded at that by using a task of naming objects based on a visually presented definition. They tested 21 patients with both fMRI and Wada test. Most patients had lateralizing activation in both frontal and temporal regions (Fig. 2B), while in most previous studies temporal activations were not well lateralized. fMRI provided lateralizing activation in 90% of patients, and visual assessment and quantitative analysis provided similar results that agreed.
with the Wada test lateralization, except where one test suggested unilateral dominance while the other favored bilateral representation. In a subsequent study, the same group evaluated 26 patients with both the Wada test and the fMRI using a battery of tasks (Gaillard et al., 2004). They found the panel superior to any single task with respect to interrater agreement. However, there were still some disagreements between the fMRI panel and the Wada test when it came to distinguishing between unilateral dominance and bilateral speech representation.

Rutten et al. (2002) also tried to improve the detection power of fMRI for hemispheric language dominance with a panel of four tasks, but used a statistical manipulation strongly favoring activity that occurs in all tasks as compared to activity in one subset of tasks. They studied 11 patients with left dominance, three with right dominance and four with bilateral language representation by Wada test. The analysis method yielded more robust and more reliable results than any of the individual task analyses, and both frontal and temporal lateralized activations were noted with the combined method. However, the fMRI classification was not concordant with the Wada test for one patient in each language dominance group. Nevertheless, it was clear that this method was superior to single task analysis for patients with bilateral representation by the Wada test. The verb generation task, which was the best individual task, only identified one of the four bilateral representation patients. In addition to identifying three of the four patients with bilateral representation, the new combined analysis demonstrated dissociation between right frontal and left temporoparietal activations in these three patients. Another statistical manipulation that was reported to improve concordance with the Wada test and to reduce variability is a method that bases lateralization on the direct statistical comparison of the magnitude of task-induced activation in homotopic regions of the two hemispheres. The method identifies regions in which left and right task-induced activations are statistically different (Liegeois et al., 2002).

Not all fMRI studies had an equally high correlation with the Wada test. Benke et al. (2006) studied 68 consecutive epilepsy patients undergoing presurgical work-up, using an adaptation of the semantic decision paradigm used by Binder et al. (1996). Patients were given nouns designating common objects and responded by pressing a button “yes” for objects they considered to be available in a supermarket and to cost less than 7 euros (Benke et al., 2006). The fMRI activation maps were interpreted by visual rating to reproduce clinical everyday procedure. Frontal and temporoparietal regions were rated separately. All patients showed activations in the frontal and temporoparietal areas, mostly asymmetrical. Overall, a high correspondence between language fMRI and the Wada test was found in only 79% of patients. The correspondence between the fMRI and the Wada test was higher in right temporal lobe patients and when frontal activations were judged. The authors concluded that perhaps semantic decision is not the best test for language lateralization.

It seems clear that both the Wada test and the fMRI face challenges with patients that have atypical and bilateral language lateralization. In favor of fMRI is that the Wada test has time constraints that do not exist in fMRI. In addition, fMRI can provide localization of areas involved in language processing while the Wada test is only lateralizing. On the downside for fMRI, it is a test of activation, and an area that is activated may or may not be necessary for the language task. In addition, it is difficult to dissociate true activations from spurious ones. The use of thresholding can both help and hurt. A low threshold may result in bilateral activation as well as spurious unrelated activation, which may drown the dominance affect. A high threshold may mask activation of the other hemisphere and suggest a unilateral language representation where it really was bilateral. One suggested solution is region of interest analysis in known language areas without thresholding (Kloppel and Buchel, 2005). However, localization of language areas may vary tremendously between patients and such method may miss displaced language representation.

**COMPARISON OF NONINVASIVE METHODS FOR CEREBRAL DOMINANCE**

Based on the findings summarized above, the Wada test cannot be replaced by structural MRI measurements or by ERP topographical analysis, for individual determination of dominance. It also appears that repetitive transcranial magnetic stimulation is not yet reliable for individual determination of language dominance. fTCD is a reasonable alternative for pure lateralization of dominance, but it requires additional validation, particularly with patients who have atypical language representation. NIRS is another option for lateralization, mainly for frontal dominance. One comparative study found that when there was strong lateralization by fMRI, there was also strong lateralization by NIRS (Kennan et al., 2002). NIRS has an advantage of not being affected by head movement because the probes are mounted firmly on the head, and therefore provides freedom in task design that allows the monitoring of output (not possible with silent motionless tasks). The method is also much less expensive than the Wada test, PET, or fMRI, and easy to use without the need for specialized rooms. However, it is limited to monitoring of superficial cortical activation. It also requires additional validation due to small number of subjects tested and the lack of reliability in one study that included operated patients. PET and fMRI are similar in many respects, but PET involves the administration of radioactive ligands, which limits the number of times that a study can be repeated. In addition,
PET is not widely available. SPECT is widely available and is an alternative technique if fMRI is not. However, additional studies would be needed to validate it. Baseline and activation SPECT scans have to be performed on separate days. SPECT also uses radioactive ligands. Both SPECT and PET have a low spatial resolution compared to fMRI. One study that compared PET and fMRI in verb generation task found 92% of PET activations duplicated by fMRI, but fMRI detected 64% more activations than PET (Xiong et al., 1998).

fMRI is the leading candidate to replace the Wada test, due to its wide availability, its high resolution and its ability to provide both localization and lateralization. However, fMRI has many limitations. The key one is serious degradation by motion artifact that makes it not possible in an individual who cannot be still. The presence of metal in the head or a pacemaker precludes fMRI. The presence of large structural lesions and high flow vascular malformation can result in false fMRI lateralization and localization. Patients who are claustrophobic or excessively obese also cannot have the test. Furthermore, many of the language tasks used are covert and silent such that there is no way to determine that the patient has actually followed the requested task. A method to verify vigilance to the task and cooperation would be desirable.

fMRI needs to be more fully standardized with respect to the optimal language tasks used and the optimal method of analysis.

MEG is a very promising method for language localization. Unlike fMRI, which evaluates the hemodynamic response to cerebral activation, MEG directly measures neurophysiological activation and has a very high temporal resolution that can exclude from consideration earlier activation of primary sensory cortex. It may also be superior in instances where the hemodynamic response to activation could be disrupted due to the presence of structural lesions such as vascular malformations. However, MEG has not been as widely tested as fMRI and is not yet widely available in medical centers.

**CONCLUSIONS**

Several methods provide sufficiently good lateralization of language representation that they could be considered reasonable alternatives to the Wada test. For all alternative methods to determine language dominance, standardization will be essential before widespread application. In addition, these tests may replace the Wada test only in instances where determining memory distribution is not essential and only language dominance is needed before surgery. Among the modalities discussed, only MEG and fMRI have potential to provide the memory component of the Wada test (Table 1). Several studies suggest that they have promise in the identification of memory lateralization and memory reserves (Breier et al., 1999; Rabin et al., 2004; Richardson et al., 2004; Janszky et al., 2005), but they are not quite ready to replace the Wada test for that purpose. Of these two modalities, it is likely that fMRI will be the most widely used method to replace the Wada test as a routine component of the presurgical evaluation. A simple algorithm for considering the use of fMRI or MEG in the localization of language dominance before epilepsy surgery is illustrated in Fig. 3.

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