Discrepant findings for Wada test and functional magnetic resonance imaging with regard to language function: use of electrocortical stimulation mapping to confirm results

Case report

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The Wada test is still considered the gold standard for determining the language-dominant hemisphere prior to brain surgery. The authors report on a 34-year-old right-handed woman whose Wada test results indicated that the right hemisphere was dominant for language. In contrast, functional magnetic resonance (fMR) imaging was indicative of bilaterally represented language functions. Activation in the left hemisphere demonstrated on fMR imaging was most pronounced in the Broca area. Importantly, fMR imaging results in this area were confirmed on electrocortical stimulation mapping. These contradictory findings indicated that a right hemisphere dominance for language according to the Wada test should be questioned and verified using electrocortical stimulation. Nonetheless, the question remains whether involvement of these areas in the left frontal hemisphere is critical for language, as these were spared during surgery.

KEY WORDS • functional magnetic resonance imaging • Wada test • electrocortical stimulation • language • brain mapping • epilepsy

Epilepsy surgery is performed to relieve the patient of seizures by removal of epileptogenic tissue. To avoid damage to critical language structures and to prevent postoperative aphasia, the neurosurgeon can rely on two clinical procedures: the intracarotid artery amobarbital (or Wada) test and ESM. For approximately half of the previous century, the invasive Wada test has been the gold standard for assessment of the language-dominant hemisphere. This procedure mimics functional deficits that might follow surgery by temporarily inactivating one hemisphere with the use of a short-acting barbiturate agent (sodium amobarbital). Despite good clinical results, authors of several studies have questioned the validity of the Wada test and asserted that it is not infallible. For instance, the incidence of left, right, or bilateral language representation widely varies among the different epilepsy centers, indicating that differences in methodology may affect outcome of the Wada test.

Electrocortical stimulation mapping is used for more precise localization of critical language areas. By definition, this method is undertaken in an awake patient. Performed intraoperatively, the procedure has practical problems. The anesthesia-related risk of morbidity or death aside, factors such as operating room settings, limited testing time, and, most importantly, patient cooperation may complicate interpretation of test results. The emerging use of intracranial electrode grids allows for extraoperative ESM. The latter method allows for prolonged testing of large neocortical areas by using different language tests, without restrictions on time and the effects of anesthesia. Whereas the Wada test is usually regarded as the gold standard for language lateralization, ESM is considered the gold standard for language localization.

Functional magnetic resonance imaging is a noninvasive method of determining whole-brain functional neuroanatomy preoperatively. It is generally considered a very promising method with which to replace the Wada test. Discrepancies between Wada test and fMR imaging results are difficult to resolve because there are usually no other standards against which results can be compared. We report on a patient in whom Wada test results indicated exclusive right-hemisphere language dominance, whereas both fMR imaging and ESM studies revealed language areas in the left inferior frontal lobe (Broca area).
Case Report

Summary of Case. This 34-year old right-handed woman had suffered from medically intractable epilepsy since the age of 9 years. She was admitted to the Dutch Collaborative Epilepsy Surgery Program to evaluate the possibility of undergoing epilepsy surgery. She suffered from complex partial seizures with automatisms and postictal confusion. Although there was no spontaneous speech during seizures, comprehension was good and there was no sign of postictal aphasia. Findings on preoperative neurological and neuropsychological evaluations (including language testing) were normal (Wechsler Adult Intelligence Scale: verbal intelligence quotient 114, performance intelligence quotient 112). Results of MR imaging revealed left-sided mesial temporal sclerosis and a lesion at the left temporoparietal junction, indicative of focal cortical dysplasia. Scalp EEG indicated a left anterior temporal seizure propagation but could not exclude a more posterior source of onset. It was therefore decided to pursue invasive monitoring. Results of subdural electrode grid monitoring supported mesiotemporal but not posterior neocortical involvement in seizure generation. Consequently, a left anterior temporal resection was performed with total amygdalohippocampectomy was performed. One year after this procedure the patient is still seizure free. Prior to surgery, language functions were assessed with the use of fMR imaging as part of a research protocol, for which the patient gave written informed consent. Clinical evaluation included a Wada test, which is routinely performed before electrode implantation, and ESM via subdural grid electrodes. The Wada test was used to establish language lateralization and contralateral memory function.

Wada Testing. The Wada test involved the injection of 125 mg sodium amobarbital into the internal carotid artery via transfemoral catheterization and was monitored through EEG and video recording. Language and memory were assessed using a standardized protocol. There was no contralateral transfer of contrast medium exhibited on angiography.

The patient underwent two Wada tests on two different occasions. On the first occasion amobarbital was injected on the left side. She immediately exhibited right-sided hemiparesis. Verbal comprehension was normal, but naming tasks were difficult to interpret because the patient had problems with her vision. This was probably caused by her right-sided hemianopia and left-sided ptosis. When her left eyelid was raised manually 45 seconds after amobarbital injection, she correctly named objects. We decided to repeat the left-sided injection to exclude any bias in test results. Again, a right-sided paresis occurred but now there was no ptosis. The patient was immediately able to name familiar objects. When asked about her job, she related details in fluent, grammatically correct sentences. On right internal carotid artery injection, which had been planned for another day, there was a clear left-sided hemiparesis and instantaneous mutism lasting for 40 seconds, after which object naming was disturbed by paraphasia and perseveration. She also lost the ability to comprehend simple verbal commands and to describe fluently and grammatically the Cookie Theft Picture of the Boston Diagnostic Aphasia Examination. Dysphasia lasted for at least 4.5 minutes. On all three Wada tests, EEG asymmetry after injection lasted more than 5.5 minutes and there were no contralateral changes. Videotapes of all sessions were reviewed by four observers (two neuropsychologists, a clinical neurophysiologist, and a neurosurgeon). Their unanimous conclusion was that critical language functions resided exclusively in the right hemisphere.

Functional Magnetic Resonance Imaging. Blood oxygen level-dependent fMR images were obtained prior to surgery by using the technique of three-dimensional navigated principles of echo shifting with a train of observations (PRESTO). Language tasks and image analysis procedures have been described in detail elsewhere. In short, a conjoint analysis was performed on four visually presented language tasks: picture naming, verb generation, letter fluency, and sentence comprehension. This analysis targets brain areas commonly activated by multiple language tasks, thereby focusing on regions critical for language processing. In a previous study in which we used this same protocol, we showed that typical—that is, left-hemisphere dominant—patients can be reliably distinguished from atypical ones.

Significant fMR imaging activity was demonstrated in both hemispheres with an asymmetric distribution (Figs. 1 and 2A). In each hemisphere, eight regions of interest were segmented manually on an anatomical MR image, blinded for fMR imaging activity. An LI was calculated as 100(L−R)/(L+R), where L and R are the number of significant voxels in the left and right hemispheres, respectively. The LI was 30 when activity in all ROIs was combined. The LIs for frontal and temporoparietal ROIs were 39 and −13, respectively. In particular the left inferior frontal gyrus and sulcus showed enhanced activity. Data from a previous study by our group has shown that an LI greater than 75 is always predictive of left-sided language representation and that a low LI correlates with bilateral or right-sided language representation. Therefore, we concluded that language representation in the patient in the present report was bilateral.

Grid Implantation and ESM. A total of 104 subdural grid electrodes were implanted via an extensive left-sided trepanation (Fig. 2B). A computerized tomography scan was ob-
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The ESM was conducted using a stimulator (Grass-Telefactor, West Warwick, RI) with 5-second trains of 50 Hz in 0.2-msec biphasic blockpulses at 5 to 8 mA between adjacent electrode pairs. Stimulation was applied between both horizontal and vertical pairs and, in case of positive findings, also diagonally. First, all grid electrodes were systematically investigated using a normal picture-naming task with standard black and white line drawings (bare nouns) and the Token Test (a sensitive test used to detect comprehension disturbances). No language errors were noted during stimulation of temporal and parietal sites, although stimulation over the left inferior frontal gyrus reproducibly elicited speech arrest and paraphasia during the picture-naming task, thus implying that this area plays a critical role in language production. No errors were observed during the Token Test.

On subsequent days, these positive electrode sites as well as neighboring electrodes were tested again. Disruption of picture naming was replicated and thus confirmed. Next, we applied a modified version of this task, which required the patient to start naming with the carrier phrase, “This is a . . .” followed by a noun depicted in a picture. This led to pure naming errors in that during stimulation the patient was indeed able to say “This is a” but was unable to name the picture. We then applied a test for assessing syntactic comprehension, which consisted of auditorily presented sentences with varying degrees of syntactic complexity and prompted the patient to point to a corresponding picture. Sentences were presented during stimulation. The patient in the present case correctly understood all different degrees of syntactic complexity according to the electrodes in the inferior frontal gyrus.

Based on ESM, we concluded that the left inferior frontal gyrus contained specific language production facilities and was critically involved in naming objects. This area corresponded with the location of fMRI imaging activity (Fig. 2C).

Discussion

The Wada test is the current gold standard for assessment of hemispheric language dominance. In the patient in the current study, the Wada test indicated right-hemisphere dominance—results at odds with findings on both fMRI imaging and ESM, which detected left inferior frontal language areas.

To our knowledge, only two studies have featured a discrepancy between Wada test results and ESM or postsurgical language outcome. Hunter, et al., described a patient who showed left-hemisphere dominance according to acti-

Fig. 2. A: Brain activity (red voxels) from the combined analysis of four language tasks as depicted on a surface rendering of the left and right hemispheres in the patient. B: Position of electrode grids on the patient’s brain. The temporoparietal lesion is marked in purple. C: View of electrode positions relative to fMRI imaging activation. The positions that reliably induced naming errors on stimulation are marked with a green line. Note that fMRI imaging activation is not shown for deeper layers of the cortex.
vation positron-emission tomography scanning during language tasks, whereas the Wada test indicated right-hemisphere dominance. After a left temporal lobectomy, the patient demonstrated language impairments that persisted for 6 months, thus supporting the positron-emission tomography scanning data. Wyllie, et al., reported that in two of nine right-handed patients who were right-hemisphere dominant according to the Wada test, electrocortical stimulation revealed language areas in the left hemisphere.

There are several ways to interpret the discrepancies among the results of these three tests (Wada, ESM, and fMR imaging) in the well-documented case featured in the present report. One might question both the fMR imaging and ESM results. Both techniques are routinely performed at our hospital and proceeded without difficulty in this particular case. Moreover, the tests yielded similar results. Predicting whether resection will result in language deficits is normally based on sites where ESM repeatedly interferes with naming tasks. Resection of brain tissue within 1 cm of ESM-detected language sites is thought to be correlated with postoperative dysphasia, but this hypothesis is not substantiated with scientific evidence. Although presurgical fMR imaging is still experimental, in our hands the paradigm yields an LI that is reproducible and demonstrates robust activity patterns that can differentiate between typical and atypical patients.

One might also argue that the language areas detected on ESM and fMR imaging were not critical in the sense that lesioning of these areas would not cause postoperative language deficits. Perhaps electrocortical stimulation causes transcallosal stimulation of contralateral homotypical areas in that way affected language. Transcranial magnetic stimulation, a technique that affects cortex with a magnetic pulse, has been shown to exert effects on the contralateral hemisphere. This possibility has not been raised in the ESM literature; however, this hypothesis leaves open the question of whether the stimulated area is critical. For obvious ethical reasons, no one has ever attempted or described resection of ESM-detected language areas. With regard to the fMR imaging data, note that our imaging paradigm consists of four different language tasks and that the analysis is optimized to detect regions active in multiple tasks, thereby favoring the likelihood that detected areas are significant for general language functions.

Should we reconsider the Wada test outcome? At our institute more than 600 bilateral amobarbital tests have been performed since 1986. Based on the angiography studies, the EEG asymmetry, and the clinical manifestations obtained in the featured case, we are confident that the procedure was technically correct; interpretation of the results was straightforward. One might speculate that if this case represents true bilaterality of language, anesthesia of the left hemisphere was not sufficient to disrupt language function at a level detectable by using the Wada test. The fact that anesthetizing the right hemisphere did disrupt language would then imply a differential effect of amobarbital on both hemispheres.

Conclusions

In summary, this case leaves us with several questions. Nevertheless, we concluded that an exclusive right hemisphere language dominance as indicated on the Wada test should be questioned. It would probably be wise to reexamine such a finding by using an ESM procedure, as suggested by Wyllie, et al., or fMR imaging. This case also demonstrates that recent developments in functional neuroimaging may have potential for clinical use in the preoperative assessment of hemispheric language dominance and localization. Indeed, left hemisphere involvement in language was only suspected after preoperative fMR imaging language assessment in a scientific setting.

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References


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