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Non-invasive alternatives to the Wada test in the presurgical evaluation of language and memory functions in epilepsy patients

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ABSTRACT – The cognitive outcome of the surgical removal of an epileptic focus depends on the assessment of the localisation and functional capacity of language and memory areas which need to be spared by the neurosurgeon. Traditionally, presurgical evaluation of epileptic patients has been achieved by means of the intracarotid amobarbital test assisted by neuropsychological measures. However, the advent of neuroimaging techniques has provided new ways of assessing these functions by means of non-invasive or minimally invasive methods, such as anatomical and functional magnetic resonance imaging, positron emission tomography, single-photon emission computed tomography, transcranial magnetic stimulation, functional transcranial Doppler monitoring, magnetoencephalography and near infrared spectroscopy. This paper aims at comparing and evaluating the traditional and recent preoperative approaches from a neuropsychological perspective.

Key words: epilepsy surgery, neuroimaging technique, intracarotid amobarbital test, language, memory

Surgery to remove epileptic brain tissue (*i.e.*, lobectomy, lesionectomy, hemispherectomy) is a widely used and effective treatment for patients suffering from intractable seizures (Gates and Dunn 1999). It has been demonstrated that the outcome of neurosurgery at the one-year follow-up is superior to that of medical therapy in these cases (Wiebe *et al.* 2001). The goal of the surgery is to remove the epileptogenic tissue without causing additional neurological or neuropsychological deficits while providing complete seizure control and improved quality of life. The outcome of the surgery depends on accurate localization and lateralization of the epileptogenic zone as well as on the functional efficacy of the cerebral zones which need to be spared in the surgical intervention, especially language and memory areas.

The exact brain regions controlling language functions vary considerably between patients and must be individually determined prior to surgery. This applies specifically to frontal lobe

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and temporal lobe resection. For patients undergoing other types of surgery, such as amygdalo-hippocampectomy, language lateralization may not be required as emphasis is rather put on memory assessment in these cases.

Until recently, the intracarotid amobarbital test or Wada procedure has been the only and most widely used technique in the presurgical evaluation of language lateralization and memory functions in candidates slated for temporal and frontal lobectomy (Fried 1993). However, the procedure is invasive and uncomfortable for most patients. Furthermore, to determine hemispheric dominance for language and unilateral memory capacities, the two hemispheres have to be assessed separately, which involves repetition of the procedure and more discomfort for the patient.

Over the past decade, functional neuroimaging techniques such as fMRI and PET have found growing application in neurology and neuropsychology. These methods allow to indirectly measure neuronal activity by means of oxygenation, blood flow and metabolism. The difference in activation levels between the two hemispheres, while the patient performs a language task, can be used to estimate laterality. These techniques are non-invasive or minimally invasive and present fewer risks for the patient. For this reason, many epilepsy centers have started to replace the traditional Wada method with these non-invasive imaging techniques in the presurgical exploration of language lateralization and memory. This trend has been accelerated by a recent shortage of the amobarbital product (Grote and Meador 2005). The present paper aims at evaluating each of these non-invasive techniques and comparing them with the traditional Wada procedure.

Invasive methods of language and memory exploration

Intracarotid amobarbital test (IAT)

The procedure, first described by Wada in 1949, consists of unilateral injection of sodium amobarbital into the internal carotid, which temporarily anaesthetizes the hemisphere ipsilateral to the injection site. While one hemisphere is anaesthetized, language and memory functions of the hemisphere contralateral to the injection site can be tested. After the effect of the anaesthesia has dissipated, the process is repeated with the other hemisphere. In most centers, the procedure is carried out on different days.

IAT and language lateralization

Numerous studies using IAT have revealed a relatively high incidence of atypical right hemisphere or bihemispheric representation of speech in epileptic patients (Helmstaedter and Kurthen 1997, Ogden 1988, Rasmussen and Milner 1977, Staz *et al.* 1988). This phenomenon has been linked to early brain lesions and weaker right hand dominance in this population (Springer *et al.* 1999). In particular, early insult to the left hemisphere bears a greater risk of transfer of language to the right hemisphere or shared language functions between the hemispheres due to the plasticity of the immature brain (Rasmussen and Milner 1977).

To test cerebral dominance for language, the patient has to perform a number of simple tests involving expressive and receptive language. While protocol and procedure may vary between centers, tasks usually include counting and object or picture naming to probe frontal language areas, and repetition, responding to verbal commands and reading to explore posterior language zones. The protocol can be adapted (*i.e.*, simplified) for children or mentally-challenged individuals as long as they possess expressive language and are able to understand the instructions. The tests are administered before the injection to provide a baseline measure and repeated after the anaesthesia has taken effect. If the hemisphere dominant for speech is anaesthetized, the patient is temporarily rendered mute. This is not the case when the non-dominant hemisphere is deactivated. When each hemisphere retains some language functions following unilateral injection, there is reason to suspect bilateral organization of speech.

IAT and memory testing

IAT is also used to assess memory functions. The tests administrated by neuropsychologists during the procedure typically consist of recalling or recognizing pictures or objects that have been shown to the patient prior to the injection (e.g. Kurthen *et al.* 1993). Memory testing during the Wada procedure serves to evaluate the ability of the healthy hemisphere to sustain memory functions after surgery. This is necessary to avoid the creation of an amnesic syndrome following temporal lobectomy (Lee *et al.* 2005, Milner *et al.* 1962, Wada and Rasmussen 1960, Wyllie *et al.* 1991). IAT memory testing can predict post-surgical memory impairment and thus plays an important role in patient selection (Chiaravalloti and Glosser 2001, Kneebone *et al.* 1995). It has been shown that patients exhibiting adequate memory capacities in the hemisphere contralateral to the lesion are considered to be good candidates for anterior temporal lobectomy (Andelman *et al.* 2006). Since memory testing during IAT has become standard procedure, global amnesia following temporal lobe resection has become rare. Only minor material-specific memory deficits have been reported in patients who performed well on the Wada test. A decline in verbal memory after left temporal lobectomy can nonetheless be observed (Holliday and Brey 2003, Wyllie *et al.* 1991), whereas a decline in non-verbal memory following right temporal lobectomy is less well documented (Chiaravalloti and Glosser 2001).

Limitations of the IAT

Although the Wada test has long been considered as the gold standard for preoperative language and memory exploration, apart from intracortical stimulation, the method has many flaws. First, as mentioned before, one major disadvantage of the IAT is that the procedure is highly invasive and quite uncomfortable for most patients. More importantly, there is a certain risk of morbidity, even death, due to complications resulting from the intracarotid cathetization (Loddenkemper *et al.* 2002; Muller *et al.* 2000). A major drawback for language assessment is that the procedure requires a verbal response of the patient. This makes it more difficult to obtain reliable results from young children and mentally-challenged patients. Finally, the Wada test only provides information about lateralization but not localization of cognitive functions.

As Loring *et al.* (1992) have pointed out there are also methodological limitations to the IAT. First, the method is not standardized across centers, and even the criteria used to determine whether or not a patient has failed the test vary between centers. Secondly, there is no consensus regarding the testing procedure and the stimuli used (*i.e.*, word lists, drawings, abstract figures, etc.) (Valton and Mascott 2004). Thirdly, the procedure is time constrained by the short action of the sodium amytal which precludes the use of more complex language and memory tests (Breier *et al.* 1999). Lastly, the validity of the IAT cannot be verified by test-retest studies (Binner 1992). In the few patients reported in the literature who initially failed the test, contradictory results have been obtained upon retesting (Dinner *et al.* 1987). In fact, there is evidence that the IAT may even yield false results. Both, false positives (patients who failed the Wada without suffering post-operative amnesia) (Novelly and Williamson 1989) and false negatives (patients who passed the Wada but presented post-operative amnesia) (Jones-Gotman 1993, Loring *et al.* 1990) have been reported. This may be attributable to the fact that the IAT preferentially perfuses lateral temporal regions and less frequently mesial temporal areas which include the hippocampus (Jeffrey *et al.* 1991, Hong *et al.* 2000). Similarly, the IAT may yield false results in patients with varying degrees of bihemispheric language representation (Oxbury and Oxbury 1984, Loring *et al.* 1990).

From the clinical point of view, an important drawback is the variability in the cerebral distribution of the product (Jeffery *et al.* 1991). Furthermore, there is the risk of anomalous anaesthetization due to cross-flow or abnormal vascularization. In patients with abnormal intracranial vascularization, the IAT may give false results due to incomplete perfusion of the drug (Hietala *et al.* 1990). Impairment of consciousness or a strong behavioural reaction (e.g., anxiety, panic attack), induced by the injection, as well as excessive agitation of the patient can also obscure the results (Loring *et al.* 1992).

These important limitations, along with the uncertainty regarding the availability of the product in the future (Grote and Meador 2005), have prompted many centers to look for other means of evaluating language and memory in patients slated for epilepsy surgery. However, the efficacy of these methods in the pre-surgical exploration of language and memory still remains to be more thoroughly evaluated. The merits and limitations of the different techniques are presented in *table 1*.

Intraoperative electrocortical stimulation mapping (ioESM)

This technique shall only be addressed briefly since the aim of the paper is to compare IAT with non-invasive techniques of investigating language lateralization and memory functions in surgery candidates. Intraoperative cortical stimulation is required when resection borders must be determined during the actual surgery. In this procedure, an electrical current is applied to stimulate cortical regions while the patient, who is awake during the operation, is performing a linguistic task. Although it is without doubt the most reliable method of localizing language functions in the brain, this technique is not always feasible in clinical practice since it requires the patient's full collaboration and the expertise of the surgical team in this technique (Rutten *et al.* 2002). Moreover, procedures have yet to be developed in order to provide information regarding memory functions.

Noninvasive behavioural methods

Neuropsychological assessment

Neuropsychological assessment is a behavioural method that does not involve sophisticated and expensive equipment. Furthermore, the tests are non-invasive and can be easily administered to children and adults of all ages. The assessment consists of detailed history-taking, including information obtained through interviews and questionnaires completed by the patient and/or family members, and the administration of a battery of standardized tests conceived to assess cognitive abilities and problem-solving skills, as well as motor and sensory functions. The tests require verbal and non-verbal responses, memorization of verbal and visual stimuli and manipulation of figural material (e.g., objects, blocks, images). The neuropsychological profile derived from the assessment allows for the identification of individual patterns of strengths and weaknesses.

Neuropsychological testing not only plays a crucial role in determining the patient's preoperative cognitive status and cerebral dominance it can, like IAT, be employed to predict postsurgical outcome and thus contributes to patient selection for epilepsy surgery.

Furthermore, postoperative follow-up provides a direct measure of neuropsychological outcome of the surgery in terms of improvement or deterioration of cognitive functions and quality of life (Dodrill 2001). Neuropsychology may also be able to localize brain lesions, based on cognitive impairment, in the absence of a discernible structural anomaly (Andelman *et al.* 2004). Finally, neuropsychological assessment can contribute to the determination of the laterality of the epileptic focus (Loring and Meador 2000). Hence, strong material-specific memory asymmetries, observed during pre-surgical neuropsychological evaluation, can provide information about seizure onset laterality (Engel *et al.* 1981). For instance, it has been shown that left temporal epilepsy is associated with poor verbal memory and right temporal epilepsy with poor visuospatial memory (Helmstaedter *et al.* 1999, Kim *et al.* 2003, Perrine *et al.* 1993). These patterns can then be used in conjunction with medical information derived from EEG and other techniques to predict post-operative outcome. Thus, comparing several techniques in 87 surgical candidates, Lineweaver *et al.* (2006), found that neuropsychological test scores and MRI-based hippocampal volumetric analysis were as accurate as Wada findings in predicting verbal and visual memory outcome following anterior temporal lobe resection. In the same vein, Loring *et al.* (2004), in a single case study, observed that neuropsychological testing was superior to MRI in predicting post-operative cognitive changes. A high level of agreement between the results of the diverse methods with regard to the localization and laterality of the seizure focus has a good prognosis for the outcome of the surgery, whereas lack of concordance between these techniques and neuropsychological findings may suggest atypical brain organization, probably due to more widespread cerebral damage and/or functional reorganization. In this case, the outcome of the surgery is less predictable.

Limitations of neuropsychology

The premise of neuropsychology is that there exists a consistent relationship between the behaviour that the neuropsychological tests purport to assess and the underlying brain region. In a clinical population, it can be assumed that there is a greater variability with regard to brain organization. Variables such as age, age at seizure onset (Risse and Hempel 2001), frequency of interictal activity (Janszky *et al.* 2006), localization of the seizure focus (Briellmann *et al.* 2006) and duration of epilepsy (Yuan *et al.* 2006) may result in a shift in laterality due to ongoing maturational changes and cerebral plasticity of the developing brain. Furthermore, performance patterns that are typical for adult patients may not hold for children (e.g., Gonzalez *et al.* 2007). For instance, hippocampal sclerosis, which is commonly associated with poor memory in adults, may not affect memory functions in children (Stanford *et al.* 1998). Furthermore, while neuropsychological tests may be the best method to objectively evaluate language and memory, some of the brain-behaviour relationships obtained by neuropsychological testing are less consistent and thus less conclusive. In this context, it has been shown that the relationship between left temporal structures and performance on verbal memory tests is quite stable (Deblaere *et al.* 2002; Hermann *et al.* 1987) whereas the relationship between right temporal lobe and visual memory functions is more variable (Barr 1997). Neuropsychological tests alone may therefore not be sufficient to predict the risk for post-operative memory decline.

Other behavioural techniques

Both dichotic listening and its visual equivalent, tachistoscopy, are behavioural methods that can be employed as complementary techniques to IAT in the determination of hemispheric dominance for speech (Fernandes and Smith 2000, Hughdahl *et al.* 1997, Kurthen *et al.* 1993, Strauss *et al.* 1987). These techniques can be applied in children and adults. Furthermore, the equipment is portable and inexpensive. Both techniques are based on the observation that the hemisphere controlling speech is more efficient than its counterpart in recognizing and reporting verbal stimuli.

Tachistoscopy and language lateralization

In this technique, the subject is asked to report verbal stimuli (letters, words) that are rapidly flashed into one visual half-field, thereby limiting visual input to the contralateral hemisphere. Right-handers usually show a right-visual field advantage for verbal stimuli, as determined by the speed and correctness of the responses (Belin *et al.* 1990).

Dichotic listening

The rationale underlying this technique is that contralateral projections from each ear override ipsilateral projections when both ears are simultaneously presented with an auditory stimulus (e.g. a speech sound or a musical tone) and the subject has to report what he/she has heard (Kimura 1967). Individuals with left hemisphere dominance for speech generally show a right-ear advantage for verbal stimuli. The stimuli, most commonly consonant-vowel syllables or monosyllabic words, are presented to the participant *via* ear phones. To determine language lateralization, a laterality index, using the formula [(REar-LEar)/(Rear+LEar)]x 100 (Hughdahl *et al.* 2003), can be computed on the number of correct stimuli reported for each ear, where a positive index indicates right ear advantage (REA), and a negative index indicates left ear advantage (LEA). With bilateral language representation no ear advantage or only a weak ear advantage is observed.

Several studies have attempted to validate the DL paradigm for language dominance by comparing ear advantage data obtained from surgical candidates with results from other techniques, such as IAT and fMRI.

Table 1. Comparison of various techniques used in the presurgical exploration of language and memory functions in epilepsy patients.

Technique	Procedure	Expressive language	Receptive language	Memory assessment	Advantages	Disadvantages
IAT	deactivation by anesthesia	yes	yes	yes	direct measure, possibility to assess unilateral functions	invasive, uncomfortable, risk of morbidity, no localization, less suitable for young and mentally-challenged individuals
ioESM	electrical stimulation	yes	yes	yes	direct measure, precise localization	invasive, requires patient's cooperation and surgical team expertise
Neuropsy. assessment	behavioural testing with standardized test batteries	yes	yes	yes	non-invasive, affordable, applicable to children and adults of all ages	no localization
Tachistoscopy	determination of visual field advantage	yes	yes	no	non-invasive, affordable, portable	no localization
Dichotic listening	determination of ear advantage	yes	yes	no	non-invasive, affordable, portable	no localization, requires patient's attention
MRI	structural assessment	no	no	yes (inference)	non-invasive, requires minimal cooperation, good spatial resolution	expensive, limited to structural abnomalities
fMRI	hemodynamic response to activation	yes	yes	yes	non-invasive, good localization and spatial resolution	expensive, requires patient's cooperation, less suitable for young and mentally-challenged individuals
PET	hemodynamic response to activation	yes	yes	yes (inference)	provides asymmetry in hypometabolism	expensive, ± invasive, poor spatial and temporal resolution
SPECT	hemodynamic response to activation	yes	no	no	affordable	± invasive, poor spatial and temporal resolution
rTMS	deactivation by electrical interference	yes	no	no	non-invasive, direct measure, affordable	no reliable results within individuals and across centers
MEG	magnetic flux directly asssociated with activation	no	yes	no	non-invasive, direct measure, good temporal resolution	expensive, poor spatial resolution, limited with regard to depth of penetration, requires patient's cooperation
NIRS	hemodynamic response to activation	yes	yes	no	non-invasive, affordable, equipment portable, casily used in children	data acquisition limited to cortical surface, requires patient's cooperation
fTCD	hemodynamic response to activation	yes	yes	no	not-invasive, inexpensive, good temporal resolution, easily used in children	poor spatial resolution, no localization

Comparisons between DL and Wada have yielded a concordance ranging from 80 to 95 percent (Fernandes and Smith 2000, Hughdahl *et al.* 1997, Strauss *et al.* 1987, Zatorre 1989). Similar results have been obtained from studies investigating the relationship between ear advantage and fMRI findings in healthy subjects (Hund-Georgiadis *et al.* 2002) and epileptic patients (Fernandes *et al.* 2006). Thus, Fernandes *et al.* (2006) observed a strong concordance between the scores of a Fused Dichotic Words Test (FDWT) and fMRI activation in response to a verb generation task in children with epilepsy. The authors pointed out that the degree of lateralization afforded by both methods is particularly important in epileptic patients in that it allows determining the contribution of each hemisphere to language processing. In children, it would also provide a measure of the development of lateralization as part of cerebral maturation.

Limitations of tachistoscopy and dichotic listening

Both techniques have several disadvantages. Tachistoscopic half-field visual presentations require the patient to fixate a central point during the entire procedure in order to avoid eye movements that would convey information to both hemispheres. Sophisticated eye-movement recordings are therefore required to control for this factor. Moreover, the stimuli must be presented quickly (ideally under 200 ms) and such rapid presentations may not be sufficient to elicit proper identification by epileptic patients who are often slowed down because of concomitant medical conditions. Finally, the laterality indices obtained by this technique are weak in detecting right hemisphere dominance or bilateral speech representation (Channon *et al.* 1990, Kurthen *et al.* 1992).

Like tachistoscopy, dichotic listening has been found to be less accurate in detecting right- or bi-hemispheric language organization (Kurthen *et al.* 1992). Another limitation is that the individual has to be attentive to the auditory stimuli. However, attentional processes are frequently compromised in patients with intractable epilepsy, especially those who are heavily medicated. In addition, young children and mentally-deficient patients may not be testable with this technique. Finally, both the dichotic listening and tachistoscopic procedures are not easily adaptable to the assessment of memory functions.

Recent advances in neuroimaging techniques provide the surgeon with an additional tool for the presurgical assessment of language and memory functions and the prediction of postsurgical outcome.

Non-invasive or minimally invasive imaging techniques

Anatomical magnetic resonance imaging (MRI)

During the past two decades, anatomical magnetic resonance imaging has become an integral part of the preoperative work-up of candidates for epilepsy surgery. This technique permits to detect structural abnormalities and volumetric changes in the brain. MRI has been found to identify anatomical abnormalities in approximately 85% of the cases (Duncan 1997). In the context of pre-operative evaluation of surgical candidates, MRI-based hippocampal volumetric measures have proven to be useful in predicting surgery outcome and provide therefore a valuable tool for patient selection (Lineweaver *et al.* 2006). For instance, a meta-analysis, conducted by Tonini *et al.* (2004) on 3511 surgical cases reported in the literature, indicated that the presence of the most common abnormalities, mesial sclerosis and tumors, detected by MRI were associated with good outcome.

Often, the main regions of interest for the surgeon are the medial temporal lobes which harbour the substrate of memory. The presence of hippocampal sclerosis presents an important risk for memory decline after temporal lobectomy (Paglioli *et al.* 2006).

High resolution MRI is now routinely used to determine hippocampal volumes (for review see Duncan 1997). In fact, hippocampal sclerosis can be detected and hippocampal atrophy can be correctly lateralized with a sensitivity close to 100% by means of qualitative and quantitative analyses of the volume of the hippocampal signal (Jack 1992; Tonini *et al.* 2004; Van Paesschen *et al.* 1997).

MRI findings have been found to correlate with both neuropsychological memory scores and Wada asymmetry indices. For instance, Loring *et al.* (1995) found a strong correlation between memory asymmetries determined by the Wada test and hippocampal volume asymmetries observed in the MRI. Lencz *et al.* (1992) reported significant correlations between left hippocampus volume and verbal memory scores in patients with left temporal lobe foci but no such correlation was obtained for non verbal memory performance.

The advantage of MRI is that the technique is non-invasive and does not require any cooperation from the subject. Valid results can even be obtained when the patient is asleep, which makes the procedure accessible to patients of all ages. On the other hand, anatomical MRI only provides information about structural abnormalities, which precludes its application to the assessment of language lateralization. A combination with functional techniques is therefore necessary for a comprehensive preoperative evaluation.

Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging is one of the neuroimaging techniques that is gradually supplanting the more invasive Wada procedure in many epilepsy centers. The technique is based on haemodynamic changes determined by cerebral activity (Spinelli *et al.* 2003). fMRI allows, among others, the identification of eloquent cortex to be spared during surgery. However, the primary objectives of presurgical fMRI are to lateralize and localize language and memory functions in order to predict and prevent postoperative complications. The most widely used method to obtain cerebral activation maps for the language areas is to compare the blood oxygen-level-dependent (BOLD) signal obtained while the subject performs a language task to the baseline signal when the subject performs a non-linguistic control task. A laterality index (LI) can then be obtained by determining the difference in activation between the hemispheres (Chlebus *et al.* 2006). In addition, regression models can be used to relate the LI to other variables (e.g., Janszky *et al.* 2006, Yuan *et al.* 2006).

fMRI and language lateralization

fMRI studies in healthy subjects, using naming and semantic decision making tasks, have yielded robust laterality effects, which were most marked in the frontal areas (Seghier *et al.* 2002; Weber *et al.* 2006.). In clinical populations, fMRI findings have shown promising correlations with the IAT for language lateralization and memory in small cohorts of patients (Abou-Khalil 2007, Aldenkamp *et al.* 2003, Desmond *et al.* 1995, Binder *et al.* 1996, Benbadis *et al.* 1998, Binder *et al.* 1996, Yetkin *et al.* 1998, Rabin *et al.* 2004, Richardson *et al.* 2004). Although most of the studies have focused on expressive speech, some have successfully employed receptive language paradigms (Weber *et al.* 2006, Gaillard *et al.* 2004). Interestingly, performance measures did not always correlate with the lateralization of activation, which would suggest that effort may be as important as performance in producing the desired results (Weber *et al.* 2006).

While high resolution fMRI is desirable, it is not a necessity for obtaining reliable data regarding language lateralization. For instance, Deblaere *et al.* (2002), using a simple word generation paradigm, showed that fMRI language lateralization can be reliably assessed in a clinical setting MR operating at low field strength (1 T). However, Mayer *et al.* (2006) concluded that increased sensitivity at high field strength is useful in reducing the time required to localize functional activation patterns, which has advantages for pre-surgical mapping. Fernandez *et al.* (2001) assessed the reliability of real-time fMRI during routine clinical investigations. The authors found that real-time fMRI (1.5T) allowed for the reliable determination of language lateralization in less than 15 minutes using this procedure.

Limitations of fMRI in language lateralization

Comparing fMRI- and IAT-based laterality quotients for speech in TLE patients, Benke *et al.* (2006) found a concordance of 89.3% in right temporal lobe patient (rTLE) and of 72.5% in left temporal lobe patients (lTLE). However, while fMRI correctly detected atypical right hemisphere speech in all cases, it missed left hemisphere dominance of speech in 17.2% of patients with TLE. Furthermore, the method tended to be less sensitive to bilateral speech representation. Anderson *et al.* (2006), studying a heterogeneous sample of 35 children, found concordance between fMRI activation patterns and IAT or cortical stimulation in the majority of patients for whom these procedures were available. However, two of the patients showed bilateral activation with fMRI where other measures indicated left hemispheric language dominance. Although these results have yet to be replicated, they suggest that there may be a certain margin of error with fMRI compared to IAT and other techniques.

Some of the divergent results can also be attributed to procedural differences. Like for the Wada test, the paradigm used to evaluate language lateralization by means of fMRI varies considerably between studies. Using a semantic task, a verbal fluency task, covert sentence repetition, and story listening, Lehericy *et al.* (2000) found that the semantic language tasks such as verb generation in response to noun categorization or noun generation were more effective than covert sentence repetition in lateralizing language. Moreover, the use of multiple tasks increased the likelihood of detecting the language areas. There are other limitations to this technique. First, areas activated by a particular fMRI paradigm may not be crucial for the performance of the task. Secondly, it is difficult to determine to what extent the right hemisphere participates in language processing in patients with bilateral speech representation. Thirdly, not all areas involved in a task may be activated by a particular fMRI paradigm. Another disadvantage is that the patients have to lie motionless in the scanner during data acquisition which makes this technique less suitable for children and special populations. Furthermore, it should be borne in mind that the technique does not provide a measure of the competence with the task. In this respect, IAT and fMRI differ regarding the type of information they convey.

fMRI and memory testing

Functional MRI has been employed to investigate preoperative lateralization of memory as well as prediction of outcome following temporal lobectomy. However, conception of a reliable paradigm for memory is more challenging than for language. There are many components to consider, such as the different aspects of memory (*i.e.*, encoding, retrieval, recognition), and the stimuli to be memorized (verbal, figural), since these are mediated by different brain regions (Aldenkamp *et al.* 2003, Deblaere *et al.* 2002). Avila *et al.* (2006) demonstrated the necessity of combining encoding and recall tasks in order to obtain lateralized activation patterns in parahippocampus and fusiform gyri during peroperative memory exploration. Both tasks elicited posterior parahippocampal activation, but the encoding task yielded larger activations than the recall task. Half of the patients showed lateralized activation on the side contralateral to the lesion on both tasks.

Encoding tasks, on the other hand, have shown their predictive value with regard to postsurgical memory outcome. Thus, Richardson *et al.* (2004) found that fMRI activation during an encoding task was a good predictor of verbal memory decline in right-handed patients with left hippocampal resection. On their part, Rabin *et al.* (2004) reported a strong correlation between mesial temporal lobe activation asymmetry ratios obtained during encoding of a complex visual scene and postsurgical memory outcome. The latter performed a Region-of-Interest (ROI) analysis which included the hippocampus, the parahippocampus and the fusiform gyrus. Healthy subjects showed an almost symmetrical activation in these regions, indicating that both hemispheres were involved in the encoding. This would suggest that the subjects exploited visuospatial as well as verbal encoding strategies to perform the task. Although the asymmetry ratios did not correlate significantly with the laterality index obtained by intracarotid amobarbital testing, it was a good predictor of postsurgical memory outcome. However, no normative data comparing the two methods have been established so far due to the small number of healthy and epileptic subjects who have been tested with these procedures. Therefore, at this stage, fMRI should not be used as the sole method to assess critical memory areas prior to surgery.

Positron emission tomography (PET)

PET is a functional neuroimaging technique that allows for the measurement of regional variations in glucose metabolism using ^{18}FDG, to map cerebral blood flow (CBF) by means of ^{15}O-labelled water and 11C-flumazenil to quantify benzodiazepine receptors. The procedure consists of the injection of a radioactive tracer, most frequently ^{18}FDG. The uptake of this substance in brain tissue allows for the construction of a cartography of cerebral metabolism (Chiron *et al.* 2004). In addition, PET with specific ligands may be used to identify specific receptors in the brain (Theodore 1999).

PET and language lateralization

The use of PET in the identification of language regions usually requires the injection of the tracer ^{15}O-water. Evidence from case studies indicates that this method can be reliably used in the pre-operative mapping of speech areas (Ohta *et al.* 2003). Furthermore, several studies have reported good concordance between PET language assessment and IAT (Hunter *et al.* 1999, Tatlidil *et al.* 2000) as well as PET and intraoperative electro-cortical stimulation mapping (Bookheimer *et al.* 1997). In contrast, one multi-center study evaluating the reliability of PET in language lateralization has revealed large differences across centers (Poline *et al.* 1996) with respect to the language areas identified by this technique. However, these differences may be explained by several variables such as the scanner sensitivity, the field of view of the scanner and the scanning protocol. Moreover, apparent failures to reproduce results are often due to statistical threshold setting.

PET and memory testing

While PET, like anatomical MRI, has been mainly employed to localize epileptic foci (e.g., Csaba 2003, Hong *et al.* 2000), the technique has also proved to be useful in evaluating memory functions in candidates for temporal lobectomy (Akanuma *et al.* 2003, Griffith *et al.* 2000, Griffith *et al.* 2004, Hong *et al.* 2000, Salanova *et al.* 1999). In this context, several studies have revealed that preoperative asymmetries in hypometabolism, detected by PET, can be used to infer lateralized memory impairments and to predict memory outcome after surgery (Akanuma *et al.* 2003, Salanova *et al.* 1999).

Limitations of PET

One important drawback of PET is its limited spatial and temporal resolution compared to fMRI or MEG. Another limitation is that the procedure is somewhat invasive since it requires an injection with radioactive materiel. For this reason it is rarely performed in paediatric patients or healthy subjects. Economical reasons may also limit the use of this technique. The equipment and the procedure are expensive. It is therefore not the method of first choice in the preoperative assessment of memory in surgical candidates, especially in smaller centres.

Furthermore, studies comparing PET with other procedures have yielded divergent results. On the one hand, Hong *et al.* (2000), comparing FDG-PET and Wada asymmetry indices in the same patients, found significant correlations between hypoperfusion in mesial temporal lobe regions and Wada memory lateralization. Similary, Hunter *et al.* (1999) found that compared to IAT, the predictive value of PET for language lateralization ranged from 88 to 91 percent, based on visual inspection of the images by experienced neuroradiologists. Based on region-of-interest analysis, the predictive value was 80 percent. On the other hand, Palez *et al.* (1998), failed to detect a linear relationship between FDG-PET metabolism and percent recall following amobarbital injection of the contralateral hemisphere.

In a study exploring the relationship between volumetric and metabolic measures, Salanova *et al.* (1999) observed that FDG-PET was more sensitive than anatomical MRI in detecting temporal deficiencies in patients below the age of 18 years. The results revealed that 85.7% of the young patients showed ipsilateral hypometabolism although more than half (58%) of the younger patients in the authors' series had a normal MRI as opposed to only 21% of the adult patients. In contrast, Griffith *et al.* (2004) demonstrated that metabolic measures of hippocampal functioning were *less* sensitive than volumetric measures in predicting memory performance. The authors observed a strong relationship between hippocampal volume, determined by MRI, and verbal memory measures whereas no such relationship was found between MRI, PET and nonverbal memory performance. The results emulate those of other studies (e.g., Arnold *et al.* 1996, Jokeit *et al.* 1997, Rausch *et al.* 1994). There is to date no conclusive answer to the question of which of the two techniques (MRI or PET) is more sensitive to memory functions in epileptic patients. It seems that PET is most efficient in lateralizing the seizure focus in patients with temporal lobe epilepsy, whose MRI is normal. For instance, in the older literature, FDG-PET has been shown to detect mesial temporal sclerosis in cases where lower tesla MRI failed to do so. PET may therefore be considered to be a valuable complementary technique to MRI and other functional procedures.

Single-photon emission computed tomography (SPECT)

This nuclear imaging technique, which measures blood flow distribution in the brain, is based on the assumption that localized neural activity increases regional cerebral blood flow (rCBF). Single photons, emitted by an injected radioactive substance, usually ^{99m}Tc-HMPAO, and captured on a gamma camera, are used to trace regional variations in blood flow associated with the performance of a given task as compared to a resting condition. Multiple images, taken from different angles, can then be reconstructed in the same manner as those obtained from CT, MR and PET (Chiron 2004).

Like PET, SPECT has been used to study hemispheric dominance for language. Although some of the results have been inconclusive (e.g., Beversdorf *et al.* 1995) at least one study (Borbély *et al.* 2003) has shown that increases in rCBL can effectively determine language lateralization in epilepsy patients. The authors used a "fluent verbal activation task" as opposed to auditory-verbal stimulation (Beversdorf *et al.* 1995) by asking the patient to speak continuously about a given topic. Increases in rCBL predominated in posterior frontal cortex and contralateral cerebellum and correlated well with functional transcranial Doppler monitoring (fTCD, see below) performed in the same patients. With respect to memory assessment, only correlation studies have been performed, comparing memory indices to regional cerebral blood flow (e.g., Kim *et al.* 2000).

The main advantage of SPECT is that the equipment and procedure are less expensive than MRI and PET and therefore more easily accessible. On the negative side, the procedure is somewhat invasive in that it requires intravenous injection of a radioactive substance. Furthermore, the spatial and temporal resolutions of SPECT are relatively poor.

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation is to date the only non-invasive technique that permits investigators to interfere with brain activity. In doing so, it allows to infer brain-behaviour relationships. TMS depolarizes neuronal populations through the skull by inducing haemodynamic changes through a rapid sporadic magnetic pulse (Gaillard *et al.* 1997). A wire coil, placed on the scalp, is energized by means of a rapidly changing current. An orthogonally oriented magnetic field then induces electrical currents in the brain (Wassermann *et al.* 1999).

While single-pulse TMS stimulation is bound to the duration of the task, repeated transcranial magnetic stimulation (rTMS) can affect cortical excitability beyond the duration of the stimulation (Berardelli *et al.* 1998, Pascual-Leone *et al.* 1998, Saint-Amour *et al.* 2005). Thus, rTMS can have prolonged focal effects on cortical processing. In particular, this technique has well documented effects on several aspects of speech and language processing.

rTMS and language lateralization

One of the most striking effects of this technique is its induction of speech arrest. Lateralized arrest of speech can be produced by stimulating the motor speech area (Broca's area) of the hemisphere dominant for language Jennum *et al.* 1994, Pascual-Leone *et al.* 1991). The technique has therefore the potential to be used in the presurgical exploration of language lateralization in epileptic patients.

Pascual-Leone *et al.* (1991) as well as Jennum *et al.* (1994) compared the results obtained with rTMS with those obtained with intracarotid amobarbital test in several epilepsy patients. In their studies, frontal and temporal cortices were stimulated in each hemisphere at a frequency of 30 Hz, which was increased in intensity until speech was inhibited. A word list and a forward and backward counting task were used to assess speech arrest. The results revealed excellent correlation with the IAT in all but one patient. By contrast, a more recent study, comparing rTMS and Wada test results, has yielded an abnormally high proportion of cases with bilateral or right-hemisphere lateralization (Epstein *et al.* 2000). Furthermore, when postoperative language deficits were present, they correlated more closely with IAT results than with rTMS findings (Epstein *et al.* 2000).

Limitations of rTMS

The results of rTMS studies regarding speech arrest are thus inconsistent. To date, rTMS procedures have not produced reliable results in individual subjects. For instance, Michelucci *et al.* (1994) demonstrated speech arrest in only seven out of 14 epileptic patients. Moreover, a major limitation of this technique is that it assesses mostly expressive speech and is therefore predominantly a measure of the frontal language areas. Finally, investigating the usefulness of rTMS in the preoperative exploration of memory functions, Duzel *et al.* (1996) observed qualitative changes only in the left temporal lobe epilepsy group. Quantitative changes were not significant in any of the cases. Taken together the data do not make a strong case for rTMS as a potential alternative to the traditional Wada procedure in the preoperative assessment of surgery candidates (Théoret and Pascual-Leone 2002).

Magnetoencephalography (MEG)

Although not widely used in medical centers, MEG has the potential to localize neurophysiological processes within the whole brain. The technique is very different from those based on haemodynamic responses. In this procedure, a magnetic flux, induced by intracellular electrical currents, can measure more directly than other imaging techniques the cerebral activation during performance of a cognitive, (Breier *et al.* 1999) sensory, (Kakigi *et al.* 2000) or motor task (Castillo *et al.* 2004). Compared to other functional imaging techniques such as fMRI and PET, MEG has excellent temporal resolution. Moreover, source localisation in MEG greatly increases spatial resolution and gives rise to a good combination of high temporal resolution and moderate spatial resolution.

Magnetoencephalography and language lateralization

There is evidence that MEG may also be useful in determining hemispheric dominance of language in presurgical patients (Bowyer *et al.* 2005, Papanicolaou *et al.* 2004). However, before language mapping by MEG can be tested in a clinical setting, it is crucial to establish reliable results in healthy subjects and clinical populations. In this context, a language mapping protocol, employing a spoken word recognition task, has been shown to be robust in several studies (Lee *et al.* 2006, Papanicolaou *et al.* 2004). Thus, Papanicolaou *et al.* (2004) reported a high degree of concordance (87%) between MEG and IAT for hemispheric language dominance in 100 surgical candidates. Similarly, Breier *et al.* (1999) showed excellent concordance between MEG and Wada laterality indices by using a word recognition task in 26 epileptic patients, aged 8 to 56 years. In a subsequent study, Breier *et al.* (2001) compared MEG and IAT data obtained from 19 children and adolescents, aged 8-18 years, with intractable epilepsy on a word recognition task. The language laterality indices of the two techniques were highly correlated ($r = 0.87$). Furthermore, MEG results emulated IAT results in 17 out of the 19 cases. Using a similar mapping procedure, Maestú *et al.* (2002) obtained comparable results with MEG and IAT in seven out of nine subjects.

Lee *et al.* (2006) investigated the test-retest reliability and the inter-rater reliability of a language mapping task (*i.e.*, recognition of spoken words) that had previously been used for comparisons between MEG and IAT in 21 candidates for epilepsy surgery. The results revealed a robust test-retest and inter-rater reliability and excellent intra-subject reliability on measures of hemispheric asymmetry.

Another advantage of MEG is that, unlike IAT, the procedure is not limited in time so that exhaustive testing with different tasks of longer duration is possible. Furthermore, while the results of IAT may be contaminated by cross flow or unusual vascularization, there is no such risk with MEG. In addition, MEG has few, if any, health risks. Replacing IAT by non-invasive MEG in the preoperative exploration of language lateralization would thus have considerable methodological advantages.

Limitations of MEG

When comparing MEG with IAT several disadvantages must be considered. Hence, the IAT can evaluate both receptive and expressive language functions, whereas MEG studies are limited to the investigation of receptive language. Evidence suggests that expressive and receptive language abilities may reorganize independently in the epileptic brain (Kurthen 1992). There is thus a need for assessing both aspects. MEG is also limited with regard to source depth, the geometry of the active areas, the algorithm used and the signal-to-noise ratio of the magnetic flux recordings (Breier *et al.* 2001). Moreover, head movement software has yet to be developed in order to correct for head movements, thereby precluding the use of MEG with young children or children with attentional deficits or hyperactivity who typically cannot remain motionless in the apparatus. Finally, although MEG has been used to investigate cognitive processes such as attention and working memory, there are as yet no studies that have been conducted to evaluate memory functions. This area of research needs to be further developed in order for MEG to become a reliable replacement of IAT.

Near infrared spectroscopy (NIRS)

Near infrared spectroscopy (NIRS) or optical imaging is another non-invasive technique that may be used to investigate language lateralisation. Like fMRI, NIRS measures cerebral blood flow associated with cortical activity. Optic fibers of a wavelength ranging from 680 and 1000 nm are directed to the subject's head. The light entering the brain is then recaptured by detectors located on the scalp. The different light absorption spectra of oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) reflect concentration changes of these substances in living tissues and can thus provide information about activity in areas of interest.

NIRS has a relatively good spatial resolution. Furthermore, it has the advantage that it allows for the independent measurement of oxy-Hb and deoxy-Hb. Another important aspect is that the procedure imposes few constraints on movement and can therefore be used in young children and mentally-challenged patients who cannot be tested by other methods. By the same token, it allows for the execution of experiments under more natural conditions. For instance, unlike in fMRI, subjects can give an oral response. This advantage over other imaging techniques greatly reduces the possibilities of misinterpreting the origin of the cortical activation obtained during performance of a language task.

NIRS has already been effectively used to assess language laterality in healthy subjects (Kennan *et al.* 2002, Noguchi *et al.* 2002) and epileptic adults (Watanabe *et al.* 1998, Watson *et al.* 2004). Preliminary data acquired in our own laboratory indicate good concordance with the IAT (Gallagher *et al.* 2006).

Limitations of NIRS

One of the disadvantages of the technique is its sensitivity to light absorption, which restricts data acquisition in patients with a thick skull and/or dense, dark hair. However, this disadvantage may be overcome by shaving the hair of surgical candidates who present this problem. The main limitation of the technique concerns the shallow penetration of the photons within the brain. Hence, it might be difficult, even impossible, to visualize the activation of mesial structures involved in memory functions. The use of NIRS as a pre-surgical investigative tool might therefore be limited to language assessment. In fact, no studies exploring memory functions have been reported so far.

Functional transcranial doppler sonography (fTCD)

Functional transcranial Doppler Sonography is an inexpensive and easily applied method which, like NIRS, is very promising in children. The technique is based on the linkage between cerebral activation and perfusion. Perfusional changes associated with blood flow velocity modulations in the supporting basal intracranial arteries can be continuously measured by this method. The changes can be calculated by the Doppler frequency shift of an ultrasound beam reflected from moving blood particles. The relative changes occurring during task performance are expressed in terms of percentages relative to the baseline which has the value of 0.

fTCD and language lateralization

The usefulness of fTCD in the assessment of hemispheric language dominance has been validated in several studies (Knecht *et al.* 1996, 1998a,b; Deppe *et al.* 2000; Rihs *et al.* 1999; Knake *et al.* 2003). fTCD can be repeated and used in follow-up examinations. Knecht *et al.* (1998a) demonstrated that fTCD has strong retest reliability within subjects. Furthermore, the method showed good concordance with IAT findings (Knecht *et al.* 1998b). In the latter study, the correlation between the lateralization indices obtained by IAT and fTCD were highly significant. Similar results were obtained by Rihs *et al.* (1999) and Knake *et al.* (2003, 2006). Good qualitative and quantitative concordance was also observed between fTCD and fMRI laterality indices (Deppe *et al.* 2000).
fTCD also has excellent temporal resolution. In addition it has the advantage that it provides quantitative information that is not biased by variable statistical threshold determination. The procedure is automated, objective, and relatively inexpensive compared to the other techniques discussed in this article. The technique is available in a growing number of centers and easy to perform. fTCD can also be applied in patients who are unsuitable candidates for fMRI, such as young children and patients with low IQ (Lohmann *et al.* 2005; Knake *et al.* 2003). Taken together, the results suggest that fTCD may be a useful and valid tool for the determination of language dominance in epilepsy surgery patients.

Limitations of fTCD

A major drawback of fTCD is its limited spatial resolution, which only allows for the calculation of a lateralization index but fails to provide information about intrahemispheric localization of the language areas. Furthermore, no robust studies have been published evaluating memory functions. For these reasons, the technique can only be used as an adjunct to other techniques in the pre-operative exploration of language and memory.

Conclusion

Functional imaging techniques represent a potential alternative for the traditional Wada procedure in the presurgical exploration of language lateralization in epilepsy patients. Apart from eliminating the discomfort and risk of morbidity associated with intracarotid amobarbital testing, functional imaging techniques have the advantage of sampling the entire brain and providing reliable test-retest data. Most importantly, they provide precise information about intrahemispheric localization of the areas involved in language processing, and these findings have been found to be consistent with the results of intraoperative electrocortical stimulation (Papanicolaou *et al.* 1999, Simos *et al.* 1999).
The high concordance between the findings of intracarotid amobarbital testing and neuroimaging techniques, especially fMRI, MEG, fTCD and possibly NIRS, is encouraging and holds promise that the Wada procedure will be eventually replaced by these non-invasive techniques. However, these methods still need to be refined, and certain incongruities between the Wada procedure and these techniques have to be addressed. For instance, fMRI provides little information regarding right hemisphere participation in language processing in patients with bilateral speech representation. MEG has the disadvantage that it is limited to the evaluation of receptive language. Furthermore, to obtain conclusive and reliable activation patterns, both fMRI and MEG require that the patient remain motionless in the scanner and comply with the test instructions. This restricts the application of these imaging techniques in young children and special populations.
There are at least four requirements that functional imaging must fulfill in order be a useful tool in the preoperative evaluation of surgical candidates. These are:
1) a highly predictive power for the presence or absence of critical language or memory functions in specific regions of the brain,
2) a user-independent statistical methodology,

3) high spatial resolution and

4) the production of reliable activation maps at the individual level.

At present, there is no single imaging procedure that responds to all criteria. The techniques vary with regard to their spatial and temporal resolution. fMRI has good spatial resolution and relatively poor temporal resolution. The reverse is true for MEG. Furthermore, different techniques target different functions. As Klopper and Buchel (2005) have pointed out, there is a need for standardized paradigms with good comparability between centres that activate all language and memory systems. A multimodal approach, combining several techniques, is therefore the safest way to provide the surgeon with reliable information. In this context, a study, combining fMRI for expressive speech mapping with MEG for receptive language exploration, has yielded excellent concordance with IAT (Kamada *et al.* 2007).

Neuropsychology and dichotic listening retain their important role in determining cerebral dominance for language. In combination with imaging techniques they provide a powerful tool both for the exploration of language and memory functions and the prediction of the outcome of the surgery. Furthermore, the neuropsychologist is actively involved in the development of the language and memory paradigms and the actual testing during imaging.

With regard to methodology, language paradigms that include verb generation, sentence comprehension and a picture naming have shown to be most sensitive to the detection of the critical language regions. Importantly, the results obtained by combining the three tasks have been found to be more informative than those obtained from either task alone (Rutten *et al.* 2002).

On the other hand, the exploration of memory functions remains a major challenge for neuroimaging techniques. Both PET and fMRI have been successfully used to assess memory functions. However, while PET has been found to be useful in predicting memory outcome, the predictive value of fMRI memory paradigms still remains to be validated. Imaging techniques like MEG and NIRS have the disadvantage that they cannot assess the deep structures mediating memory functions because of the shallow penetration. This is an important limitation since the structures mediating memory functions are localized in the mesial temporal lobe, and these structures are frequently affected by epilepsy. Moreover, it is difficult to elaborate paradigms that will allow comparisons between the signal obtained during task performance and during a control condition since almost every condition requires a certain degree of memory processing. Evidently, further research in these areas is necessary before imaging techniques can supplant traditional methods of preoperative assessment of memory functions. □

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References

Abou-Khalil B. An update on determination of language dominace in screeningf for epilepsy surgergy: the Wada test and newer noninvasice alternatives. *Epilepsia* 2007; 48: 442-55.

Akanuma N, Koutroumanidis M, Adachi N, *et al.* Presurgical assessment of memory-related brain structures: the Wada test and functional neuroimaging. *Seizure* 2003; 12: 346-58.

Aldenkamp A, Boon P, Deblaere K, *et al.* Usefulness of language and memory testing during intracarotid amobarbital testing: observations from an fMRI study. *Acta Neurol Scand* 2003; 108: 147-52.

Andelman F, Neufeld MY, Fried I. Contribution of neuropsychology to epilepsy surgery. *Isr J Psychiatry Relat Sci* 2004; 41: 125-32.

Andelman F, Kipervasser S, Neufeld, *et al.* Predictive value of Wada memory scores on postoperative learning and memory abilities in patients with intractable epilepsy. *J Neurosurg* 2006; 104: 20-6.

Anderson DP, Harvey AS, Saling MM, *et al.* FMRI lateralization of expressive language in children with cerebral lesions. *Epilepsia* 2006; 47: 988-1008.

Arnold S, Schlaug G, Niemann H, *et al.* Topography of interictal glucose hypometabolism in unilateral mesiotemporal epilepsy. *Neurology* 1996; 46: 1422-30.

Avila C, Barros-Loscertales A, Forn C, *et al.* Memory lateralization with 2 functional MR imaging tasks in patients with lesions in the temporal lobe. *AJNR Am J Neuroradiol* 2006; 27(3): 498-503.

Barr WB. Examining the right temporal lobe's role in nonverbal memory. *Brain Cogn* 1997; 35: 26-41.

Belin C, Jullien S, Perrier D, Larmande P. La tachistoscopie: une méthode expérimentale d'étude de la spécialisation hémisphérique. *Fr Ophthalmol* 1990; 13: 293-7.

Benbadis SR, Binder JR, Swanson SJ, *et al.* Is speech arrest during the Wada testing a valid method for determining hemispheric representation of language? *Brain Lang* 1998; 65: 441-6.

Benke T, Koylu B, Visian P, *et al.* Language lateralization in temporal lobe epilepsy: a comparison between fMRI and the Wada Test. *Epilepsia* 2006; 47: 1308-19.

Berardelli A, Inghilleri M, Rothwell JC, *et al.* Facilitation of motor evoked responses after repetitive cortical stimulation in man. *Exp Brain Res* 1998; 122: 79-84.

Beversdorf D, Metzger S, Nelson D, Alonso R, Knight J. Single-word auditory stimulation and regional cerebral blood flow as studied by SPECT. *Psychiatry Res* 1995; 61: 181-9.

Binder J, Swanson S, Hammeke T, *et al.* Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology* 1996; 49: 978-84.

Binner Jr. RA, Ginsberg B, Bloch EC, Mason DG. Anesthetic management of a pediatric Wada test. *Anesth Analg* 1992; 74: 621-2.

Bookheimer SY, Zeffiro TA, Blaxton T, *et al.* A direct comparison of PET activation and electrocortical stimulation mapping for language localization. *Neurology* 1997; 48: 1056-65.

Borbély D, Gjedde A, Nyáry I, Czirják S, Donauer N, Buck A. Speech activation of language dominant hemisphere: a single-photon emission computed tomography study. *Neuroimage* 2003; 20: 987-94.

Bowyer SM, Moran JE, Weiland BJ, *et al.* Language laterality determined by MEG mapping with MR-FOCUSS. *Epilepsy Behav* 2005; 6: 235-41.

Breier JI, Simos PG, Wheless JW, *et al.* Language dominance in children as determined by magnetic source imaging and the intracarotid amobarbital procedure: a comparison. *J Child Neurol* 2001; 16: 124-30.

Breier JI, Simos PG, Zouridakis G, *et al.* Language dominance determined by magnetic source imaging: a comparison with the Wada procedure. *Neurology* 1999; 53: 938-45.

Briellmann RS, Labate A, Harvey AS, *et al.* Is language lateralization in temporal lobe epilepsy patients related to the nature of the epileptogenic lesion? *Epilepsia* 2006; 47: 916-20.

Castillo EM, Simos PG, Wheless JW, *et al.* Integrating sensory and motor mapping in a comprehensive MEG protocol: Clinical validity and replicability. *Neuroimage* 2004; 21: 973-83.

Channon S, Schugens MM, Daum I, Poldey CE. Lateralization of language functioning by the Wada procedure and divided visual field presentation of a verbal task. *Cortex* 1990; 26: 147-51.

Chiaravalloti N, Glosser G. Material-specific memory changes after anterior temporal lobectomy as predicted by the intracarotid amobarbital test. *Epilepsia* 2001; 42: 902-11.

Chiron C. L'imagerie fonctionnelle chez l'enfant. *Rev Neurol (Paris)* 2004; 160(Hors Série1): 131-7.

Chlebus P, Mikl M. Brazdil M, Pazourkova M, Krupa P. Rektor I. fMRI evaluation of hemispheric language dominance using various methods of laterality index calculation. Exp Brain Res, 2006.

Csaba J. Positron emission tomography in pre-surgical localization of epileptic foci. *Ideggyogy Sz* 2003; 56: 249-54.

Deblaere K, Backes W, Hofman P, *et al.* Developing a comprehensive presurgical functional MRI protocol for patients with intractable temporal lobe epilepsy: a pilot study. *Neuroradiology* 2002; 44: 667-73.

Deppe M, Knecht S, Papke K, *et al.* Assessment of hemispheric language lateralization: a comparison between fMRI and fTCD. *J Cereb Blood Flow Metab* 2000; 20: 263-8.

Desmond JE, Sum JM, Wagner AD, *et al.* Functional MRI measurement of language lateralization in Wada tested patients. *Brain* 1995; 118: 1411-9.

Dinner DS, Lüders H, Morris HH, *et al.* Validity of intracarotid amobarbital (Wada test) for evaluation of memory function. *Neurology* 1987(Suppl 1): 142.

Dodrill CB. Overwiew: presurgical neuropsychological evaluation. In: Lüders HO, Comair YG, eds. *Epilepsy surgery*. Philadelphia: Lippinicott Williams and Wilkins, 2001: 475-80.

Duncan JS. Imaging and epilepsy. *Brain* 1997; 120: 339-77.

Duzel E, Hufnagel A, Helmstaedter C, Elger C. Verbal working memory components can be selectively influenced by transcranial magnetic stimulation in patients with left temporal lobe epilepsy. *Neuropsychologia* 1996; 34: 775-83.

Engel JJ, Rausch R, Lieb JP, Khul DE, Crandall PH. Correlation of criteria used for localizing epileptic foci in patients considered for surgical therapy in epilepsy. *Ann Neurol* 1981; 9: 215-24.

Epstein CM, Woodard JL, Stringer AY, *et al.* Repetitive transcranial magnetic stimulation does not replicate the Wada test. *Neurology* 2000; 55: 1025-7.

Fernandes M, Smith ML. Comparing the fused dichotic words test and the intracarotid amobarbital procedure in children with epilepsy. *Neuropsychologia* 2000; 38: 1216-28.

Fernandes MA, Smith ML, Logan W, Crawley A, McAndrew MP. Comparing language lateralization determined by dichotic listening and listening and fMRI activation in frontal and temporal lobes in children with epilepsy. *Brain Lang* 2006; 96: 106-14.

Fernandez G, de Greiff A, von Oertzen J, *et al.* Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. *Neuroimage* 2001; 14: 585-94.

Fried I. Anatomic temporal lobe resections for temporal lobe epilepsy. *Neurosurg Clin N Am* 1993; 4: 233-42.

Gaillard WD, Balsamo L, Xu B. FMRI language task panel improves determination of language dominance. *Neurology* 2004; 63: 1403-8.

Gaillard WD, Bookheimer SY, Hertz-Pannier L, Blaxton TA. The noninvasive identification of language function. Neuroimaging and rapid transcranial magnetic stimulation. *Neurosurg Clin N Am* 1997; 8: 321-35.

Gallagher A, Thériault M, Maclin E, *et al.* New technique for investigating language lateralization in epileptic patients with near-infrared spectroscopy (NIRS): An fMRI and Wada test comparison. *12th Annual Meeting for Human Brain Mapping Organization*, Florence, Italy, June 2006.

Gates J, Dunn M. Presurgical assessment and surgical treatment for epilepsy. *Acta Neurol Belg* 1999; 4: 281-94.

Gonzalez LM, Anderson VA, Wood SJ, Mitchell LA, Harvey AS. The localization and lateralization of memory deficits in children with temporal lobe epilepsy. *Epilepsia* 2007; 48: 124-32.

Griffith HR, Perlman SB, Woodard AR, *et al.* Preoperative FDG-PET temporal lobe hypometabolism and verbal memory after temporal lobectomy. *Neurology* 2000; 54: 1161-5.

Griffith HR, Pyzalski RW, Seidenberg M, Hermann BP. Memory relationships between MRI volumes and resting PET metabolism of medial temporal lobe structures. *Epilepsy Behav* 2004; 5: 669-76.

Grote CL, Meador K. Has amobarbital expired? Considering the future of Wada. *Neurology* 2005; 65: 1692-3.

Helmstaedter C, Kurthen M. Patterns of language dominance in focal left and right hemisphere epilepsies: relation to MRI findings, EEG, sex, and age at onset of epilepsy. *Brain Cogn* 1997; 33: 135-50.

Helmstaedter C, Kurthen M, Elger CE. Sex differences in material-specific cognitive functions related to language dominance: an intracarotid amobarbiltal study in left temporal lobe epilepsy. *Laterality* 1999; 4: 51-63.

Hermann BP, Wyler AR, Richey ET, Rea JM. Memory function and verbal learning ability in patients with complex partial seizures of temporal lobe origin. *Epilepsia* 1987; 28: 547-54.

Hietala SO, Silfvenius AJ, Olivecrona M, Jonsson L. Brain perfusion with intracarotid injection of 99mTc-HM-PAO in partial epilepsy during amobarbital testing. *Nucl Med (Stuttg)* 1990; 16: 683-7.

Holliday S, Brey R. Patient Page. Memory problems after epilepsy surgery. *Neurology* 2003; 60: E3-E5.

Hong SB, Roh SY, Kim SE, Seo DW. Correlation of temporal lobe glucose metabolism with the Wada memory test. *Epilepsia* 2000; 41: 1554-9.

Hughdahl K. Dichotic listening in the study of auditory laterality. In: Hughdahl K, Davidson RJ, eds. *The asymmetrical brain*. Cambridge, MA: MIT Press, 2003: 441-75.

Hughdahl K, Carlsson G, Uvebrandt P. Lundervold AJ. Dichotic listening performance and intracarotid injections of amobarbital in children and adolescents. *Arch Neurol* 1997; 54: 1494-500.

Hund-Georgiadis M, Lex U, Friederici D, Von Cramon DY. Non-invasive regime for language lateralizatrion in right– and left-handers by means of functional MRI and dichotic listening. *Exp Brain Res* 2002; 145: 166-76.

Hunter KE, Blaxton TA, Bookheimer SY, *et al.* (15)O water positron emission tomography in language localization: a study comparing positron emission tomography visual and computerized region of interest analysis with the Wada test. *Ann Neurol* 1999; 45: 662-5.

Jack CR. Epilepsy surgery and imaging. *Radiology* 1992; 189: 635-46.

Janszky J, Mertens M, Janszky I, Ebner A, Woermann FG. Left-sided interictal epileptic activity induces shift of language lateralization in temporal lobe epilepsy: an fMRI study. *Epilepsia* 2006; 47: 921-7.

Jeffrey PJ, Monsein LH, Szabo Z, *et al.* Mapping the distribution of amobarbital sodium in the intracarotid Wada test by use of Tc-99m HMPAO with SPECT. *Radiology* 1991; 178: 847-50.

Jennum P, Friberg L, Fuglsang-Frederiksen A, Dam M. Speech localization using repetitive transcranial magnetic stimulation. *Neurology* 1994; 44: 269-73.

Jokeit H, Seitz RJ, Markowitsch HJ, *et al.* Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. *Brain* 1997; 120: 2283-94.

Jones-Gotman M, Barr W, Dodrill C, *et al.* Controversies concerning the use of intraarterial amobarbital procedures. In: Engel J, ed. *Surgical treatment of the epilepsies*. New York: Raven Press, 1993: 445-9.

Kakigi R, Hoshiyama M, Shimojo M, *et al.* The somatosensory evoked magnetic fields. *Prog Neurobiol* 2000; 61: 495-523.

Kamada K, Sawamura Y, Takeuchi F, *et al.* Expressive and receptive language areas determined by non-invasive reliable method using functional magnetic resonance imaging and magnetoencephalography. *Neurosurgery* 2007; 60: 296-305; (discussion 305-6).

Kennan RP, Kim D, Maki A, Koizumi H, Constable RT. Non-invasive assessment of language lateralization by transcranial near infrared optical topography and functional MRI. *Hum Brain Mapp* 2002; 16: 183-9.

Kim H, Yi S, Son EI, Kim J. Material-specific memory in temporal lobe epilepsy: effects of seizure laterality and language dominance. *Neuropsychology* 2003; 17: 59-68.

Kimura D. functional asymmetry of the brain in dichotic listening. *Can J Psychol* 1967; 15: 156-65.

Klopper S, Buchel C. Alternatives to the Wada test: a critical view of functional magnetic resonance imaging in preoperative use. *Curr Opin Neurol* 2005; 18: 418-23.

Knake S, Haag A, Hamer HM, *et al.* Language lateralization in patients with temporal lobe epilepsy: a comparison with functional Doppler sonography and the Wada test. *Neuroimage* 2003; 19: 1228-32.

Knake S, Haag A, Pilgram G, *et al.* Language dominance in mesial temporal lobe epilepsy: A functional transcranial Doppler sonography study of brain plasticity. *Epilepsy Behav* 2006; 9: 345-8.

Knecht S, Deppe M, Ebner A, *et al.* Noninvasive determination of language lateralization by functional transcranial Doppler sonography: a comparison with the Wada test. *Stroke* 1998; 29: 82-6.

Knecht S, Deppe M, Ringelstein EB, *et al.* Reproducibility of functional Doppler sonography in determining hemispheric language lateralization. *Stroke* 1998; 29: 1155-9.

Knecht S, Henningsen H, Huber T, *et al.* Successive activation of both cerebral hemispheres during cued word generation. *Neuroreport* 1996; 7: 820-4.

Kneebone AC, Chelune GJ, Dinner DS, Naugle RI, Awad IA. Intracarotid amobarbital procedure as a predictor of material-specific memory change after anterior temporal lobectomy. *Epilepsia* 1995; 46: 97-103.

Kurthen M. The intra-carotid amobarbital test--indications--procedure--results. *Nervenarzt* 1992; 63: 713-24.

Kurthen M, Solumosi L, Linke D. Der intrakortidale Amobarbitaltest. *Radiologe* 1993; 33: 204-12.

Lee I, Jerman TS, Kesner RP. Disruption of delayed memory for a sequence of spatial locations following CA1- or CA3-lesions of the dorsal hippocampus. *Neurobiol Learn Mem* 2005; 84: 138-47.

Lee D, Sawrie SM, Simos PG, Killen J, Knowlton RC. Reliability of language mapping with magnetic source imaging in epilepsy surgery candidates. *Epilepsy Behav* 2006; 8: 742-9.

Lehericy S, Cohen L, Bazin B, *et al.* Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. *Neurology* 2000; 54: 1625-33.

Lencz T, McCarthy G, Bronen RA, *et al.* Quantitative magnetic resonance imaging in temporal lobe epilepsy: relationship to neuropathology and neuropsychological function. *Ann Neurol* 1992; 31: 629-37.

Lineweaver TT, Morris HH, Naugle RI, Najm IM, Diehl B, Bingaman W. Evaluating the contributions of state-of-the-art assessment techniques to predicting memory outcome after unilateral anterior temporal lobectomy. *Epilepsia* 2006; 47: 1895-903.

Loddenkemper T, Morris HH, Perl J. Carotid artery dissection after the intracarotid amobarbital test. *Neurology* 2002; 59: 1797-8.

Lohmann H, Drager B, Muller-Ehrenberg S, Deppe M, Knecht S. Language lateralization in young children assessed by functional transcranial Doppler sonography. *Neuroimage* 2005; 24: 780-90.

Loring DW, Meador KJ. Pre-surgical evaluation for epilepsy surgery. *Saudi Med J* 2000; 21: 609-16.

Loring DW, Meador KJ, Lee GP. Criteria and validity issues in Wada assessment. In: Benett I, ed. *The neuropsychology of epilepsy*. New York: Plenum Press, 1992: 233-45.

Loring DW, Meador KJ, Lee GP, Smith JR. Structural *versus* functional prediction of memory change following anterior temporal lobectomy. *Epilepsy Behav* 2004; 5: 264-8.

Loring DW, Meador K, Lee GP, *et al.* Wada memory asymmetries predict verbal memory decline after anterior temporal lobectomy. *Neurology* 1995; 45: 1329-33.

Loring DW, Lee GP, Meador K, *et al.* The intracarotid amobarbital procedure as a predictor of memory failure following unilateral temporal lobectomy. *Neurology* 1990; 40: 605-10.

Maestú F, Ortiz T, Fernandez A, *et al.* Spanish language mapping using MEG: a validation study. *Neuroimage* 2002; 17: 1579-86.

Mayer AR, Xu J, Pare-Blagoev J, Posse S. Reproducibility of activation in Broca's area during covert generation of single words at high field: a single trial FMRI study at 4 T. *Neuroimage* 2006; 32: 129-37.

Michelucci R, Valzania F, Passarelli D, *et al.* Rapid-rate transcranial magnetic stimulation and hemispheric language dominance: Usefullness and safety in epilepsy. *Neurology* 1994; 44: 1697-700.

Milner B, Branch C, Rasmussen T. Study of short-term memory after intracarotid injection of sodium amytal. *Trans Am Neurol Assoc* 1962; 87: 224-6.

Muller E, Huk W, Pauli E, Wenkel H. Maculo-papillary branch retinal artery occlusion following Wada test. *Arch Clin Exp Ophthalmol* 2000; 8: 715-8.

Noguchi Y, Takeuchi T, Sakai KL. Lateralized activation in inferior frontal cortex during syntactic processing: event-related optical topography study. *Hum Brain Mapp* 2002; 17: 89-99.

Novelly RA, Williamson PD. Incidence of false-positive memory impairment in the intracarotid amytal procedure. *Epilepsia* 1989; 30: 7-11.

Ogden JA. Language and memory functions after long recovery periods in left hemispherectomized subjects. *Neuropsychologia* 1988; 26: 645-59.

Ohta Y, Nariai T, Ishii K, *et al.* Meningo-angiomatosis in a patient with focal epilepsy: value of PET in diagnoses and preoperative planning of surgery. *Acta Neurochir (Wien)* 2003; 145: 587-91.

Oxbury SM, Oxbury JM. Intracarotid amytal test in the assessment of language dominance. *Adv Neurol* 1984; 42: 115-23.

Paglioli E, Palmini A, Portuguez M, *et al.* Seizure and memory outcome following temporal lobe surgery: selective compared with nonselective approaches for hippocampal sclerosis. *J Neurosurg* 2006; 104: 70-8.

Palez JM, Geller EB, Wong O, *et al.* Relationship of quantitative FDG-PET temporal lobe metabolism and lateralized memory function and Wada testing. *Epilepsia* 1998; 39(Suppl 6): 246.

Papanicolaou AC, Simos PG, Breier JI, *et al.* Magnetoencepahlographic mapping of the language specific cortex. *J Neurosurg* 1999; 90: 85-93.

Papanicolaou AC, Simos PG, Castillo EM, *et al.* Magnetoencephalography: a non-invasive alternative to the Wada procedure. *J Neurosug* 2004; 100: 867-76.

Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology* 1991; 41: 697-702.

Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 1998; 15: 333-43.

Poline JB, Vandenberghe R, Holmes AP, *et al.* Reproductibility of PET activation studies: Lessons from a multi-center European experiment. EU concerted action for functional imaging. *Neuroimage* 1996; 4: 34-54.

Perrine K, Gershengom J, Brown ER, Choi IS, Luciano DJ. Devinsky O. Material-specific memory in the intracarotid amobarbital procedure. *Neurology* 1993; 43: 706-11.

Rabin ML, Narayan VM, Kimberg DY, *et al.* Functional MRI predicts post-surgical memory following temporal lobectomy. *Brain* 2004; 127: 2286-98.

Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. *N Acad Sci* 1977; 29: 355-69.

Rausch R, Henry TR, Ary CM, Engel JJ, Maziotta J. Asymmetric interictal glucose hypometabolism and cognitive performance in epileptic patients. *Arch Neurol* 1994; 51: 139-44.

Richardson MP, Stange BA, Thompson PJ, *et al.* Pre-operative verbal memory fMRI predicts post-operative memory decline after left temporal lobe resection. *Brain* 2004; 127: 2419-26.

Rihs F, Sturzenegger M, Gutbrod K, Schroth G, Mattle HP. Determination of language dominance: Wada test confirms functional transcranial Doppler sonography. *Neurology* 1999; 52: 1591-6.

Risse GL, Hempel A. Early signs of lateralization in focal epilepsy. In: Jambaqué I, Lassonde M, Dulac O, eds. *Neuropsychology of childhood epilepsy*. New York: Kluver Academic/Plenum Publishers, 2001: 85-96.

Saint-Amour D, Walsh V, Guillemot JP, Lassonde M, Lepore F. Role of primary visual cortex in the binocular integration of plaid motion perception. *Eur J Neurosci* 2005; 21: 1107-15.

Salanova V, Markand O, Worth R, *et al.* Presurgical evaluation and surgical outcome of temporal lobe epilepsy. *Pediatr Neurol* 1999; 20: 179-84.

Seghier ML, Lazeyras F, Annami JM, Khateb A. Inter-individual variability of fMRI activations in phonologic and semantic judgment tasks. *Int J Psychophysiol* 2002; 45: 121.

Simos PG, Papanicolaou AC, Breier JI, *et al.* Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping. *J Neurosurg* 1999; 91: 787-96.

Spinelli L, Lazeyras F, Willi JP, *et al.* Les nouvelles techniques d'imagerie du cerveau. *Rev Med Suisse Romande* 2003; 123: 51-3.

Springer JA, Binder JR, Hammeke TA, *et al.* Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. *Brain* 1999; 122: 2033-46.

Stanford LD, Chelune GJ, Wyllie E. Neuropsychological functioning of children with hippocampal sclerosis. *Epilespsia* 1998; 39(Suppl 6): 249.

Staz P, Strauss E, Wada J, Orsini DL. Some correlations of intra- and interhemispheric speech organization after focal brain injury. *Neuropsychologia* 1988; 26: 345-50.

Strauss E, Gaddes WH, Wada J. Performance on free-recall verbal dichotic listening task and cerebral dominance determined by carotid amytal test. *Neuropsychologia* 1987; 25: 747-53.

Tatlidil R, Luther S, West A, Jadvar H, Kingman T. Comparison of fluorine-18 deoxyglucose and O-15 water PET in temporal lobe epilepsy. *Acta Neurol Belg* 2000; 100: 214-20.

Theodore WH. (15)O water positron emission tomography in language localization: a study comparing positron emission tomography visual and computerized region of interest analysis with the Wada test. *Ann Neurol* 1999; 45: 662-5.

Théoret H, Pascual-Leone A. Transcranial magnetic stimulation in the study of cognition. In: Hugdahl K, ed. *Experimental methods in neuropsychology*. Netherlands: Kluwer Academic Publishers, 2002: 1-24.

Tonini C, Beghi E, Berg AT, *et al.* Predictors of epilepsy surgery outcome a meta-analysis. *Epilepsy Res* 2004; 62: 75.

Valton L, Mascott CR. Quelle est la place du test de Wada dans le bilan préchirurgical des épilepsies pharmaco-résistantes chez l'adulte? *Rev Neurol* 2004; 160(HS 1): S164-S169.

Van Paesschen W, Revesz T, Duncan JS, *et al.* Quantitative neuropathology and quantitative magnetic resonance imaging of the hippocampus in temporal lobe epilepsy. *Ann Neurol* 1997; 42: 756-66.

Wada J. A new method for the determination of the side of cerebral speech dominance. *Am J Psychiatry* 1949; 14: 221-2.

Wada J, Rasmussen T. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance: experimental and clinical observations. *J Neurosurg* 1960; 17: 266-82.

Wassermann EM, Blaxton TA, Hoffman EA, *et al.* Repetitive transcranial magnetic stimulation of the dominant hemisphere can disrupt visual naming in temporal lobe epilepsy patients. *Neuropsychologia* 1999; 37: 537-44.

Watanabe E, Maki A, Kawaguchi F, *et al.* Non-Invasive assessment of language dominance with near-infrared spectroscopic mapping. *Neurosci Lett* 1998; 256: 49-52.

Watson N, Dodrill C, Farrel D, Holmes MD, Miller JW. Determination of language dominance with near-infrared spectroscopy: comparison with the intracarotid amobarbital procedure. *Seizure* 2004; 13: 399-402.

Weber B, Wellmer J, Schur S, *et al.* Presurgical language fMRI in patients with drug-resitant epilepsy: effects of task performance. *Epilepsia* 2006; 47: 880-6.

Wiebe S, Blume WT, Girvin JP, Eliasziw M. Effectiveness and efficacy of surgery for temporal lobe epilepsy study group. A randomized controlled trial of surgery for temporal lobe epilepsy. *N Engl J Med* 2001; 345: 311-8.

Wyllie E, Naugle R, Awad I, *et al.* Intracarotid amobarbital procedure: Prediction of decreased modality-specific memory scores after temporal lobectomy. *Epilepsia* 1991; 32: 857-64.

Yetkin FZ, Swanson S, Fischer M, *et al.* Functional MR of frontal lobe activation: comparison with Wada language results. *AJNR* 1998; 19: 1095-8.

Yuan W, Szaflarsky JP, Smithorst VJ, *et al.* fMRI shows atypical language lateralization in pediatric epilepsy patients. *Epilepsia* 2006; 47: 593-600.

Zatorre RJ. Perceptual asymmetry on the dichotic fused words test and cerebral speech lateralization determined by the carotid sodium amytal test. *Neuropsychologia* 1989; 27: 207-19.