154 The Wada Test-60th Year Anniversary Update-In Epilepsy Surgery

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Prologue

This is the 60th and 53rd Anniversary year, respectively, of the first Carotid Amytal Injection performed in Japan in 1948 [1] and its introduction to North America via the Montreal Neurological Institute in 1955 [2,3]. During this time, the prevailing neuro-investigative landscape of over a half century ago when these events had taken place were all invasive in nature except for 8 channel EEG and skull X-ray. Neuropsychology was a budding research tool.

Prior to the development of the Wada Test, the understanding of the brain mechanism of cognitive function was elusive and based largely on a chance encounter with a localized lesion with postmortem clinical–pathological correlation. The introduction of the Wada Test added an entirely new dimension since it enabled us to electively assess each cerebral hemispheric function through reversible deactivation in a behavioral state. The rapidity with which the Wada test was accepted and disseminated worldwide may be viewed as a reflection of the then prevailing unmet need for the prevention of postsurgical cognitive side effects. Such need was obviously greatest for an elective procedure especially for epilepsy surgery.

The publication in 1954 of Penfield and Jasper's [4] "Epilepsy and the Functional Anatomy of the Human Brain" had significantly invigorated interest in epilepsy surgery and therefore a need was most acutely felt in an ever expanding community of neurologists and neurosurgeons involved in the management of medically refractory epilepsy as an increasing number of epilepsy centers were created during the latter half of the twentieth century.

During this period, the Wada Test not only provided an unambiguous result on the pattern of language representation as it was originally concei ved, but also lead to further speculation and investigations into hemispheric specialization for example, the melodic/prosodic expression which we observed during Wada testing at UBC as well as attentional asymmetry [6,221]. There has also been verification that the mechanism underlying sign language is the same as that for spoken language [227,229]. It has also provided a hypothesis that later learned languages may be more bilaterally represented than the first language learned [9]. Most importantly, it has given us invaluable insight into the plastic reorganization of language function in patients with epilepsy.

The memory component that was later added to hopefully predict rare but devastating global amnesia, had produced challenging results. Indeed severe postoperative amnesia has been rare since the inception of the Wada Test but debate continues on the prediction and the nature of postoperative "poor memory." However, the outcome of the memory component so far appears to have added a complementary component along with other diagnostic measures pointing to epileptogenic laterality.

In the mean time, unexpected discontinuation of Amytal production by Eli Lilly had a profound effect. Although the supply issue was eventually resolved by the resumption of amytal production by Ranbaxy, the crisis prompted many epilepsy centers to search for drugs that can possibly be employed as a substitute to amytal. As a result, the use of sodium secobarbitol [10], methohexital [11], propofol [12–14], and etomidate [15] were reported. In the latter, serial infusions are made to maintain a level of anesthesia at an added risk due to prolonged catheterization. With the amytal shortage, expectation was raised for brain imaging, a research tool, to become a valid and dependable clinical tool for the presurgical assessment of language and memory function in individual patient with epilepsy.

In 1993, 45 years after the Wada Test was born, a worldwide survey response of 71/102 epilepsy centers indicated that 95% of them were using the Wada test, and 85% very frequently as a tool for presurgical investigation [16]. Three/71 centers responded that they were not using the Wada test due to non-medical reasons. Fifteen years later in 2008, another international survey response of 92/207 epilepsy centers indicated that 87% of responding epilepsy centers were using the Wada test; nearly 40% frequently and 47% less frequently. Thirteen percent were reported not using it for medical reasons. Concentrations of using centers in North America were assumed to be related to medical-legal implications [17].

An informal survey conducted on the David Loring's NPSYCH listserve [18], which is largely subscribed to by neuropsychologists, revealed that many sites continue to do the Wada test now. This was a very limited informal survey as there are epilepsy centers where the neurologist conducts the testing and they would not have been aware of this survey. Twenty nine of 31 sites identified that the Wada test is being used. Two of 31 sites were using Methohexital instead of amytal. Eight of 31 sites were doing selective Wada protocols, for example just on suspected cases for atypical language dominance or patients with a left temporal focus. Optical imaging had replaced Wada testing at one site. Another site relied on PET/SPECT/MRI and CCTV-EEG monitoring. Again, many active epilepsy centers were not approached during this informal survey. In Europe, 16/23 sites surveyed there during 2000–2005 continued to do a Wada protocol with a relatively low risk (1.02%) of morbidity (personal communication Frank Oltmans).

These results appear to represent a transitional state in the back drop of a remarkable transformation of a neuro-diagnostic landscape surrounding epilepsy surgery during the past decades including the maturation of neuropsychology as a clinically relevant subspecialty, the development of long term video/EEG monitoring (electro-clinical correlation leading to better definition of semiology and objective peri-ictal and ictal cognitive assessment), and the development and proliferation of brain imaging approaches particularly high definition structural MRI. They all contributed to the gradual phasing out of earlier invasive procedures except for occasional use of intracranial EEG monitoring.

Ten years ago in 1998, 50 years after the Wada test was developed we wrote a chapter on this topic. This updating chapter (1) highlights information derived by the Wada test with emphasis on dynamic reorganization of language representation and memory related issues, (2) a selective review on the evolving state of brain imaging with some emphasis on commonly used ones as a complementary tool for presurgical cognitive evaluation, and (3) the Wada Test beyond 2008.

The Assessment of Language Via Wada Protocol

It has been recognized that severe epilepsy can affect language function and lead to atypical cerebral dominance. Intractable, frequent generalized tonic–clonic seizures and status epilepticus are associated with language problems, particularly if the seizure focus is lateralized to the language dominant hemisphere. The neurosurgeon and epileptologist can decide if more detailed localization is required via intraoperative mapping techniques once cerebral hemispheric dominance for language has been established. When chronic seizures begin at an early age, prior to age six, with or without a structural lesion, there is a higher risk for the presence of cerebral reorganization. More recently, this phenomenon has been demonstrated using pediatric populations [226] and by using different techniques such as MEG [20]. The patterns of hemispheric language dominance which we discussed in our first chapter are seen in *Table 154-1*. These ranges come from studies completed at epilepsy centers.

The diversity in Wada protocols has contributed to the range of incidence in atypical patterns of language. Each center has established protocols where the emphasis has been on speech production including naming (i.e., name the object being shown to you), automatic or sequenced speech (i.e., counting) as well as repetition. Over time, many protocols began to incorporate auditory comprehension including following simple commands (i.e., stick out your tongue), repetition of short phrases, and the reading of simple statements.

However a more critical question is "What does the data reflect?" Is it the language impairment of the injected hemisphere or the language capacity of the uninjected hemisphere? This becomes most challenging when one is determining the possible bilateral hemispheric representation of language. It also supports the recommendation of having an EEG recording simultaneously throughout the test to chronologically assess the cerebral effects of the amytal and the recording of behavioral changes over time.

Our clinical experience at UBC was that patients with bilateral dominance would name objects, follow commands, repeat a nursery rhyme, and read simple cards with injection to either hemisphere. We also observed that some patients had speech production transfer to the right hemisphere but language comprehension appeared to reside in the left hemisphere. These patients were identified as having bilateral dissociated or asymmetrical representation.

Risse and her group accurately point out that certain tasks such as simple rote speech in the right hemisphere may not be a valid example of bilateral language. More importantly, she suggests that not all patterns of bilateral language are a reflection of insult and language reorganization. It may in fact be representing a normal developmental variant explaining that there may be some genetic predisposition that allows the development of language in both hemispheres [22].

The Assessment of Memory Via Wada Protocol

Milner [23] noted that there was an urgent clinical need in the early 1950s to assess potential surgical risk for lasting anterograde amnesia following a unilateral temporal lobectomy. The ipsilateral deactivation by amytal of the healthy temporal lobe was expected to create a brief amnestic state if the contralateral hippocampus is compromised. The clinical challenges at this

Table 154-1

Patterns of hemisphere dominance for language [21]

	Left Hemisphere dominance	Bilateral Hemisphere dominance	Right Hemisphere dominance
Right-handers	92–96%	7%	4–15%
Left handers	50–70%	19%	15–20%
Mixed handedness	50–70%	15–20%	15–20%

time included that the injection was still being made into the common carotid artery and without angiography. There was no assurance of actual drug distribution. The memory protocol had to assess memory capacity but not be confounded by the presence of aphasia. Successful recognition testing of the test stimuli from a multiple-choice array would be accepted as a "pass" as amnestic patients often failed both free recall and recognition memory tasks. Behaviorally, it had been observed that patients could often recognize objects that they could not name during drug effect and that some individuals could also not recognize objects that they had named correctly. More importantly, the original purpose of memory testing during a Wada test was to attempt to predict only the risk for global amnesia [24,25].

As mentioned in our original chapter, the Wada technique has provided an opportunity to investigate material-specific memory problems. However the material-specific/dual-encodability factor of test stimuli has created challenges. Most nonverbal material can have verbal labels attached to it. There are very few stimuli or tasks that are so material-specific that only the unilateral, nondominant hemisphere is involved in the processing. Meador and Loring [26] pointed out that Wada protocols typically have not relied on word memory tasks due to the aphasia confound when the language dominant hemisphere is injected. They cautioned that these results could not be generalized to all other Wada procedures due to the aphasia confound. More importantly, the results from Wada testing may have limited correlation to the variable of seizure outcome postoperatively.

Secondly, the relationship between Wada test results to hippocampal function is one of controversies. Variability in the memory test results correlating with different hippocampal subfields may in part be reflecting histological technical differences. Meador and Loring [5] discuss how the Wada test does not typically perfuse the posterior two-thirds of the hippocampus. However, no significant correlation between filling of the posterior cerebral artery and Wada memory score was found while injecting contrast agent before the Wada to detect posterior cerebral arterial filling [27]. The likely explanation would be, therefore, deafferentation of the posterior hippocampus from the cortical areas is more relevant than direct anesthesia of the structure. Results of EEG observation during Wada test are consistent with this view [28,29].

Memory scores from Wada protocols may be affected by the timing of the injection. Grote et al [30] demonstrated that Wada memory scores were lower for the second injection when performed on the same day but were similar for the first and second injections if they were conducted on separate days. Various epilepsy centers have compared the left and right memory scores as a percentage of the total possible score while also balancing the injection order between the epileptic focus and nonfocus side of injection. This finding highlights some of the potential challenges when comparing studies from different epilepsy centers.

The general approach during a Wada protocol is to present stimuli while one hemisphere has been anesthetized. Recall and recognition are done when the amytal effects have dissipated. It is reported to have a 48% predictive value for postoperative amnesia [31]. It is more challenging when one has anesthetized the language dominant hemisphere but allowing the patient to have a multisensory experience including touching the object, hearing the name of the object and ensuring that it is in the correct visual field is essential for optimizing test administration. Many seasoned Wada assessors have realized that information is often encoded by what appears to be an obtunded patient.

Another approach (Dodrill Seattle protocol) involves a memory protocol that is reported to have a 76% predictive value for postoperative memory states, and shows the test stimuli prior to injection and continuously shows the items following injection. The subject names the object, then experiences a brief interference task, and then is asked to recall the object just before the card. High risk for postoperative amnesia is determined when a patient cannot recall the named item and that the hemisphere injected is the one needed for memory functioning [31–33].

Again it can be controversial about what is being tested. If items are remembered correctly and a passing score is obtained, is the nonanesthetized lobe intact to handle memory? If there is poor performance, then does the non-anesthetized hemisphere have poor capacity to handle memory? There has also been the interpretation that if recognition does not occur, then memory function relies heavily on the hemispheric injected. Our UBC experience has been to view that the test scores obtained have been a reflection of the non-anesthetized hemisphere. It has been reported that muteness, dysphasia and the arterial distribution of amytal may not significantly impact on the interpretation of Wada memory testing [34].

Aberrant Organization of Cognitive Function

Epileptic activity has been known to not only exert noxious/adverse effects on cerebral function in general but also activate plastic and compensatory hemispheric processes. Potential significance of the latter is suggested by increased cognitive risk with later- but not early-onset seizure group postoperatively [7]. Differences found are small and relative but this “age of onset effect” may reflect age dependent cognitive plasticity that diminishes with age in response to focal epileptogenesis [35]. Some comments relevant to organization/reorganization of hemispheric language and memory function are given as follows in the light of the results of Wada test and some imaging technologies.

Language

Several risk factors that had been underscored for promotion of atypical language representation were (1) greater tissue loss in the left hemisphere, (2) early seizure onset, (3) handedness, and (4) proximity of epileptic lesion to language area [36]. The significance of early seizure onset has been repeatedly confirmed [37–40] though the upper age limit appears to extend beyond 9–16 years of age depending on the circumstances [41–44].

The third issue of handedness is intriguing and the precise relationship between handedness and cerebral language dominance remains unclear. It was stated that “an early lesion that does not modify hand preference is on the whole unlikely to change speech representation” [36]. Although handedness is a useful clinical marker, change of laterality of handedness and language dominance can occur independently. There is also a possibility of naturally endowed right language dominance in which a right cerebral lesion may cause laterality change in handedness/language dominance either alone or together [45]. Finally, the significance of lesion location has to be viewed with a new perspective based on our experience that the functional consequence of localization related epilepsy is often not localization related. For example, an extensive cyst formation next to language areas may not cause shift of language function [46]. Partial seizures associated with lesions near the frontal and temporal language areas maintain left hemisphere language in children. In adults epileptogenic lesions in the vicinity of language area may cause perilesional language reorganization [47]. Later onset disease in childhood and left-sided congenital lesions tended to maintain left representation [37,48,49]. Reorganization of cortical function is known to result from abnormal, neuronal/glial proliferation (cortical dysplasia) but not abnormal cortical organization (polymicrogyria) [50]. Transhemispheric transfer of language function occurs frequently in mesial temporal lobe epilepsy [20,48].

On the other hand, Wada tested cases of left mesial temporal lobe epilepsy has fMRI evidence of more bi-hemispheric distribution of language organization including contralateral homologous areas both pre- and postoperatively [51–53] though evidence of precise homology is lacking [54]. In addition to age factor, some functional elements appear to play an important role for reorganization of language function: atypical representation cases verified by Wada test with left mesial temporal lobe epilepsy were found to have higher interictal discharge frequency and lateral temporal-related sensory aura (presumably due to seizure spread) than those left language dominant cases [55]. This finding poses an important question as to potential long-term consequence of interictal discharge since it is conceived to have only a transient disruptive effect on cortical cognitive function [56].

The general pattern of language representation found by the Wada test in epilepsy population indicates a continuum from left to right, i.e., L, L > R, L = R, L < R and R. Our observation suggests that hemispheric language representation is not a clear cut dichotomous but rather continuous variable which appears more compatible with many neuroimaging results. Indeed combined quantitative–qualitative evaluation of Wada test results yields a more graded account of the varieties of language representation [57–59]. Among the atypical language patterns, bilateral L > R representation appears to be the majority. L = R is rare but displays expressive and receptive difficulty bilaterally and equally. Historically, there have been suggestions that only a unilateral injection was needed during a Wada investigation but this data would support that both hemispheres need to be assessed for language. Unilateral injection judged to be appropriate may lead to erroneous conclusion [60]. Also, there are patients with no linguistic disruption despite hemiplegia on either side. Two of the three such patients had no language impairment following left and right temporal lobectomy, respectively [61]. The absence of linguistic impairment with the Wada test does not exclude ipsilateral language representation [62] and no cortical mapping was done in the reported cases. It is noteworthy that one of our UBC series with no language disruption bilaterally despite hemiplegia was ambidextrous as were the reported three cases. Some bilateral cases have asymmetrical dissociated representation with the Broca on one side and the Wernicke on the other [59,63–65]. The finding suggests that anterior frontal and posterior temporal functions may be differentially affected [29] and that reorganization of expressive and receptive language capabilities can occur independently [57,58,66].

Atypical language representation with right dominance or bilateral representation has been discussed largely on the basis of left hemisphere epilepsy. However, suggestive evidence of transfer of language function from a “natural” right dominant hemisphere to the left exists in some right hemisphere epilepsy. Among right hemisphere epilepsy, atypical representation occurs in later- rather than early-onset. The latter observation raises a potential scenario of early right hemisphere epilepsy interfering with the establishment of “natural” right language dominance and causing it to shift to the left hemisphere in a person predisposed to develop right dominance [67]. Likely existence of “natural” bilateral representation must be kept in mind [58,68]. In this regard, structural basis of transhemispheric language representation and more specifically how white matter pathways are affected in aberrant processes of brain reorganization remains unknown. A recent MRI study revealed maturational changes including increased axonal fiber organization especially in the arcuate fasiculus (AF), during late adolescence (age 16) suggesting that fiber organization rather than myelination may play a greater role in the AF development [69]. The AF is the important anatomical language pathway in classical aphasiology. One way of evaluating morphological correlates of language reorganization would be to use diffusion tensor imaging (DTMRI – see later). The presence of a "natural" right hemisphere dominance and its potential reorganization particularly in right-sided epilepsy is obviously an intriguing area of future enquiry since recent brain imaging studies of right-handed healthy population suggest 4–6% bilateral representation [70,71] and up to 7.5% right dominance [218] though a fMRI study of a 100-right-handed healthy population failed to identify a single person with right dominance [71].

Experience with hemispherectomy in children with severe epilepsy taught us that extensive left hemisphere damage can cause contralateral transfer of language with good language capability though with a crowding effect on right hemisphere functions. Through Wada test results, we now know that a well-circumscribed left epileptogenic focus remote from eloquent cortical area can also cause atypical representation. Hippocampal focus appears to be particularly potent in activating "reorganizational force" [73–77].

Cortical mapping studies in left mesial temporal lobe epilepsy found aberration of the left temporal language area either more anteriorly placed [228] or having a noncontiguous pattern [78]. The latter was more frequent among those with Wada verified cases with bilateral dominance [79]. This finding needs to be replicated but suggests a pervasive nature of reorganizational force in patients with mesial temporal lobe epilepsy. Altogether, early onset epileptic activity particularly that involving the hippocampus within the language dominant hemisphere appears to play a powerful role in initiating reorganization of language function.

Memory

Aberrant language organization has claimed a lion's share of our attention for the cognitive consequence of epilepsy. However, a similar process appears to take place in hemispheric memory mechanism. Patients with early onset seizure disorder tend to have less cognitive decline in the domain of memory after left temporal lobectomy [80–82]. Among temporal lobe epilepsy, Wada-verified atypical language organization was found more frequently in early seizure onset group (70%) than late onset group (30%). Those with atypical organization showed relatively better postsurgical memory outcome in several neuropsychological measures than typical organization group. This "age of onset effect," presumably protective in nature, was conceived to be due to presurgical functional reorganization of memory mechanism [35]. A Wada memory study on left temporal lobe epilepsy found a significant correlation between right memory function and age at onset with onset after 5 years of age being associated with poor memory function, suggesting a "critical period" for right hemisphere reorganization of verbal memory before that age [83]. Results of recent brain imaging studies support this notion. fMRI studies have shown that in left temporal lobe epilepsy verbal memory tasks involve the right temporal lobe, a pattern that is not found in healthy normal population [84,85]. This is consistent with the reported predictive value of memory associated event-related potentials recorded from the right hippocampus in left temporal lobe epilepsy [86]. Similarly, a magnetoencephalographic study showed activation of right mesial temporal lobe with a trend of less left mesial temporal neuromagnetic activity during verbal memory task in left temporal lobe epilepsy with hippocampal dysfunction than in normal control subjects. The finding suggests that the patients with left hippocampal dysfunction are more likely to recruit the right mesial temporal lobe for verbal memory tasks [87]. The effectiveness of such reorganization is not well understood and how it interacts with atypical language representation remains to be explored [88]. Different patterns of reorganization for language and memory function was also found in right language dominant patients with left temporal lobe epilepsy when compared with left language dominant patients with left or right temporal lobe epilepsy [89]. Differential reorganization mechanisms between language and memory function, i.e., a shift of verbal memory to the non-dominant right hemisphere can occur independently without concomitant change of hemispheric language organization in left temporal lobe epilepsy is highly suggestive [90,91]. It is obvious that the outcome of verbal memory function must depend on the extent and the quality of language/memory reorganization involving both dominant and non-dominant hemispheres and, therefore, how to precisely define the nature and pattern of reorganization is the challenge facing us now.

The hippocampus has been regarded as a crucial component in the process of episodic memory but it appears to contribute to other cognitive capabilities such as semantic memory [223]. A recent neurophysiological study suggested a possibility that the left hemisphere language may be linked to a process of learning and memory trace formation with putative advantage of building up memory traces for any language elements [93]. The nature of such advantage remains unknown. However, since hippocampal focus/lesion in many intractable temporal lobe epilepsy is assumed to have occurred during first years of life, it implies that the hippocampus plays a substantial role not only in the memory process but also in establishing language dominance.

Alternate Techniques for Determining Language Dominance & Memory Capacity

Historically, noninvasive approaches such as tachistoscopic presentations or dichotic listening have attempted to determine dominance. However, no method has been able to unequivocally measure cerebral dominance. Visual half-field approaches must consider several methodological factors [94,95] to maximize the effectiveness of this approach. Bourne also points out that divided visual field tasks can be complex and fatiguing. Dichotic listening [96] has not reached reliability for atypical language dominance such as bilateral representation and fMRI imaging has suggested that dichotic listening may involve frontotemporal and not just temporal networks [97]. The lack of reliability of ear advantage in dichotic listening was revealed by Strauss et al. [98] who showed that although the right ear advantage was consistent in 86% left hemisphere dominant – Wada tested subjects; a right ear advantage was also evident for 50% of the right and 71% of the bilateral dominance, respectively. A more recent study aiming to examine the magnitude of ear advantage on an individual basis, the fused rhymed dichotic words test (FDWT) in 61 Wada tested patients indicated extreme asymmetries are associated with contralateral speech dominance while lesser asymmetries are more often associated with bilateral speech representation [99]. Another FDWT study reported concordance but the number of patients involved is very small, i.e., 5 Wada tested children with three left and two bilateral representation [100].

Electrophysiological study of Wada tested patients with spectral analysis of photic and click evoked response showed over 90% of accuracy with miscalculation in 1/16 left dominance and 1/6 right dominance [101]. Event related potential analysis in 12 Wada tested patients including 4 bilateral dominance cases yielded unreliable and conflicting results [102].

The past two decades have witnessed spectacular advances in invivo imaging technologies for morphological to functional assessment of the human brain in health and disease. In the epilepsy population, the evolution of MRI scanning has provided a solid window to the anatomical structure, asymmetries, pathologies, and has changed the vista of clinical epilepsy. Based on well established prenatal peri-Sylvian asymmetry [103,104], a structural MRI study found concordance between planum temporale (PT) asymmetry and Wada tested patients (10 left dominance with PT L > R; 1 right dominance with PT R > L) [105]. However, another study with larger number of Wada tested patients (20 left, 11 right and 13 bilateral representation) failed to correlate laterality between PT and language. Interestingly, this study found more white matter in the dominant Broca's area in either left or right dominant group but there was no reliable difference to identify individual language laterality [106]. In this regard, the development of functional diffusion tensor imaging (DTMRI) opens a new vista. It is dependent on the tendency of water molecules to diffuse in the direction of myelinated fiber bundles, enabling diffusion-weighed MRI to yield tensor maps of fiber orientation [107]. Thus DTMRI allows the reconstruction of white matter pathways leading to virtual in vivo dissection of the human brain [108] and has so far disclosed details of peri-Sylvian language networks [109] and arcuate fasiculus (AF) asymmetry with higher fractional anisotropy (FA), i.e., measure of magnitude and direction of fiber tracts, in the left hemisphere [110] of healthy subjects. The significance of FA in the left temporal lobe and reading ability in children (8–18 years) has been shown [111]. An image from Arjan-Hillebrand's work also visually demonstrates the role of the left temporal lobe in letter fluency for "group-averaged" data. In refractory epilepsy, evidence of reorganized language function has been identified by combined DTMRI and fMRI [112,113]. In addition, a recent DTMRI study with a small number of patients suggested that integrity of AF is related to memory performance in the left but not right temporal lobe epilepsy [114]. Although replication with larger sample sizes will be required, this study not only indicates a promising future of DTMRI for further exploration of structure–function correlation in language reorganization but also has potential for contributing insight into epilepsy-induced functional alteration such as secondary epileptogenesis.

It has been estimated that MRI scans can be interpreted as being "normal" in 30% of the cases identified as nonlesional epilepsy [115]. However, structural MRI has also significantly contributed not only to quantitative analysis but also to the identification of pathology such as mesial temporal sclerosis. Although structural MRI does not directly reveal functional information of the structures imaged, it can help identify hippocampal asymmetry, for example, that may provide a sensitive index for their functional state and surgical outcome [116]. Voxel-based morphometry yields significant group difference between the brains of healthy and epilepsy population but it appears to have little clinical utility for individual comparison [117]. How much more clinically relevant information can be extracted from quantitative/volumetric analysis of structural MRI in the individual patient remains a challenge.

Many other brain imaging approaches began to be applied in epilepsy as a clinical research tool primarily for the cognitive evaluation and validation purpose with Wada tested patients. Data obtained by brain imaging based on activation and the Wada Test based on deactivation are complementary while discordance between the two continues to be debated. For the purpose of this chapter, the emphasis will be on more commonly used techniques for the investigation of language dominance and memory performance in the context of Wada test. *Table 154-2* provides a synopsis of techniques available for presurgical evaluation with respective limitation.

TMS – Transcranial Magnetic Stimulation

TMS is a noninvasive method of "deactivation" by using electromagnetic induction. Repetitive transcranial magnetic stimulation (rTMS) can induce longer lasting effects, which may lend itself well to assessing cognition by the induction

Table 154-2

Utility and limitations of presurgical cognitive assessment techniques

Procedure	Principle	Language	Memory	Comments
Wada	Deactivation	+	+	Invasive, efficient utility for lateralization of language dominance
rTMS	Deactivation	+	–	Speech arrest can assist in determining language dominance, however one needs to know where to stimulate
MRI	Structure	–	+	Expensive, structural asymmetries and/or mesial temporal sclerosis may imply dysfunction, expensive
DTMRI	White matter pathways	+	–	Expensive, inference from arcuate fasciclus asymmetry
fMRI	Activation hemodynamic change	+	–	Expensive, difficult with young children and the cognitively challenged, utility may be in localization
MEG	Magnetic flux directly associated with event-related activation	+	–	Expensive, poor spatial resolution, only receptive language has been assessed in controls
fTCD	Activation hemodynamic change	+	–	Lack of temporal bone window in 15–20% general population, utility is in lateralization
NIRS/OT	Activation hemodynamic change	+	–	Superficial brain areas only, inability to access deep brain structures, surface data only
SPECT	Activation hemodynamic change	+	–	Minimally invasive, poor spatial/temporal resolution, utility in lateralization
PET	Activation hemodynamic change	+	+	Expensive, minimally invasive, poor spatial/temporal resolution. Utility in lateralization, inferred dysfunction if hypometabolism present

of speech arrest for example. This technique has been reported to correlate reasonably well with Wada test results [118–120]. Wassermann et al's study found that rTMS of language areas produces an increase in errors of visual naming but not word reading. It was the first study to show rTMS effects on spoken language without induction of speech arrest. On the other hand, in Jennum's study, dysphasia secondary to the contralateral facial and laryngeal muscle contraction was difficult to differentiate from aphasia. The validity of cognitive evaluation by rTMS depends on reliable elicitation of speech disruption unencumbered by the accompanying involuntary muscle activity. EMG analysis indicated that rTMS applied over a posterior site, lateral to the motor hand area of both left and right hemisphere caused speech disruption accompanied by mentalis muscle activation while rTMS applied over an anterior site on the left but not the right hemisphere resulted in the speech disruption without mentalis muscle activation [121]. This nonmotor class of speech disruption is the one which suggests potential utility of rTMS in clinical setting. Another rTMS study of Wada-tested 17 epilepsy surgery candidates, reported a lack of reliability for the presurgical evaluation of language dominance [122]. Theodore [123] also reports that rTMS appears to reveal significant bilateral language function in patients with uncontrolled partial seizures and it remains unclear if this is an artifact of the technique or some other physiological phenomenon. At this time, he did not feel that rTMS could be used clinically for the determination of language dominance or memory lateralization. His paper provides an overview of some of the parameters of this technique. For memory assessment by rTMS, a study found no quantitative but qualitative changes only in the left temporal lobe epilepsy patients [124].

In addition to facial and laryngeal muscle contraction interfering with speech performance, rTMS carries a small but definite risk for seizures, particularly in epileptic patients [8]. For potential benefit, rTMS could play a complementary role in an individual through deactivation to characterize behavioral effects in fMRI assessment [125] since, as is discussed later, task dependent fMRI activation does not independently confirm that such activation is necessary or critical. More recent reviews are by Devlin and Watkins [126] and Robertson, Theoret and Pascual-Leone [22].

fTCD-Functional Transcranial Doppler Sonography

fTCD measures cerebral perfusion changes related to neuronal activation in a way comparable to fMRI and $_{15}$O PET. fTCD makes it possible to compare perfusion changes (by measuring blood flow velocities) during repeated performance of a task (word generation by letter) within the territories of the 2 middle cerebral arteries that comprise the potential language zones. This quantitative technique provides an operational laterality index which resembles the one obtained by Wada [3,127,128]. It has been validated by direct comparison of results with Wada testing [129] and fMRI results [130]. In Knecht et al's study [129], 4/19 Wada tested patients could not be examined due to the absence of acoustic temporal bone window for insonation while of the remaining 11 patients, 8 left and 3 bilateral dominance representation were concordant. Another study assessed 12 Wada tested patients but an acoustic temporal window was missing in 1 [131]. Among the remaining 11 patients, 9 left, 1 right and 1 bilateral representation, fTCD and Wada results were concordant [131]. Similarly, 2/13 patients lacked temporal window but the remaining 11 patients, 9 left, 1 each right and bilateral representation, were concordant [132]. Finally, in 17 surgical candidates including 14 epilepsy patients, language lateralization either left or right representation (but no bilateral case) the results between fTCD and SPECT was concordant [133].

fTCD allows the determination of hemispheric language dominance in individual subjects including children and cognitively challenged people [132]. This is significant since young age and cognitive impairment have been identified as predictive of inconclusive Wada test results [134]. Considerable amount of normative data on the fTCD patterns of language representation, including left, right and bilateral dominance in healthy population are available [68,72,135,136].

fTCD is an effective, reliable, inexpensive and noninvasive procedure for language lateralization with excellent temporal but limited spatial resolution. As for all functional imaging techniques, fTCD cannot determine whether an activated region during a particular task is a critical region that, when damaged, will result in a loss of that particular function. An additional limitation is that fTCD cannot be used in a minority (15–20%) of patients who lack an acoustically penetrable bone window. However, auxiliary techniques are becoming available that allow fTCD assessment even in the presence of thick bones [137]. The most serious drawback is the inability to define memory function particularly for the verbal modality.

NIRS – Near-infrared Spectroscopy and OT – Optic Topography

NIRS is a relatively new noninvasive technique, which enables measurement of hemodynamic changes associated with neural activity. The different light absorption spectra of oxyhemoglobin (oHb) and deoxyhemoglobin (dHb) within the near infra-red spectra allow for in-vivo measurement of concentration of these substances. Near-infrared light of two wave lengths between 680 and 1,000 nm is directed through optic fibers to the head of the patient. The amount of detected light reflects the amount of absorption of the two wave lengths in targeted cerebral regions a few centimeters below the scalp, informing on concentration changes of oHb and dHb in the region. Cerebral activation usually results in an increase in blood flow that is disproportionate to the metabolic rate of oxygen. Regions that are activated will have a greater oxygenation and a greater ratio of oHb to dHb. This would allow for the assessment of blood flow change in the superficial brain areas.

NIRS was used for language laterality assessment using a word generation task and was concordant in Wada tested 4 left and 2 right dominant patients [138]. Similarly, a group of 16 epilepsy, Wada tested patients was studied with a complex design by Watson et al. [139] preoperatively while 6/16 and 10/16 had NIRS pre- and postoperatively, respectively. Eleven patients that included two atypical representation were concordant (5/6 preoperative and 6/10 postoperative cases). Among 5 discordant patients, 4 and 1 were pre- and postoperative NIRS cases, respectively. NIRS appears reasonably accurate for lateralizing language in normally developed individuals with presumed left hemisphere dominance. However there may be limitations for atypical language dominance. More recently, NIRS was concordant in 5 Wada tested epilepsy patients: one adult (left dominant) and 4 pediatric (ages 9–15 years old: 3 left dominance, 1 bilateral) [140]. Same group of investigators reported that the combined and prolonged NIRS-EEG monitoring in a 10-year-old epileptic boy found its utility not only for language lateralization but also for the identification of ictal onset zone [141].

Optical topography (OT) is based on the same principle as NIRS. OT functionally maps the human cerebral cortex. The major difference between OT and NIRS is that OT measures spectroscopic reflection and scattering simultaneously from multiple measurement points whereas NIRS measures them with one or a few pairs of a light emitter and detector. OT has been successfully used for the identification of activation in the temporal [222] and inferior frontal cortex [142] during speech recognition and syntactic processing, respectively in healthy adults. In another study of 54 Wada tested patients, concordance rate for 43 left dominance was 74.5% (32/43), 6 right dominance 83% (5/6) and 3 bilateral representation 60%(3/5) [10].

The advantage of this method is that it is a relatively inexpensive, portable, with no major restriction on movement or verbalization during recording and it can be used in young children and babies as well as the cognitively challenged person. It is also clear that NIRS cannot assess deep structures because of the shallow penetration of the photons (between 3 and 5 cm), that renders it difficult to collect reliable information from subcortical structures. Therefore it will be limited for language assessment only. Another area of the NIRS utility is the assessment of differential hemodynamic pattern according to seizure type and lateralization [143–145,225].

fMRI – Functional Magnetic Resonance Imaging

In the early 1990s, fMRI a MRI innovation, allowed images weighted by blood oxygenation level to be obtained in as little as a few tens of milliseconds. Since bold oxygenation is finely controlled and responds promptly to local energy demand, voxel-by –voxel estimation of changes in blood oxygenation represents maps of brain activation. Thus, it is based on hemodynamic changes, i.e., blood oxygenation level dependent (BOLD) signal determined by cerebral activity. The increase in cerebral blood flow in activated cerebral areas surpasses the increase in metabolic rate for oxygen, which induces increased capillary and venous oxygenation level while reducing the relative concentration of deoxyhemoglobin which is paramagnetic. This increase and decrease of oxygenated and decreased deoxyhemoglobin result in an increased BOLD signal.

fMRI has been used to lateralize and localize language and memory functions for prediction and prevention of cognitive complication of epilepsy surgery. Many epilepsy centers have attempted to compare fMRI (activation) with the Wada test (deactivation) for validation purpose. Not surprisingly, comparison of fMRI and the Wada language assessment is challenging despite general agreement because of different fMRI language tasks, analysis, scoring and classification of laterality as well as varying Wada techniques and scoring involved. Lesser [146] points out that reproducibility of language results may be variable dependant on what aspects of language dominance (frontal vs. temporal) one is assessing.

Concordant results reported for fMRI and Wada language determination are: using visually presented words in 6 left and 3 right dominant patients [147]; semantic decision task (presentation of animal names from which subject was to pick domesticated ones)in 18 left and 4 atypical representation [148]; with semantic language activation task in 39 left, 11 atypical (3 right and 8 bilateral) representations [71]; with word generation task in 8 left, 1 right and 4 bilateral representation [19]; 8 left, 3 right and 2 bilateral representation [149]; and 15 left, 1 right and 3 bilateral representation [51]. Concordance was also seen with three language tasks (object naming, single word reading, verb generation) in 9 left and 3 atypical representations [150], and another three language tasks (semantic verbal fluency, story listening,covert sentence repetition) in 10 patients [127,146] respectively. In the latter study, the former two tasks were concordant with frontal asymmetry while temporal asymmetry using covert sentence repetition and story listening had no correlation with Wada asymmetry. Partial concordance is reported using read response naming in 3/21 patients, i.e., one Wada tested left dominant-fMRI bilateral, two Wada tested bilateral dominance-fMRI left [151], 1/20 Wada right-fMRI bilateral [152], covert word generation in 9/100 patients [153] and visually presented object naming in 2/21 patients [154].

A battery of tasks was found to yield better lateralization in 26 patients but bilateral representation remained a challenge [154]. The use of 4 tasks and statistical manipulation produced more robust result but one each of 11 left, three right and four bilateral dominance cases remained discordant [59]. Similarly, the use of semantic decision task (presentation of nouns designating inexpensive common object and pressing a "yes" button) in 68 patients showed mostly asymmetrical frontal and temporal activation with 21% discordance [155]. It is noted that in the latter study, while discordance rate was 11% in right temporal lobe epilepsy, it was 27.5% in left temporal lobe epilepsy. It is also noted that fMRI correctly classified all right dominance cases with less sensitivity to bilateral representation while it missed 17% of left dominance. In one recent fMRI study of a diverse group of 35 pediatric patients, three were found to be discordant to Wada test results, electrical cortical stimulation or other measures of lateralization [156]. Finally, it is rare but false fMRI language lateralization can occur [157,158].

The validity of fMRI in defining language lateralization may be tested by prediction of language deficit subsequent to dominant hemisphere surgery. In this regard, fMRI prediction with the Boston naming test was favorable in 24 Wada tested patients having greater sensitivity in predicting verbal naming difficulty following left anterior temporal lobectomy [159]. Another approach for validation involves correlation of language fMRI (activation) with direct cortical stimulation (inactivation). A reasonably good correlation is reported by several studies [160–164] but contrasting results are reported by others indicating fMRI by itself cannot be used to decide which cortical region can be resected [59,165,166]. It is noted that the result of extraoperative cortical stimulation language mapping in 10 pediatric and 14 adult Wada tested patients indicated the superiority of the Wada test in younger age group [92]. This confounding factor is not limited to only fMRI since the question of whether every speech arrest site by cortical stimulation is responsible for speech generation remains unanswered [167]. Clearly, much development is needed to standardize paradigms and procedures in fMRI.

fMRI has been seen as an imaging technique that would provide more detailed information regarding language reorganization. Atypical and particularly bilateral representations are challenges not only for the Wada test but also for fMRI since bilateral activation in the latter is also dependent on task difficulty, for example [146,168]. Furthermore it may not tell the complete story. Hertz-Pannier et al. [42] describe a young patient with seizure onset at 5.5 years of age and Rasmussen's encephalitis. He had normal language and his first fMRI indicated left hemisphere language dominance using a word fluency task. Left hemispherectomy at age nine was preceded by two prior partial resections at age seven. Immediately after surgery he became mute and was unable to read. Eighteen months later, a fMRI revealed a right-sided homologous language network that was not evident on the initial fMRI. There was also neuropsychological evidence of bilateral receptive but not expressive language. It appears that there may be a longer critical period for language plasticity due to the nature and extent of the injury (i.e., in this case, serial injury ending with hemispherectomy), the cognitive domain involved (i.e., the receptive functions of language) as well as the nature of the task (silent word fluency and sentence generation). They also acknowledge the possible artifact in design or data analysis, which would include picking a particular cognitive function and an appropriate experimental task as well as the need for an appropriate baseline task to control for brain activation not related to the experimental task. This particular case highlights the test–retest advantage of fMRI. A similar Rasmussen Encephalitis case with delayed language reorganization has been reported [220].

Atypical language representation in epilepsy as a reflection of injury-induced reorganization of the brain has been discussed in terms of differences in methodology and determination of language dominance. Some fMRI studies have correlated their findings with those of the Wada test: the correlations are not perfect, possibly reflecting differences in the language tasks and the criteria for establishing language dominance. Even when there is an indication of asymmetry or a "strong lateralization," fMRI may indicate bilateral activation [170]. Complex cognition such as language may often incorporate bilateral activation. Not all activated areas may be critical for the task. It is difficult to decipher the extent and nature of the right hemisphere's contribution and whether bilateral fMRI activation implies that either side can mediate language function independently or that both hemispheres are necessary. In a right hemiparetic patient with an early onset left temporal lobe epilepsy, the result of Wada testing (125 mg amytal) was judged to indicate right language dominance with no change in speech or right hemiparesis following left injection but left hemiplegia and a loss of consciousness with right injection. Motor functional fMRI showed strong left sided activation with right paretic hand movement. This strikingly contrasting result between Wada deactivation and fMRI activation illustrates potential complementary contributions of each procedures [219].

fMRI assessment of memory has yielded promising results and has revealed presurgical memory lateralization and prediction of postoperative memory [171–173]. However, the theoretical framework of developing appropriate and reliable paradigms appears more challenging than for language since one has to consider different aspects of memory such as encoding, retrieval, recognition and possible material specific influences such as verbal and nonverbal stimuli and different patterns of presentation. For predictive value of fMRI for postsurgical memory outcome, high correlation was found in 16 right mesial temporal lobe epilepsy not tested by the Wada test on a single subject level [171]. Another study also suggested that fMRI testing of visual memory correlates well with Wada test results and predicted postoperative visual memory deficit in patients going on to temporal lobe resection [172], the gold standard for fMRI and Wada. This study involved 30/35 Wada tested epilepsy patients. All underwent both fMRI using a complex scene encoding task and Wada testing. Encoding performance was assessed by the follow-up recognition test. Twenty-three patients who subsequently underwent temporal lobe resection completed the same task outside of the scanner in an average of 6.9 months postresection. Asymmetry ratio (AR) was calculated for activities in the region of interest: Hippocampus alone (H) and hippocampus, parahippocampus and fusiform gyrus (HPF). Healthy controls showed symmetrical AR indicating bihemispheric verbal and visuospatial involvement while patient's AR correlated with Wada for HPF but not H. In addition, ipsilateral HPF and AR showed a significant inverse correlation with good post-operative memory outcome (i.e., the lower ipsilateral fMRI absolute activation, the better the memory outcome). This finding is encouraging since it demonstrates that fMRI can predict post excisional visual memory deficit in intractable temporal lobe epilepsy patients. However, no normative data comparing the two methods have been established. Most intriguingly, AR differences in either H or HPF did not show the same correlation between seizure outcome and Wada memory results as previously reported [169,174]. Recently, prediction of postoperative verbal memory decline was also reported by using fMRI language lateralization measure in 60 left temporal lobe epilepsy [175].

Although fMRI represents a major advance, since it is noninvasive and fast, it still relies on indirect measures of neuronal activity. Increases and decreases in measured activity are difficult to interpret because the processes that regulate oxygen supply are complex and not fully understood. Ultimately, the measurements still rely on blood supply. Despite promising results, fMRI exploration of memory function remains a major challenge.

MEG – Magnetoencephalography

Magnetoencephalography (MEG) measures the magnetic fields produced by electrical activity in the brain via extremely sensitive devices such as superconducting quantum interference devices (SQUIDs). These measurements are commonly used in both research and clinical settings. MEG has the advantage of measuring brain activity over time as a cascade of extremely fast events and the unfolding of specialized processes, segregated in space and time and organized into well defined stages of processing.

It has been useful in mapping and localizing epileptic activity in both children [176] and adults. This technique can measure the activation of language-associated cortex. The dewars (helmet shaped device that the patient inserts their head into) can contain hundreds of sensors measuring brain activity. MEG relies on the averaging of brain responses evoked by a given stimulus. This technique has been advantageous when studying primary sensory and motor regions. However when studying a complex process such as language, it is reflecting a network of activation in primary sensory cortex followed by activation in the association cortex such as language. Beamforming techniques analyze oscillatory changes across cortex unlike traditional analysis and may be more useful in studying cortical networks involving sensory and higher level cognitive processes [177].

With a word recognition task, MEG has yielded robust language lateralization concordant with the Wada test results: 87.5% in 16 patients [27], 100% in 11 patients [178], 87% in both 19 [9] and 15 pediatric patients [179], 100% in 15-right-handed patients [180], 87% in 85 patients [181], 95% in 20 patients [182], and 89% in 27 patients [183]. Similarly robust test–retest reliability was obtained in 21 patients [184]. One Spanish validation study with 8 Wada tested patients is worth quoting [185]. Seven patients with left dominance were concordant though typically MSI (magnetic source imaging) activity sources were found bilaterally in language specific areas. Wada test results of the remaining right handed, right mesial temporal lobe epilepsy patient were "inconclusive" with extremely rapid postinjection recovery within 40 s suggesting an inadequate deactivation. MEG repeated twice indicated bilateral dominance and then right dominance. This patient had a secondarily generalized convulsion after right anterior temporal lobectomy and with a transient postictal "global aphasia" lasting for 15 min. It is likely that this patient had bilateral asymmetrical representation. MEG use in determining language function has been largely confined to the area of receptive language which may be a disadvantage since, as already discussed, reorganization of receptive and expressive function can occur independently. Some have addressed this issue using picture [180] and action [186,224] naming but largely in healthy populations.

MEG evidence of transhemispheric and intrahemispheric receptive language reorganization was reported in mesial temporal and lesional epilepsy patients, respectively [20]. Pre- and post operative MEG evaluation of receptive language in Wada tested mesial temporal lobe epilepsy patients showed more right hemisphere participation after surgery in bilateral representation cases while left dominant cases were more likely to show intrahemispheric changes with a slight inferior shift of the putative location of Wernicke's area even when the resection did not impinge on Wernicke's area [187].

No study has been published that has addressed evaluating memory function. However, in addition to relatively robust neuromagnetic activity in the left peri-Sylvian and temporoparietal structures, the verbal memory task for language lateralization was reported to evoke less robust activity in the ipsilateral mesial temporal structures [181]. This observation was recently investigated in mesial temporal lobe epilepsy patients and healthy subjects [188]. The study not only affirmed mesial temporal activity but also demonstrated some evidence of reorganization of memory function in left temporal lobe epilepsy. It suggests a potential role for MEG in memory assessment to become a clinically relevant measure, but further development of paradigms that can reliably generate robust neuromagnetic mesial temporal activity will be required.

MEG has a great potential for measuring very early reaction time in auditory and linguistic processing including speech perception, and contributes significantly to the characterization of the successive stages in language processing. In addition, it has the potential advantage of being able to localize neurophysiological processes associated with cognitive function within the whole brain and can provide high temporal and moderate spatial resolution suited for detailed spatial/time analyses of cognitive activation but the impact of age and education remains unclear. MEG is expensive and considerable technical support is required for both the administration and data analyses.

PET – Positron Emission Tomography

PET started the modern era of functional brain imaging in the early 1980s. It relies on the detection of emission from radioactivity labeled molecules introduced as a bolus into the bloodstream.

With each bolus, the concentration of radioactivity labeled molecules increases for a few minutes, particularly in metabolically active area. Injections of a bolus are given in separate sessions, some just before the subject executes a task (the active sessions), and some while the subject rests (the baseline sessions). Comparing the difference or some statistical measure of the detected radioactivity emanating from each brain voxel provides a map of the activated areas. Thus, it requires a radiotracer for measurement of glucose metabolism with 18 FDG, cerebral blood flow with $_{15}$O-labeled water or quantification of Benzodiazepine receptors with [$_{11}$C] Flumazenil.

PET is somewhat invasive since it requires radioactive materials. It offers a measure of hemispheric topographic organization and potential identification of eloquent language area. A European multicenter evaluation of PET in language lateralization disclosed significant differences across centers [189]. Many tasks and paradigms have been used including verb generation, story listening, object naming, and verbal fluency. It has been useful in establishing language dominance with significant concordance between regional PET data and Wada test results in children and adolescents: the activation of inferior frontal lobe with listening to and repetition of sentences and Wernicke's area for repetition [190]. Factors contributing to discordance between PET and Wada test results include: simplistic and limited language tasks/the sensitivity of the PET, a higher number of Wada tested atypical representation, and motion artifacts in their pediatric cases. The inability to distinguish critical primary regional activations for a task versus secondary activations may have also contributed to these results.

Successful use of $_{15}$O water has been reported in identifying the language area in a partial epilepsy patient with angiomatous malformation [191]. A PET study with auditory and visual confrontational naming activation involving 12 Wada tested patients(10 Left and 2 Right dominance) reported a considerable interrater variation of lateralization. There was a complete discordance in a left temporal lobe epilepsy patient with Wada right dominance and PET left dominance. The patient had language difficulty following left anterior temporal lobectomy. The Wada test had used 75 mg amytal and bilateral $R > L$ representation could have been missed [192]. Another PET study with verb generation from words and/or pictures in Wada tested patients had concordance in 23/24 (20 left and 3 right dominance) but a mixed handed patient with Wada left dominance was PET right dominant. This patient had decline of verbal function following right anterior temporal lobectomy [193]. Again, possible bilateral representation could not be excluded. For the purpose of validating PET language activation with both visual and auditory naming tasks, 7 Wada tested patients, 6 left and 1 right dominant patients underwent extraoperative cortical stimulation mapping. Not all the activated area stimulated caused language disruption but cortical regions that showed activation during the tasks were located in the same regions as electrodes that caused language disruption during stimulation [194]. The study suggests that PET can direct to likely eloquent areas that should be tested for more precise localization within the Wada identified hemisphere.

PET has also been reported to be useful for the evaluation of memory function in temporal lobe epilepsy [195,196] and detected PET hypometabolism can infer lateralized memory impairment for postsurgical prediction of memory outcome [197,198]. While memory alone is a complicated process [199], Krause et al. have shown differences based on the PET data analyses technique used. Covariance analysis-based data analysis allows for functional interactions between brain regions of a neuronal network in comparison with a subtraction strategy data analysis. These authors again note that functional imaging is impacted by age related changes, decrease in cortical volume in age, gender differences and handedness of volunteers.

The presence of atrophy may adversely impact on metabolic changes and may artificially lower regional metabolism and the interpretation of PET images [200]. Additional correlation with structural abnormalities on CT or MRI needs to be done in such situations. Silverman also notes that changes in cerebral metabolism due to normal development and aging are present in PET. Other potential confounding variables include sex, handedness, sensory environment, level of alertness, mood, drug effects, serum glucose levels and head fraction (the portion of administered tracer that passes into the brain). There can also be right hemisphere activation in language comprehension and production tasks in PET [201]. Again it remains unclear if the subjects had bilateral language dominance or the right hemisphere activation was related to a network of attentional processes. The authors acknowledge the right hemisphere's role in language including prosody, automatic idiom processing as well as vocabulary storage and the possible affective content of language.

Apart from the technical challenges of producing and handling of short-lived radioactive material, PET has two additional limitations. It is too slow, and safety issues limit the number of times a person can be a subject as well as the number of bolus injections given per session (hence the independent task and baseline sessions). Thus, there must be considerable infrastructure present. In turn, more investigations are needed so that variance due to scanning protocols, etc. can be accounted for different outcomes.

SPECT – Single Photon Emission Tomography

Another somewhat invasive nuclear medicine technique, SPECT measures cerebral blood flow by capturing single photons emitted by injected radioactive material. Regional blood flow is expected to increase with cerebral activation secondary to a given cognitive task performance. SPECT has been used to evaluate language lateralization in epilepsy patients with fluent verbal activation task with a reasonable success [133] while inconclusive data were reported with auditory verbal stimulation [202].

Using this technique, there has been a suggestion that injection of sodium amytal had greater functional effect on the dominant hemisphere in comparison with the nondominant hemisphere. Wada tested patients with bilateral speech showed no consistent trends. The dosage of amytal did not appear to be a factor. They suggested that their SPECT study may be revealing greater physiological effects following injection of the dominant hemisphere and in turn, why memory failures during Wada testing may be affected by the effect of dominance [203].

SPECT has been appealing due to its affordability and accessibility. However, spatial and temporal resolution is relatively poor. Scanning is time-consuming and again there can be no movement during scanning thus limiting its application to certain populations. Artifacts can occur due to uneven distribution of the radiotracer. There can also be underestimation of activity in deep structures. Coregistration with MRI images enhances anatomic accuracy. Based on a complete concordance of results between SPECT and fTCD in the assessment of language dominance in 14 and 3 patients with epilepsy and AV malformation, respectively, a suggestion was made that language mapping using SPECT might be considered when fMRI or PET are not available or contraindicated [133].

Current Status and Challenges

The Wada test has its' own challenges including universal definitions of atypical dominance, particularly bilateral dominance. One operational definition of when bilateral dominance is present is when the patient is speaking or naming an object with either the right hemisphere or left hemisphere. Some have included performance on receptive language tasks as well. We have seen individual differences such as what appears to be the transfer of speech production to the other hemisphere but not the posterior comprehension language skills. The Wada test has stimulated interest and provided a new insight in to cerebral organization of language and conceptual frameworks about reorganization of cerebral functioning.

It has been reported that patients will occasionally have catastrophic or emotional reactions that can interfere with testing. Detailed evaluation of 5/81 Wada tested patients who developed bizarre behavior failed to identify predictive factors and that premorbid personality factors did not appear to play a role. The authors suggested that thorough explanation and simulation might be helpful to lessen this risk [204]. At UBC, as a part of the preprocedure education, we would explain the procedure and would do a simulated, mock procedure. Patients are encouraged to ask questions. Anxiety, which usually contributes to the catastrophic reactions, was greatly reduced due to this effort. Introducing and orienting them to the angiogram suite and staff have also helped. Similarly concerns about unavoidable drowsiness at times is dealt with by preassessing important factors and by adjusting amytal dose accordingly with great success.

Risk of morbidity from the invasive aspects of Wada Test has always been a legitimate concern. Minor and major complications up to 11.6% in 79 Wada tested patients over 4-year period have been reported [60]. Review of relevant data specifically related to femoral artery puncture and internal carotid catheterization that are involved in the Wada test may be helpful. Recent large series of studies on the topic, (i.e., neurological complication rate of cerebral angiography) involving 2,524 [205] and 2,899 [206] procedures report 0.34 and 1.3% respectively. Two retrospective studies of neurological complication involving 569 [207] and 19,626 [208] procedures report morbidity rate of 0.5 and 2.63% respectively. The latter study involved many patients with acute severe cerebrovascular disease and had mortality of 0.06%. Common risk factors identified by these studies are advancing age (>55 years of age), acute cerebrovascular disease, duration of procedure (>10 min) and the degree of skill/expertise of the operator involved. As mentioned earlier, a recent survey of 16 Wada testing European epilepsy centers had 1.02% morbidity during a period of 5 years (personal communication Frank Oltmans). Obviously, risk and benefit have to be carefully weighed while considering the Wada test for older patients with or without cerebrovascular risk factors. With our UBC protocol, testing was performed on separate days at least 24 h apart. Following the initial injection, catheter was prompty withdrawn to aorta as soon as desired information was judged to have been obtained. Rarely a second small bolus of amytal injection was given only when a sufficient neurological deficit did not occur. We have been fortunate not to have experienced any neurological morbidity or mortality since 1960 when the test began at UBC.

The advantage of the traditional Wada protocol is that the results are evident rather quickly for most cases where establishing language dominance is crucial prior to surgery. When atypical dominance may be suspected, such as bilateral hemispheric dominance for language, more rigorous testing may be considered both during Wada testing and in utilizing other techniques such as comprehensive neuropsychological testing or other neuroimaging techniques.

Wada testing does not require considerable manpower and is typically done in existing angiogram suites. Our approach has always been to run simultaneous EEG recordings during testing as an adjunct objective measure of drug effect.

Following a hand injected angiogram, the typical time needed for testing and interpretation of test results can be done within an hour appealing to the added cost-effectiveness of the technique.

New techniques have attempted to validate by comparing them with results of the Wada test. fMRI studies correlated with Wada test results have shown the correlation with activation asymmetry in the frontal but not temporal lobes [209] and that laterality activation can differ between the frontal and temporal regions. Is it possible that fMRI may not be able to pick up brain asymmetries for all tasks, in all regions of the brain? fMRI as an activation technique may reveal areas that are involved in processing a task but may not reveal all areas of the brain involved in completing the task [210]. The nature and degree of difficulty of the task may impact on how the subject approaches the task. Some subjects may visualize the stimuli rather than focus on the linguistic aspects of the task, thus activating different areas and hemispheres of the brain. In patients with epilepsy, does the epileptogenic focus impact on the activation/inactivation of certain neural networks? What does the task become with repetition? Does novelty to the task impact on the patterns of activation? Is it the same task? Does familiarity and/or learning alter the sites of activation? Intriguing results from repeat fMRI studies on the same individuals [210] suggest that laterality clearly remained the same but localization was more consistent for frontal sites but more variability occurred in the temporal sites. These results were interpreted as suggesting that cortical mapping may still be required to localize all critical language zones. Major techniques such as fMRI, MEG and PET require a model of brain functioning in terms of knowing what stimuli or task should be chosen and speculating what areas of the brain (ROI) should be activated. However in behavioral neurosciences, the understanding of activation may be limited as we infer brain functioning from normal controls to people who may have long-standing neurological conditions (i.e., epilepsy from birth) or atypical dominance, which could impact on cortical and subcortical activation.

There are normal, developmental changes underlying the neural basis of cognitive functioning such as the final development of white matter pathways/connections continuing through the first two decades of life [211]. Also, different neural networks may be activated based on an individual's experience, familiarity and the duration of training with the task which has been demonstrated in fMRI and MEG images in the processing of music [212,213].

Other limitations of neuroimaging techniques include claustrophobia, the presence of metal (e.g., orthopedic screws) and the inability to stay still are typically the behavioral limitations leading to a patient's inability to endure techniques involving neuroimaging. Some centers will only do fMRI scanning for research purposes. The challenge for the fMRI approach in language and memory testing is what and how will the numerous confounding variables such as compromised intellectual functioning and/or pre or perinatal insult, impact on the activation patterns on fMRI? Determining what the control state will be is important. Typically it is a resting state but one wonders what a "neutral control" state is. The subject could very well be thinking about her grocery-shopping list that she must complete on her way home while she is lying in the gantry. The other important question is "are the neural networks being activated during a task essential or primary?" For example, during a naming task, cells 1, 2 and 3 are activated but in fact, cell 2 is activated more intensely when there has been injury to cell 1 and 3. It remains unclear how plasticity and neural networks are impacted when there is structural versus an epileptogenic, nonstructural seizure focus in the temporal lobe at an early age versus later onset? Imaging results may differ between normal populations and clinical populations and future studies must be responsible for providing clarification regarding these differences.

In memory processing, MEG has shown bilateral hemispheric activation for some tasks such as tone recognition. Despite the correlation of fMRI and Wada test results, there are still limitations in the assessment of atypical and bilateral hemispheric language dominant cases. The bilateral hemispheric activation and the activation of nonlanguage areas continue to exist and protocols that are sensitive to asymmetrical activation must be devised. fMRI studies of reliable individual predictions of postoperative memory changes are sparse. As Meador and Loring [26] pointed out that while group studies looked promising, fMRI on an individual basis had been less consistent with respect to the relationship between fMRI memory activation and memory outcomes following temporal lobectomy. Furthermore, chronological change in memory activation pattern may occur postoperatively as mentioned in the previous case study of postoperative changes in language activation pattern [42]. It remains unclear how stable the postoperative memory activation patterns are over time when one is investigating the relationship between pre-to postoperative memory imaging. It has been shown with a more basic motor deficit, a strong prediction from preoperative fMRI data to immediate post-operative motor deficit following a resection of medial frontal cortex but the correlations were absent following a few months [214]. It remains unclear how time impacts on pre to postoperative memory fMRI patterns.

The basis for establishing cognitive tasks for both behavioral neurosciences and clinicians utilizing newer neuroimaging techniques will be the accumulation of normative data as it remains unclear how the dynamic changes of a developing brain and critical periods for learning languages impacts on neuroimaging studies. Part of the challenge in trying to critically evaluate the clinical utility and reliability of any alternate technique are the small N's, span of age groups, diversity of cognitive tasks and paradigms used, differences in data analysis, etc. Our review of the literature is that there is much promise with many of these new techniques but the current state of the art does not allow one yet to unequivocally state that the "ABC technique" provides valid and reliable data, particularly for memory functioning for the majority of presurgical epilepsy patients. It will take years of data collection to determine if in fact memory networks are activated in a language paradigm. At this time, it is also too early to dismiss all "nonlanguage activated areas" as methodological or statistical artifacts. Prospective studies with samples that consider age and education effects as well as improvements in technical methodology will advance our understanding.

Has the Wada test been replaced? Not completely. Many of the newer neuroimaging tests are not easily accessible and affordable to some clinicians or can yield the test results within the test session due to the statistical processing and data analysis. The drowsiness and obtundation concerns from the Wada test may be no different from the concerns about claustrophobia or inability to stay still in a fMRI gantry. There are also some limitations regarding administration of test stimuli when using MEG technique (i.e., patients being unable to wear glasses, eye movement contributing artifact). There are some complex patient presentations that the Wada test may be the most appropriate technique (i.e., cerebral palsy patients with intractable seizures). We have also very limited understanding of how the alternative techniques are impacted by ESL issues or gender issues. Also requests for unique testing situations (i.e., assessing language dominance in someone who is mute/deaf but uses American Sign Language to communicate) can occur in presurgical investigations. Functional neuroimaging would not have been able to accommodate this situation due to the confound of motor movement from signing. Our own clinical experience has revealed that the presurgical evaluation of ESL patients using translators or patients with motor difficulties such as cerebral palsy can be investigated using the traditional Wada technique.

Neuroimaging approaches need to travel the same journey of concerns as the Wada test has regarding validity and reliability across age groups, the possible impact of education effects, novelty/familiarity with the task, establishing operational definitions for atypical patterns of cerebral language dominance, and how to handle the variability among centers with their test protocols. One might argue that the variability in protocols or the lack of standardization for a universal protocol has actually promoted further understanding about the subtleties and influences of test administration and test stimuli. Until there are numerous studies with larger Ns for many of the newer techniques, the data from the Wada test continue to provide valuable clinical information that is well understood in terms of its contributions and limitations particularly for individual cases.

Future imaging studies need to be clear about their apriori purpose as the field evolves. The memory testing of the Wada test initially was for the sole purpose of attempting to identify at risk patients for postoperative global amnesia. Over time, the memory scores from Wada testing have been utilized to confirm seizure focus laterality, predict postoperative memory functioning, and material specificity and sensitivity of the temporal lobes. How much of the academic insight gained from neuroimaging regarding language and memory activation patterns lends itself to clinical utility remains unknown at this time. Neuroimaging is plagued with the same issues as the Wada test including differences in protocols, data analyses, interpretation, and reliability issues for between groups as well as within the individual. Abou-Khalil [215] provides an overview of alternative techniques for determining language dominance and notes that repetitive magnetic stimulation (rTMS) does provide a methodology for deactivation of language cortex. Although fMRI and MEG have potential for determining language dominance, he is clear that these techniques have not yet proved to be a replacement for memory testing via the Wada approach.

For many centers without easy access to fMRI, the Wada test results along with other clinical information such as the patient's semiology, peri and postictal cognitive state, neuropsychological test results, patient's history and neuroimaging can provide the necessary information to make the decision about risk for significant postoperative language or memory disturbance. Killgore, et al. [216] have suggested that fMRI and Wada test data provide complementary data that may not correlate, but both accounted for nonover lapping unique variance in predicting surgical outcome.

Finally, advantages of non- or minimally invasive brain imaging technologies over Wada test in clinical setting are well recognized and the availability of multiple approaches will add to our knowledge of localization of function and the nature of reorganization. However, from both the clinical and scientific point of view they are all handicapped because they are necessarily based on highly artificial experimental protocols of limited scope. We believe that the true potential of brain imaging will be realized only when the technology allows one not only (1) to assess ecological validity of the subject-oriented approach and findings, (2) to extend beyond our current preoccupation of answering the question of "where" to "how" regarding the process of language and memory, but also (3) to address quintessential issues of natural language in health and disease, i.e., human communication from multidimensional interactive perspective including symbols, memories and emotions.

Epilogue

Conceptualization of the carotid amytal injection 60 years ago was a reflection of a life that was saved by a fluke from an act of the Second World War and then engaged in youthful exploration that has ultimately matured to stand the test of time.

For new cognitive evaluation technologies, issues of activation/deactivation, temporal/spatial resolution, standardization/validation, ecological validity and the reason for discordance between them and the Wada test, are all under debate while developing countries face the issue of affordability and availability. With surgical outcome as the gold standard, our accumulated experience has led to progressive sharpening and sophistication of clinical perception. Ultimately, there may be a smaller percentage of pre-surgical candidates requiring in-depth pre-surgical evaluation of language and memory which is an integral part of cohesive multimodal approaches to ensure patient's safety and success of surgical intervention. Clinical acumen reminds us to consider such factors to define specific investigational strategy as incongruent handedness between the patient and family history, history of early brain insult, peri/post-ictal phenomena, unclear semiology or/and semiology that is inconsistent with EEG localization, "normal" or non-focal EEG/MRI in partial epilepsy, and a left temporal lobe epilepsy focus with the absent past history of post-ictal language disturbance.

The Wada test was never meant to be a stand-alone test or an unequivocal evaluation of determination of language and memory functioning. Any investigation for epilepsy surgery is only a complementary component, the use of which depends on specific circumstances, clinical wisdom and judgment. We fully expect that non-invasive neuroimaging approach to become the new standard one day [2].

As expressed 11 years ago [217] while we await the arrival of validated safe alternatives, judicious and innovative use of the carotid amytal deactivation by a skilled, experienced clinician, when justified, cannot only continue to help patients but also create new information and hypotheses on the mechanism of function and dysfunction of the human brain in the behavioral state.

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