Title
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SUMMARY

Advances in functional imaging have provided noninvasive techniques to probe brain organization of multiple constructs including language and memory. Because of high overall rates of agreements with older techniques, including Wada testing and cortical stimulation mapping (CSM), some have proposed that those approaches should be largely abandoned because of their invasiveness, and replaced with noninvasive functional imaging methods. High overall agreement, however, is based largely on concordant language lateralization in series dominated by cases of typical cerebral dominance. Advocating a universal switch from Wada testing and cortical stimulation mapping to functional magnetic resonance imaging (fMRI) or magnetoencephalography (MEG) ignores the differences in specific expertise across epilepsy centers, many of which often have greater skill with one approach rather than the other, and that Wada, CSM, fMRI, and MEG protocols vary across institutions resulting in different outcomes and reliability. Specific patient characteristics also affect whether Wada or CSM might influence surgical management, making it difficult to accept broad recommendations against currently useful clinical tools. Although the development of noninvasive techniques has diminished the frequency of more invasive approaches, advocating their use to replace Wada testing and CSM across all epilepsy surgery programs without consideration of the different skills, protocols, and expertise at any given center site is ill-advised.
KEY WORDS: Wada testing, fMRI, Magnetoencephalography, Cortical stimulation mapping.

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Improving the risk–benefit ratio in clinical decision making by incorporating diagnostic methods with fewer associated risks is a universally shared goal and a common byproduct of advances in medical technology. To advocate the abandonment of established diagnostic procedures in favor of newer techniques, however, requires careful attention to methodologic detail and consideration of the clinical context and local environment in which diagnostic information is used to ensure that the potential benefits derived from

newer approaches are not offset by introduction of unanticipated consequences.

Based on review of the current literature, Papanicolaou et al.[1] propose that there is sufficient evidence of the superiority of several established functional assessment techniques, and in most cases, it is time "for the Wada procedure to be replaced . . . and for awake craniotomy to be put to sleep." Although there is little doubt that the number of cases undergoing Wada testing or cortical stimulation mapping (CSM) has decreased in epilepsy surgery programs in part due to the development and maturation of noninvasive language mapping techniques such as function magnetic resonance imaging (fMRI) and magnetoencephalography (MEG), there are risks in developing broad recommendations asserting that established techniques such as Wada testing and CSM should be abandoned. We will address functional assessments of language and memory separately, although in clinical practice, these constructs are tightly linked.

COMPLICATION RISK

A primary criticism of Wada testing is that as an invasive technique, it is associated with procedural morbidity risks. Fortunately, complications associated with catheter cerebral angiography have steadily decreased. When angiography is performed by neurointerventionalists, which is the case at most epilepsy centers, complication risk is estimated to be 0.3% in complex vascular disease patients.[2] Complication risks in epilepsy surgery candidates are likely even lower, since patients with epilepsy tend to be younger with less vascular disease, but might remain a concern if programs do not utilize neurointerventionalists with their high level of technical skill.

CONCORDANCE AND DISCREPANCY

Superficially, the most compelling argument for advocating the use of fMRI or MEG over Wada testing or CSM for language assessment is the high levels of agreement across different techniques. Unfortunately, high concordance rates between approaches in part simply reflect high base rates of left cerebral language dominance in both left-handed and right-handed individuals. If 95% of patients are left cerebral language dominant, then simply labeling ALL patients having left cerebral language dominant will result in a concordance rate of 95%! The more clinically relevant issue then is not overall concordance between approaches, but rather what is the sensitivity of the mathematical algorithms used in fMRI or MEG when applied to low base-rate events of right hemisphere or bilateral language representation compared to the direct observation of clinical phenomena (e.g., positive paraphasic errors).[3]

In a recent meta-analysis, Wada and fMRI language discordance was observed in 19% of the sample of 406 patients examined, with Wada/fRMI agreement in 94% of patients with typical left cerebral language dominance, but seen only in 51% of patients with atypical language representation.[4] Although discordance was highest in bilateral language cases identified by either Wada or fMRI approaches, in a comparative fMRI/Wada language report not included in that meta-analysis, the only factor that predicted discordance between approaches using multivariate techniques was the degree of atypical language on fMRI.[5] fMRI, as with other language activation mapping procedures, is often associated with varying degrees of right hemisphere activation during language processing, and as Papanicolaou[1] (and others) suggest, the discrepancy between fMRI and Wada in identifying right hemisphere language may result from either Wada testing failing to have the same sensitivity to right hemisphere language representation as does fMRI, or may be due to fMRI generating activation maps that include right hemisphere activations that are not linguistically based.

METHOD VARIANCE

A comprehensive review of certain limitations associated with current fMRI techniques has been published recently.[6] How laterality indices with fMRI are calculated varies across institutions. Magnitude values are indirect measures of the underlying process, influenced by factors such as position in the scanner, homogeneity of the magnet, to name a few, whereas "voxel counting" metrics of spatial extent are variable across individuals and even across multiple acquisitions within individuals.[7] Because fMRI does not rely on overt language errors but rather employs statistical activation maps, definitions of left, right, and bilateral activation derived from laterality indices reflect relative hemispheric language activation. There is unknown measurement error due across studies, since various laterality index thresholds with different paradigms will yield different sensitivity and specificity rates.[8]

As is the case across neuropsychological tests of the same purported construct,[9] there is significant heterogeneity not only in fMRI, but also in Wada protocols making comparisons across studies problematic. Therefore, the validity, and therefore usefulness, of Wada findings will depend in part on task characteristics.[10] Even when comparable protocols are described, careful examination of methods reveals differences that may be potentially relevant when contrasting findings across studies. For example, one recent report employed the Medical College of Georgia Wada protocol for language determination,[5] but language was assessed only during the period of complete contralateral hemiplegia prior to any resolution of induced EEG delta. This approach differs from how Wada language representation was defined at the Medical College of Georgia,[11] or more generally how testing is performed at the Montreal Neurological Institute where Wada testing was pioneered.[12,13] This by itself does not demonstrate that one approach is a more valid method than the other, but highlights how small variations in methodology may account for reported differences when contrasting techniques.

The reported superiority of fMRI over Wada in predicting postoperative Boston Naming Test (BNT) decline may reflect this approach the quantifying language during the Wada. For example, 50% of the patient sample undergoing left anterior temporal lobectomy (ATL) with bilateral Wada language defined using this approach demonstrated postsurgical declines on the BNT.[14] However, only 1 of 10 patients with bilateral Wada language undergoing right ATL experienced postresection BNT decline (2/60 points), whereas 8 of 10 had higher postoperative BNT scores. If bilateral language were correctly identified by this Wada approach, postoperative naming decline would be expected following right ATL.[15] Therefore, institutional differences in specific protocols are critical in informing the discussion regarding the advantages/disadvantages of either approach.

ACTIVATION/DEACTIVATION

The argument that Wada is a deactivation procedure, whereas fMRI and MEG involve activation methodology is well known. For mapping purposes, activation procedures identify cortical regions that are involved with task participation but that are not necessarily critical for language performance. Although one can make clinical judgment in part based on whether activated areas are likely critical because they are in known language regions, which areas are necessary remains uncertain due to thresholding and other signal-processing considerations. One obvious example illustrating the failure of critical language areas being identified is the absence of activation in critical white matter tracts for which transection would result in deficit identification. Injury to the subcortical structures can be the source of considerable morbidity,[16] and subcortical electrical stimulation mapping provides a technique to identify and preserve important subcortical fiber tracts.

Awake CSM with local stimulation is also a deactivation procedure designed to model the effects of possible resection of specific cortical regions. Although preoperative fMRI/MEG mapping may establish a general relationship of function to a lesion, the real-time data obtained with awake stimulation mapping provide unique information to guide surgical resection.[17,18] Papanicolaou et al.[1] assert that the CSM is not predictive of postoperative language outcome; however, positive evidence is ignored, although these studies are limited by lack of randomization or their retrospective nature. fMRI is a "positive" measure, and other physiologic measures, such as MEG and even surface electrocorticography engage areas beyond what is found to be relevant by CSM.[20,21] Perhaps these areas are associated with more subtle deficits when removed, which may argue for exploring even more tasks when doing CSM than the common practice of relying solely on object naming.[22] Receptive language mapping using functional MRI in sedated patients has been reported only sporadically, and we consider it premature to replace all language mapping with such an approach.

CSM use extends beyond epilepsy, and the larger neurosurgical community, including neurooncology and vascular malformation programs, has increased the use of awake mapping, presumably due to its usefulness in maximizing resections[17,23–27] and because it is well tolerated.[28] A recent meta-analysis even indicated a shorter surgery time and shorter hospital stay for awake procedures compared to general anesthesia.[29] There seems little reason to abandon a useful tool such as awake CSM if neurosurgeons and their team are facile in its application.

"PREDICTING" OUTCOME

Wada memory testing may influence clinical decision-making in different ways depending on programmatic institutional differences. In certain patients, a large Wada memory performance asymmetry may serve to confirm functional temporal lobe asymmetry, thereby allowing a patient whose noninvasive evaluation is suggestive of lateralized temporal lobe onset but still somewhat inconclusive due to inconsistency of clinical findings to undergo surgery without the need for invasive electroencephalography (EEG) monitoring. In other patients, Wada memory results may be used to identify risk for meaningful memory decline, such as with a patient with left temporal lobe epilepsy and hippocampal sclerosis, but with normal verbal neuropsychological memory and normal naming.[30]

Discussing the relationship of various techniques to language or memory outcome is often blurred by different meanings of "predict." In a statistical sense, prediction simply indicates a significant linear relationship between two variables. This relationship may or may not be clinically meaningful, and such a relationship does not necessarily mean that such findings are used to "predict" (i.e., forecast) individual patient outcome. Although there are reports of verbal fMRI tasks predicting verbal memory change in this fine-grained statistical sense,[31,32] this approach contrasts with our use of Wada memory testing to predict atypically large or disabling risk of significant postoperative memory change.

Recent systematic reviews confirm high risks of naming and verbal memory decline based on laterality of resection.[33,34] These reviews define memory decline using statistical metrics such as "reliable change" (i.e., not due to chance or practice effects), however, rather than clinical outcomes such as "minimal clinically important difference," which characterize change in clinically relevant terms such as postoperative disability or similar functional impairment. Therefore, we consider patients undergoing standard language dominant ATL to be at risk for naming and verbal memory decline, and they are counseled about these risks. Patients are never considered to be at no (or minimal) risk of postoperative cognitive decline based on Wada testing (even if it shows decreased memory performance on the dominant side), or indeed based on fMRI findings.

Although drug delivery to the hippocampal formation is not always possible with standard carotid catheterization, delta slowing recorded from intracerebral hippocampal EEG is typically induced, which has been postulated to result from functional deafferentation rather than direct effects of drug.[35] Although the mantle of "gold standard" for memory has never been conferred on the Wada test, with different memory results at times observed with repeat Wada testing,[36,37] it is also true that fMRI paradigms have not yet been optimized for memory activation for routine clinical application. Scene encoding fMRI paradigms have only modestly been predictive of verbal memory outcome following left ATL in several small series,[38,39] and fMRI asymmetry derived from verbal tasks appears to be a better predictor of verbal memory outcome than scene encoding paradigms.[31,32,40] When used to statistically predict postoperative memory change, the highest shared variance (R^2) in

two fMRI studies was only 23%, confirming considerable interindividual variability when predicting individual outcome using fMRI.[31,32] Regardless, no single test or finding, including Wada, fMRI, MEG, or CSM is used in isolation when discussing postsurgical functional outcome risks.

CONCLUSION

Advocating a universal switch from Wada testing and CSM to fMRI/MEG ignores the fact that different institutions often have greater experience with one approach than the other. Furthermore, individual Wada, CSM, fMRI, and MEG test protocols vary across institutions, resulting in different outcomes and reliability. Therefore, although reliable fMRI can be obtained at institutions with active research programs, it is less clear whether reliable fMRI data can be obtained by clinical MRI hospital services without the ongoing collaboration with clinicians and researchers who are more actively grounded in the study of brain–behavior relationships. Even in a research program with great attention to methodologic detail, 6% of patients studied failed to produce valid fMRI results.[5]

Although we do not suggest that centers who prefer noninvasive techniques as their standard approach for evaluation language and memory should change their approach to preoperative evaluation, we also believe that guidelines indicating that Wada testing and CSM should be routinely abandoned in favor of noninvasive techniques across institutions based on the success of fMRI/MEG at some institutions is ill advised. All techniques require considerable expertise and skill in both implementation and in interpretation, and rather than advocating for a universal approach "for the Wada procedure to be replaced ... and for awake craniotomy to be put to sleep," this decision should be based on the protocols, skills, and experience with these techniques at individual epilepsy programs.

DISCLOSURE OR CONFLICT OF INTEREST

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