

WADA YOU DO FOR LANGUAGE: fMRI AND LANGUAGE LATERALIZATION?

Language Lateralization in Epilepsy Patients: fMRI Validated with the Wada Procedure. Arora J, Pugh K, Westerveld M, Spencer S, Spencer DD, Todd Constable R. *Epilepsia* 2009;50(10):2225–2241. **PURPOSE:** This work examines the efficacy of functional magnetic resonance imaging (fMRI) for language lateralization using a comprehensive three-task language-mapping approach. Two localization methods and four different metrics for quantifying activation within hemisphere are compared and validated with Wada testing. Sources of discordance between fMRI and Wada lateralization are discussed with respect to specific patient examples. **METHODS:** fMRI language mapping was performed in patients with epilepsy ($N = 40$) using reading sentence comprehension, auditory sentence comprehension, and a verbal fluency task. This was compared with the Wada procedure using both whole-brain and midline exclusion-based analyses. Different laterality scores were examined as a function of statistical threshold to investigate the sensitivity to threshold effects. **RESULTS:** For the lateralized patients categorized by Wada, fMRI laterality indices were concordant with the Wada procedure results in 83.87% patients for the reading task, 83.33% patients for the auditory task, 76.92% patients for the verbal fluency task, and in 91.3% patients for the conjunction analysis. The patients categorized as bilateral via the Wada procedure showed some hemispheric dominance in fMRI, and discrepancies between the Wada test findings and the functional laterality scores arose for a range of reasons. **DISCUSSION:** Discordance was dependent upon whether whole-brain or midline exclusion method-based lateralization was calculated, and in the former case the inclusion of the occipital and other midline regions often negatively influenced the lateralization scores. Overall fMRI was in agreement with the Wada test in 91.3% of patients, suggesting its utility for clinical use with the proper consideration given to the confounds discussed in this work.

Cerebral Lesions Can Impair fMRI-Based Language Lateralization. Wellmer J, Weber B, Urbach H, Reul J, Fernandez G, Elger CE. *Epilepsia* 2009;50(10):2213–2224. **PURPOSE:** Several small patient studies and case reports raise concerns that the reliability of functional magnetic resonance imaging (fMRI) may be impaired in the vicinity of cerebral lesions. This could affect the clinical validity of fMRI for presurgical language lateralization. The current study sets out to identify if a systematic effect of lesion type and localization on fMRI exists. **METHODS:** We classify lesions typically occurring in epilepsy patients according to 1) their potential to disturb blood oxygenation level-dependent—effect generation or detection or to disturb spatial brain normalization, and 2) the proximity of lesions to protocol-specific volumes of interest (VOIs). The effect of lesions is evaluated through the examination of 238 epilepsy patients and a subgroup of 37 patients with suspected unilateral left-language dominance according to the Wada test. **RESULTS:** Patients with fMRI-critical lesions such as cavernomas, gliomas, and mass defects close to VOIs, or with severe atrophy, show lower lateralization indices and more often discordant language lateralization with the Wada test than do patients without such lesions. **DISCUSSION:** This study points seriously toward fMRI-language lateralization being sensitive to cerebral lesions. Some lesion types and locations are more critical than others. Our results question the noncritical application of fMRI in patients with cerebral lesions.

COMMENTARY

Neurosurgery is predicated on clearly delineating both functional and pathologic regions. In the simplest cases, the proposed resection is decisively outside established eloquent cortex boundaries and purely based on anatomy. In many cases, these boundaries are not as well defined and additional testing may be required to delineate the region(s) to be resected. The intracarotid amobarbital procedure (IAP) or Wada test has been the gold standard for determining language lateralization (1). However, utilization of the IAP has declined, and some clinicians have questioned its continued role in the presurgical evaluation of epilepsy patients (2). Direct cortical stimulation, either in the operating room or at the bedside utilizing implanted subdural electrodes, can provide localizing information not available from the IAP (3). Given the invasive nature of these tests, a noninvasive alternative has been sought. Magne-

toencephalography (MEG) and functional magnetic resonance imaging (fMRI) have shown promise in comparison with IAP. A literature review by Swanson et al. identified 20 studies (ranging from 6 to 94 subjects in each) that compared fMRI lateralization with IAP results and identified concordance rates between 80% and 100% (with the least concordant study at 55%) (4). Although encouraging, these results raise questions as to the diagnostic reliability and underlying mechanisms for the discrepancies between the IAP and fMRI.

When evaluating concordance with the IAP, one must consider the nature of the comparison. The IAP relies on language testing (e.g., spontaneous speech, naming, or comprehension) during a transient pharmacologic inactivation of one hemisphere, whereas fMRI and MEG assess which areas are activated during language-related tasks. These inherent differences in assessment outcome hinder direct comparisons, thus complicating the validity of IAP concordance as a comparative gold standard; the true gold standard is patient outcome following resection that demonstrates careful correlation between

resected regions and the invasive and noninvasive results. As identified eloquent regions are rarely, if ever, resected, these data are difficult to obtain.

Determining laterality of language function utilizing fMRI relies on measuring the blood oxygenation level-dependent (BOLD) response during a task. The study performed by Arora et al. explores discordance between IAP and fMRI by systematically reviewing potential variables that influence the laterality of the fMRI studies in 40 patients (including 10 left-handed patients). Patients were divided into two groups: Group A with unilateral language finding on IAP and Group B demonstrating bilateral language. Concordance within Group A was 83.9% (26/31) for reading comprehension, 83.3% (25/30) for auditory comprehension, 76.9% (20/26) for verbal fluency, and 91.3% (21/23) for conjunction analysis of the three tasks. For patients in Group B, auditory comprehension and verbal fluency each identified one patient as having bilateral language; all others were identified as unilateral (either left or right). Overall concordance for all subjects was 75% (21/28).

In reviewing discordant cases, the investigators report a general improvement in concordance (seen in four patients) when midline activations were not considered in the laterality calculation. Similarly, they found improvement in concordance (noted in two patients) by increasing the threshold score. To increase concordance in the conjunction analysis for bilateral language, the laterality index was increased to ± 95 , yielding a 60% concordance for Group B but a decrease in concordance for Group A, down to 56.5%. These data demonstrate the user-definable aspects of fMRI data analysis, which present potential confounding factors within fMRI data and highlight its limitations as a replacement for the IAP.

Given that fMRI is dependent on cerebral blood flow, Wellmer et al. explored the role of lesions on laterality. A visual semantic decision task was utilized in 238 patients undergoing presurgical evaluation for epilepsy treatment. The IAP was performed and identified left hemispheric language in 37 patients. Lesions were categorized based on the theoretical likelihood of the lesion altering cerebral blood flow, resulting in the following scale: 1) no lesion, 2) low-likelihood of lesions (e.g., dysplasia, hippocampal sclerosis), 3) potential for alteration of BOLD responses either (a) remote from or (b) neighboring/overlying language volumes of interest (VOIs) (e.g., tumor, edema, acute stroke), and 4) lesions that potentially impact automated processing of fMRI data (e.g., large resection, porencephaly). With lesions close to the left Broca's (20/172; $p = 0.008$) or left parietotemporal regions (28/169, $p =$ not significant), the lateralization index was less lateralizing. No statistically significant difference was seen in the smaller subgroup that underwent IAP testing. For patients with class 1–3a lesions, concordance with IAP was 46.2% (12/26), whereas for class 3b–4 concordance was 27.3% (3/11).

These studies demonstrate both strengths and weaknesses of current fMRI techniques. Multiple paradigms were utilized between the studies across three different MRI systems. Calculation of the lateralization index was hemispherically based for Arora et al. and volume-of-interest based for Wellmer et al. Changes in the volumes utilized for lateralization (i.e., removing midline structures by Arora et al.) improved results. Similarly, changes to the threshold settings, for determining a positive finding or bilaterality, alter the overall concordance with IAP. These technical issues contribute to the confusion and concerns that have been raised regarding fMRI for presurgical evaluation (5,6). Wellmer and colleagues have identified that structural lesions may affect language lateralization. This effect is most prominent when the lesion is near language-associated cortices. Similarly, in a series of 94 patients with an overall concordance rate of 91% between fMRI and IAP assessments, only 75% (12/16) of patients with left hemispheric extratemporal lesions were concordant (7). As a result, when the information is most needed (i.e., when pathology is near or in the left inferior frontal or posterior temporoparietal regions) may be when the data are least reliable.

Despite the limitations of fMRI in the clinical setting raised by these studies, continued investigation of precisely these patients with discordant data and/or structural lesions may lead to improved results in the future. For instance, a multimodal approach to noninvasive language lateralization utilizing fMRI and MEG in 87 patients produced 100% concordance and may prove to be of particular value in difficult cases (8). Further characterization of the impact of different types of structural lesions is necessary to allow for early identification of subjects for whom an alternative to (or augmentation of) the fMRI study is necessary. It is possible that patients with known lesions will require a multimodal approach (which may include IAP in addition to fMRI and MEG), whereas nonlesional cases with no neuropsychological or other evidence of atypical dominance could be assessed by a single modality. These studies also highlight the importance of expert review and analysis of fMRI data: paradigms must be carefully designed and executed, the data analysis stream must be reviewed, and results for individual centers considering IAP replacement with noninvasive paradigms should be internally validated against a gold standard.

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