The Effects of Localization-Related Epilepsy on Language Lateralization and Networks

Seizure Focus Affects Regional Language Networks Assessed by *f*MRI

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OBJECTIVE: To investigate the degree of language dominance in patients with left and right hemisphere seizure foci compared to normal volunteers using a *f*MRI reading comprehension task.

METHODS: Fifty patients with complex partial epilepsy, aged 8 to 56 years and 33 normal volunteers, aged 7 to 34 had fMRI (1.5 T) and neuropsychological testing. Participants silently named an object described by a sentence compared to a visual control. Data were analyzed with region of interest (ROI) analysis based on t maps for inferior frontal gyrus (IFG), midfrontal gyrus (MFG), and Wernicke area (WA). Regional asymmetry indices (AIs) were calculated $[(L - R)/(L + R)]$; AI > 0.20 was deemed left dominant and AI <0.20 as atypical language.

RESULTS: Left hemisphere focus patients had a higher likelihood of atypical language than right hemisphere focus patients (21% vs 0%, < 0.002). Left hemisphere focus patients, excluding those with atypical language, had lower regional AI in IFG, MFG, and WA than controls. Right hemisphere focus patients were all left language dominant and had a lower AI than controls in WA and MFG, but not for IFG. AI in MFG and WA were similar between left hemisphere focus/left language patients and right hemisphere focus patients. Patients activated more voxels than healthy volunteers. Lower AIs were attributable to greater activation in right homologous regions. Less activation in the right-side WA correlated with better verbal memory performance in right focus/left hemisphere-dominant patients, whereas less strongly lateralized activation in IFG correlated better with Verbal IQ in left focus/left hemisphere-dominant patients.

CONCLUSIONS: Patients had lower asymmetry indices than healthy controls, reflecting increased recruitment of homologous right hemisphere areas for language processing. Greater right hemisphere activation may reflect greater cognitive effort in patient populations, the effect of epilepsy, or its treatment. Regional activation patterns reflect adaptive efforts at recruiting more widespread language processing networks that are differentially affected based on hemisphere of seizure focus.

Left Hippocampal Pathology Is Associated with Atypical Language Lateralization in Patients with Focal Epilepsy

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It is well recognized that the incidence of atypical language lateralization is increased in patients with focal epilepsy. The hypothesis that shifts in language dominance are particularly likely when epileptic lesions are located in close vicinity to the so-called language-eloquent areas rather than in more remote brain regions such as the hippocampus has been challenged by recent studies. This study was undertaken to assess the effect of lesions in different parts of the left hemisphere, lesions present during language acquisition, on language lateralization. We investigated 84 adult patients with drug-resistant focal epilepsy with structural lesions and 45 healthy control subjects with an established functional MRI language paradigm. Out of the 84 patients, 43 had left hippocampal sclerosis, 13 a left frontal lobe lesion and 28 a left temporal-lateral lesion. All these lesions were likely to have been present during the first years of life during language acquisition. To assess the lateralization of cerebral language representation

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globally as well as regionally, we calculated lateralization indices derived from activations in four regions of interest (i.e. global, inferior frontal, temporo-parietal and remaining prefrontal). Patients with left hippocampal sclerosis showed less left lateralized language representations than all other groups of subjects ($P < 0.005$). This effect was independent of the factor of region, indicating that language lateralization was generally affected by a left hippocampal sclerosis. Patients with left frontal lobe or temporal-lateral lesions displayed the same left lateralization of language-related activations as the control subjects. Thus, the hippocampus seems to play an important role in the establishment of language dominance. Possible underlying mechanisms are discussed.

COMMENTARY

The advent and refinement of neuroimaging techniques has provided a valuable methodology to examine critical issues concerning brain structure and function. For example, recent neuroimaging studies have produced interesting and, to some extent, surprising findings regarding the potential consequences of chronic localization-related epilepsies. As pointed out by Berl et al., both regional and remote abnormalities have been detected in brain structure by quantitative MRI. In chronic temporal lobe epilepsy, for instance, abnormalities are evident not only in the hippocampus and temporal lobe but also in structures with connectivity, such as thalamus and basal ganglia, and more remote extratemporal gray and white matter. As noted by Weber et al., neuropsychological studies have demonstrated that patients with localization-related temporal lobe epilepsy frequently exhibit abnormalities in cognitive domains other than memory function (e.g., executive function). Such cognitive findings might be expected in the context of the distributed volumetric abnormalities.

These effects on brain structure and function might be expected to affect or alter classic patterns of localization of function. The two elegant studies reviewed here examine in closer detail the consequences of localization-related epilepsies on language function, specifically the localization and lateralization of language as defined by functional magnetic resonance imaging (*f*MRI). While the two studies vary in terms of their language paradigms, subject characteristics, and a host of other pertinent methodological details, they both demonstrate that focal epilepsy can significantly impact the normal pattern of left hemisphere language dominance.

Altered patterns of cerebral language representation resulting from focal epilepsy were reported by Wada testing. As established in the landmark report by Rasmussen and Milner (1) nearly 30 years ago (still commonly cited in textbooks), the frequency of atypical (i.e., nonleft) language representation is higher in patients sustaining early injury to the left hemisphere. Although the criteria used to classify atypical language varies across centers (2), the relationship appeared robust between early left seizure onset, including seizures restricted to the temporal lobes (3), and an increased likelihood of at least some of language being subserved by nonleft hemisphere regions. The specific neural regions subsuming language function remained uncertain, and *f*MRI procedures provide critical information in this regard.

Berl et al. used a "read response naming" task, for which subjects were instructed to read silently a sentence describing an object and think to themselves of a single word matching the description (e.g., "What is a long yellow fruit?" Answer: banana). Examining patterns of *f*MRI activation in 33 controls and 50 patients with complex partial seizures, the authors found widespread and focal effects of localization-related epilepsy on the regional and hemisphere distribution of language processing. For example, left hemisphere seizure focus patients had a higher incidence of atypical language dominance (20%) than patients with right hemisphere seizure focus (0%) or normal volunteers (3%). Atypical language representation was associated with early seizure onset or history of risk factors for left hemisphere brain injury before age 6.

The results of the study by Weber et al. are perhaps most surprising. Epilepsy subjects were divided into three groups according to the localization of lesion and then compared to a control group on *f*MRI tasks of synonym judgment and letter matching. Interestingly, the derived laterality indices of patients with hippocampal sclerosis were significantly lower (more abnormal) than the groups with either temporal lobe or frontal lobe lesions or than the controls. Overall, lesions of the left hippocampus were associated more frequently with atypical language dominance than were neocortical lesions in left frontal or temporal lobes, suggesting that the hippocampus plays a critical role in language lateralization. To this point, the hippocampus has not been considered a structure critically involved in the establishment of language lateralization and dominance, but rather has been viewed as a very important component in the neural network involved in episodic memory function; however, recent evidence suggests a contribution by the hippocampus to other cognitive abilities (e.g., semantic memory) (4) and now to the establishment of language dominance.

More broadly, one could argue that much of the current research suggests that localization-related epilepsies do not appear localization-related in terms of their structural and functional consequences. Continuing *f*MRI investigations in this area will help identify those factors associated with both intrahemipsheric as well as interhemispheric reorganization of language representation that result from relatively focal lesions to critical brain lesions.

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