EPILEPSY CURRENTS

Current Literature
in Clinical Science

Epilepsy Currents
2019, Vol. 19(1) 22-23

DOI: 10.1177/1535759718822032
journals.sagepub.com/home/epi
SAGE

Understanding the Cognitive Side Effects of Antiepileptic Drugs: Can Functional Imaging Be Helpful?

Effects of Carbamazepine and Lamotrigine on Functional Magnetic Resonance Imaging Cognitive Networks

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Objective: To investigate the effects of sodium channel–blocking antiepileptic drugs (AEDs) on functional magnetic resonance imaging (fMRI) language network activations in patients with focal epilepsy. Methods: In a retrospective study, we identified patients who were treated at the time of language fMRI scanning with either carbamazepine (CBZ; n = 42) or lamotrigine (LTG; n = 42), but not another sodium channel–blocking AED. We propensity-matched 42 patients taking levetiracetam (LEV) as "patient-controls" and included further 42 age- and gender-matched healthy controls. After controlling for age, age at onset of epilepsy, gender, and antiepileptic comedications, we compared verbal fluency fMRI activations between groups and out-of-scanner psychometric measures of verbal fluency. Results: Patients on CBZ performed less well on a verbal fluency tests than those taking LTG or LEV. Compared to either LEV-treated patients or controls, patients taking CBZ showed decreased activations in left inferior frontal gyrus and patients on LTG showed abnormal deactivations in frontal and parietal default mode areas. All patient groups showed fewer activations in the putamen bilaterally compared to controls. In a post hoc analysis, out-of-scanner fluency scores correlated positively with left putamen activation. Significance: Our study provides evidence of AED effects on the functional neuroanatomy of language, which might explain subtle language deficits in patients taking otherwise well-tolerated sodium channel–blocking agents. Patients on CBZ showed dysfunctional frontal activation and more pronounced impairment of performance than patients taking LTG, which was associated only with failure to deactivate task-negative networks. As previously shown for working memory, LEV treatment did not affect functional language networks.

Commentary

While it is well known that treatment with antiepileptic drugs (AEDs) is associated with cognitive side effects, the neurophysiological and anatomic mechanisms underlying those side effects remain poorly understood. The most commonly invoked explanation is that the same decrements in neuronal excitability that make AEDs effective for reducing seizures exert an accompanying negative effect on cognitive functioning. The literature, thus far, has been based on numerous studies using neuropsychological tests which have demonstrated that AED treatment is associated with mild decrements on tests assessing a wide range of cognitive functions with some AEDs affecting certain functions more than others.[1] Based on these findings, it is clear that the effects of AEDs on underlying brain mechanisms are far more complicated than what could be explained as a result of a general decrease in neuronal excitability.

Fortunately, advances in functional brain imaging have provided exciting new methods for studying the effects of pharmacological treatments and their effects on specific brain systems in studies of both patients and controls. More specifically, advances in functional magnetic resonance imaging (fMRI) have resulted in the emergence of a branch of pharmaco-fMRI (ph-fMRI), which is a methodological approach based on the premise that there are reproducible patterns of activation or deactivation elicited by performing cognitive tasks or observed through the default mode network (DMN), which can be influenced and quantified in a differential manner by various drugs.[2,3] This methodology has been used successfully in a growing number of imaging studies on AEDs, providing replication and extension of some of the findings reported in earlier studies using neuropsychological testing.

Previous neuropsychological studies had firmly established that (1) attention, processing speed, and memory were the functions most affected by AED treatment and (2) newer generation AEDs caused less severe cognitive side effects than the older drugs.[1] As an example, one well-known study, using a direct comparison of carbamazepine (CBZ) to lamotrigine (LTG), found a better outcome with the latter drug on more than half of the neuropsychological measures employed.[4] Much attention in subsequent investigations has been placed on the study of topiramate (TPM), which is found to have a more unfavorable cognitive side effect profile than other AEDs, including impairments in verbal fluency and other language functions.[5] Recent studies using ph-fMRI techniques have demonstrated differences in the brain effects of TPM compared to zonisamide.[6] The same windows into underlying brain mechanisms are now extended to the study of other AEDs.

Xiao and colleagues retrospectively studied the cognitive side effects of sodium channel–blocking AEDs in patients with epilepsy evaluated with language-based fMRI. They identified subject groups who had been taking CBZ ($n = 42$) or LTG ($n = 42$) at the time of the fMRI study. Citing studies demonstrating "normalizing" effects of levetiracetam (LEV) on cognitive fMRI, the investigators used an additional sample of 42 patients taking that drug as a patient control group, while also studying 42 healthy controls. All patients completed a covert verbal fluency paradigm while in the scanner, with a subset of patients completing clinical measures of verbal fluency outside the scanner, during routine neuropsychological testing.

Analyses of the verbal fluency data from neuropsychological testing revealed that the patients treated with CBZ performed at a lower level than those taking LTG or LEV. Consistent with those findings, the CBZ group also demonstrated a differential finding on fMRI activation during the covert fluency task, characterized by decreased task activation of the left inferior frontal gyrus (IFG). In contrast, patients treated with LTG exhibited abnormal deactivations during rest in frontal and parietal regions associated with the DMN. All of the patients exhibited bilateral decreases in activation of the putamen compared to controls, with a resulting correlation of the left putamen's activity with out of scanner measures of verbal fluency.

Findings from this study provide an interesting set of dissociations of regional brain activation associated with different AEDs. Functional MRI results in patients treated with LTG were limited to abnormal deactivation of DMN hubs, while those treated with CBZ demonstrated a specific deactivation of the IFG, a brain region associated with activation on verbal fluency tasks.[7] It is noteworthy that previous work by the same investigative team had demonstrated that patients treated with TPM, a drug associated with a more extensive cognitive side effect profile than either LTG or CBZ, exhibited a combined pattern of deactivations involving both the DMN hubs and the IFG.[6] Taken together, the findings from both studies provide preliminary evidence for a continuum of abnormal regional brain deactivation involving the DMN and left IFG associated with progressively greater cognitive side effects in patients taking different AEDs.

Task activation in this study was performed with a covert fluency task, where patients were asked to generate words in response to a visually presented letter. While this was characterized as a language task in this study, there has been some discussion in the neuropsychological literature whether letter fluency tasks are better characterized as measures of language or executive functioning. The results of a recent factor-analytic study of neuropsychological test data demonstrated that both letter and category fluency measures are more associated with language tasks than measures of executive functions.[8] While those findings favor classification as a language task, it is noted that this study also found an association between verbal fluency performance and activation of the left putamen, an area that has been associated more specifically with task switching during verbal fluency performance,[9] raising questions about whether the current findings could have implications beyond AED effects on language functioning, extending to general effects on higher-order cognition.

Whether or not the findings from this study have more relevance for AED effects on language or cognition, the authors raise an important point for interpretation of language-based fMRI tasks used in presurgical planning. While the findings from this study demonstrated no obvious AED effects on measures of language lateralization, the findings do provide a rationale for looking into this issue more closely in the future, to determine whether there is a potential for any AEDs to have a confounding influence on the results of presurgical language testing using fMRI. In the end, the continued use of ph-fMRI techniques, as employed in this study and others, will undoubtedly provide further advances in our understanding of AED efficacy and side effects, enabling us to move well beyond the black-box approach associated with prior methods.

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