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Language and Epilepsy: A Systems Issue

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Disorganization of Language and Working Memory Systems in Frontal Versus Temporal Lobe Epilepsy

Caciagli L, Paquola C, He X, Vollmar C, Centeno M, Wandschneider B, Braun U, Trimmel K, Vos SB, Sidhu MK, Thompson PJ, Baxendale, S, Winston GP, Duncan JS, Bassett DS, Koepp MJ, Bernhardt BC. *Brain*. 2022;awac150. doi:10.1093/brain/awac150

Cognitive impairment is a common comorbidity of epilepsy, and adversely impacts people with both frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE). While its neural substrates have been extensively investigated in TLE, functional imaging studies in FLE are scarce. In this study, we profiled the neural processes underlying cognitive impairment in FLE, and directly compared FLE and TLE to establish commonalities and differences. We investigated 172 adult participants (56 with FLE, 64 with TLE, and 52 controls) using neuropsychological tests and four functional MRI tasks probing expressive language (verbal fluency, verb generation) and working memory (verbal and visuo-spatial). Patient groups were comparable in disease duration and anti-seizure medication load. We devise a multiscale approach to map brain activation and deactivation during cognition, and track reorganization in FLE and TLE. Voxel-based analyses were complemented with profiling of task effects across established motifs of functional brain organization: (i) canonical resting-state functional systems, and (ii) the principal functional connectivity gradient, which encodes a continuous transition of regional connectivity profiles, anchoring lower-level sensory and transmodal brain areas at the opposite ends of a spectrum. We show that cognitive impairment in FLE is associated with reduced activation across attentional and executive systems, and reduced deactivation of the default mode system, indicative of a large-scale disorganization of task-related recruitment. The imaging signatures of dysfunction in FLE were broadly similar to those in TLE, but some patterns were syndrome-specific: altered default-mode deactivation was more prominent in FLE, while impaired recruitment of posterior language areas during a task with semantic demands was more marked in TLE. Functional abnormalities in FLE and TLE appeared overall modulated by disease load. On balance, our study elucidates neural processes underlying language and working memory impairment in FLE, identifies shared and syndrome-specific alterations in the two most common focal epilepsies, and sheds light on system behavior that may be amenable to future remediation strategies.

Commentary

Studies highlighting language mapping have ascended in recent years. We understand so much more than the old days of contemplating Broca and Wernicke, the accepted de rigueur in medical schools just a few decades ago. Now we understand how neural networks are actually systems that act in a coordinated fashion, and involve shifting or switching modes of operation. We continue to learn about the role of the default mode network, which is essentially the brain at baseline. Any active mental task requires diverting from baseline in a coordinated way. Language is a particularly complex mental task, typically involving motor instructions and sensory feedback in real time. However, with seizure activity, network disruption is inherent, so it may be no surprise that even subtle disruptions of vast networks underlying complex cognitive tasks could lead to marked impairment.

Whereas generalized seizures interfere broadly with most higher order brain functions, it may be that localization-based epilepsy offers clues about how specific cognitive functions and brain regions are connected. That is the goal of the recent functional imaging study by Caciagli and colleagues.[1] Participants were divided into those with decided frontal lobe foci and compared with those having temporal lobe foci. Both groups were adults with medically refractory epilepsy, but equal in terms of IQ and apparent functionality. The tests were

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sophisticated and included a broad array of expressive language, fluency, verb generation, and verbal working memory tests, and were assessed while undergoing a functional magnetic resonance imaging scan. Regions and networks that were active during those tasks were correlated with epilepsy subtypes.

The sample was still quite varied, given the inherent heterogeneity of seizure foci and severity, but sub analyses were done to aggregate subjects into at least somewhat homogeneous subgroups. The results were notable not in the absolute success or failure of performance on the tasks, as both groups had reasonable degrees of functionality. Furthermore, activation patterns vary for language tasks in general, as a wide range of brain regions are involved. However, what became clear is that different networks were activated depending upon seizure foci. Those with frontal lobe foci had better naming, verbal learning, and verbal recall, but worse performance on tasks requiring mental flexibility. Activation of fronto-temporo-parietal networks was worse, and the default mode network was also more difficult to deactivate than in persons with temporal lobe foci.

Somewhat predictably, patients with temporal lobe foci had worse performance on tasks requiring semantic knowledge, as proximity to posterior language areas were apparently involved. Yet the 2 groups were similar in several important aspects as well. Cognitive reorganization appeared to occur regardless of the seizure focus. In both groups, it seemed that deactivation of the default mode network was a difficult task, possibly owing to the disrupted network integrity associated with medically refractory epilepsy.

Another key finding of this study is the marked dysfunction in those with frontal lobe seizure foci. Relatively little has been reported about cognitive problems in frontal lobe epilepsy, as it has commonly been viewed as a more benign disease, especially as awareness is often preserved. However, this study suggests that the network disruption is significant in terms of language function, and possibly even more impairing than in temporal lobe epilepsy.

The upshot is that we may need to reassess how we think about language function and epilepsy subtypes. A lot of energy is still invested in procedures correlating language with lateralization in order to navigate ablation or resection procedures accordingly. However, based on these results, we essentially have overlapping networks of language function, in some cases with activation of contralateral hemispheres. These details of mapping along with the necessity for deliberate deactivation of default modes are enlightening in terms of how we are now forced to regard cognitive tasks.

As a clinician, it can be very challenging to translate research findings into clinical practice. Immediate treatment needs often supersede academic explorations, even if they are particularly interesting. To think beyond regions or networks is a stretch without tangible information that may propel such an inquisition. However, the idea that continues to advance such change is the concept of the default mode network. If frontal systems are not working properly, then often it is the default mode network that remains overactive. In other words, the brain remains stuck at baseline, being unable to recruit network resources to accomplish cognitive tasks. For this study, it did not occur so excessively in language-based tasks for those with temporal lobe foci. For that group, the problem is less that the brain is paralyzed in default mode but is instead unable to access posterior language networks, which efficiently allow a broader lexicon to be accessed.

Being "stuck" in default mode is a concept that has been proposed in other conditions, including autism spectrum disorders and aphasia.[2,3] Yet accessing "hard drive" or stored information is also a concept used to understand compromised brain function. This study suggests that for language, hard drive and connectivity are both important. Connectivity may have far reaching implications, and has recently been suggested as a biomarker that associated with responsivity to anti-seizure medicines.[4] But networks are equally important. Just because awareness may be preserved, as is often the case for frontal lobe epilepsy, cognitive function may be markedly compromised. Another supposed less severe epilepsy, benign epilepsy with centrotemporal spikes, also involves cognitive dysfunction that may be related to difficulty with deactivating the default mode network.[5] Overcoming inertia as well as activation and recruitment of network resources seems to be a clearer path to language function and possibly most other higher order cognitive functions.

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