

Current Literature

In Clinical Science



Cognitive Activation of “Hyperexcitable Cortex” in JME: Can It Trigger Seizures?

Motor System Hyperconnectivity in Juvenile Myoclonic Epilepsy: A Cognitive Functional Magnetic Resonance Imaging Study.

Christian Vollmar, Jonathan O’Muirheartaigh, Gareth J. Barker, Mark R. Symms, Pamela Thompson, Veena Kumari, John S. Duncan, Dieter Janz, Mark P. Richardson, Matthias J. Koepp, *Brain* 2011; 134; 1710–1719.

Juvenile myoclonic epilepsy is the most frequent idiopathic generalized epilepsy syndrome. It is characterized by predominant myoclonic jerks of upper limbs, often provoked by cognitive activities, and typically responsive to treatment with sodium valproate. Neurophysiological, neuropsychological and imaging studies in juvenile myoclonic epilepsy have consistently pointed towards subtle abnormalities in the medial frontal lobes. Using functional magnetic resonance imaging with an executive frontal lobe paradigm, we investigated cortical activation patterns and interaction between cortical regions in 30 patients with juvenile myoclonic epilepsy and 26 healthy controls. With increasing cognitive demand, patients showed increasing coactivation of the primary motor cortex and supplementary motor area. This effect was stronger in patients still suffering from seizures, and was not seen in healthy controls. Patients with juvenile myoclonic epilepsy showed increased functional connectivity between the motor system and frontoparietal cognitive networks. Furthermore, we found impaired deactivation of the default mode network during cognitive tasks with persistent activation in medial frontal and central regions in patients. Coactivation in the motor cortex and supplementary motor area with increasing cognitive load and increased functional coupling between the motor system and cognitive networks provide an explanation how cognitive effort can cause myoclonic jerks in juvenile myoclonic epilepsy. The supplementary motor area represents the anatomical link between these two functional systems, and our findings may be the functional correlate of previously described structural abnormalities in the medial frontal lobe in juvenile myoclonic epilepsy.

Commentary

Juvenile Myoclonic Epilepsy (JME) is classified as an idiopathic generalized epilepsy syndrome with “generalized polyspike and slow waves” on EEG. A number of clinical and electrophysiological studies in patients with JME, however, demonstrate alterations in specific cortical systems involving bilateral cortical and subcortical regions, including frontal lobe and anterior cingulate areas (1), motor cortex and supplementary motor areas (SMA) (2, 3), and thalamocortical pathways (4). JME has been associated with abnormalities in white matter pathways in the anterior internal capsule, especially in the anterior thalamic radiation fibers connecting the anterior thalamus with prefrontal cortical areas (4). Overall, these structural and functional studies support an emerging view that JME is a bilateral thalamocortical disorder with widespread cortical hyperexcitability, maximally involving the frontal lobe (1). JME, however, also appears to be a heterogeneous disorder with only mild abnormalities

in tasks dependent on frontal lobe executive regions and variable PET/MRS and MRI abnormalities (5–7). One of the most striking abnormalities in cortical function in patients with JME has been increased cortical sensitivity to transcranial magnetic stimulation (TMS), particularly in anterior brain regions, following sleep deprivation (8) and during the morning hours (9). This increased sensitivity to transcranial evoked responses suggests abnormalities in intracortical inhibitory networks (10) and corresponds to the effectiveness of antiepileptic drugs (AEDs), which modulate GABA-mediated neurotransmission in treating JME (11).

Consistent with these findings, patients with JME often report that seizures are associated with stress (83% of patients) or sleep deprivation (77%), factors which can decrease intracortical inhibition (12). A smaller proportion of patients report that seizures may be associated with “thoughts and concentration” (23%) or hand activities (20%) (12). In a new study, Vollmar et al. used fMRI to explore how praxis (“the ideation or execution of complicated movements”) activates cortical pathways in patients with JME and determined whether these pathways correspond to motor systems activated during myoclonic seizures (3). During performance of a visuospatial working memory task, patients with JME and

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normal control subjects had activation of similar bilateral SMA regions and left central areas (corresponding to right-arm manual task responses). Test accuracy was similar for patients with JME and control subjects. Subtraction of a 0 memory/manual reaction condition identified activation of bilateral frontal and parietal areas associated with a visuospatial working memory network in both JME and control subjects (13). Compared with normal control subjects, however, patients with JME had increased motor cortex and SMA activation with increased memory task loads. Patients with recent seizures also had greater activation of motor cortex and SMA compared with patients with remote seizures. The authors concluded that this motor cortex coactivation, triggered by cognitive effort, explains myoclonic jerks and their facilitation through cognitive stressors.

Although Vollmar et al. demonstrated cognitive activation of motor and SMA regions involved in myoclonic seizures, praxis-induced seizures are uncommon in JME, even in untreated patients (14). Coactivation, though, may account for the rare association of JME with reflex reading seizures (15) and may engage mechanisms involved in photosensitivity. Vollmar et al. conclude more generally, however, that the SMA may have a specific role as relay for abnormal functional connectivity between the cognitive and motor system in JME patients and explain the provocative effect of cognitive activity on myoclonic jerks. While SMA and motor cortex are sources for jerk-linked spikes recorded in patients with progressive myoclonic epilepsies, polyspike bursts with myoclonic seizures in JME are generated from more widespread areas of cortex (16). It seems likely that cognitive activation and myoclonic seizures are both manifestations of widespread cortical hyperexcitability in JME.

Epigenetic mechanisms probably account for the development of cortical hyperexcitability and these clinical phenomena in JME. Polymorphisms in a gene coding an ACh receptor subunit—CHRNA4—are associated with susceptibility to JME in some patients (17), and with decreases in performance of visuospatial and phonological memory tasks in subjects without epilepsy (18). Mutations in the gene are associated with nocturnal frontal lobe epilepsy (19). These findings suggest that epigenetic mechanisms involving CHRNA4 and other genes may trigger the onset of seizures in late adolescence in patients with JME and produce the "cortical hyperexcitability" demonstrated by Vollmar et al. during cognitive activation and by others during myoclonic seizures.

by Gregory L. Krauss, MD

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