

## BRAIN FUNCTION AND ANATOMY IN JUVENILE MYOCLONIC EPILEPSY

**Evaluation of Cognition, Structural, and Functional MRI in Juvenile Myoclonic Epilepsy.** Roebing R, Scheerer N, Uttner I, Gruber O, Kraft E, Lerche H. *Epilepsia* 2009;50(11):2456–2465. **PURPOSE:** Previous studies using advanced imaging techniques have suggested subtle structural and functional changes in patients with juvenile myoclonic epilepsy (JME), mainly associated with the frontal lobes. In addition, it has been reported that these patients show neuropsychological deficits, often summarized as frontal lobe dysfunction. The aim of this study was a comprehensive analysis of neuropsychological parameters, and functional and structural magnetic resonance imaging (MRI) in an independent cohort of patients with JME. **METHODS:** We studied 19 JME patients and 20 age-, sex-, and education-matched controls using a battery of standardized neuropsychological tests, optimized voxel-based morphometry (VBM), and two domain-specific working-memory paradigms combined with functional MRI (fMRI). **RESULTS:** Our investigations did not reveal statistically significant differences between the groups of JME patients and normal controls in either the VBM or the fMRI study of working memory. The neuropsychological examination showed a slightly worse performance for the JME patients across most tests used, reaching statistical significance for semantic and verbal fluency. **CONCLUSIONS:** In our cohort of JME patients, we could not reproduce the findings of frontal gray matter changes from previous studies, and we could not detect an fMRI correlate of previously reported differences in working memory in JME. The neuropsychological deficits may be attributed partially to antiepileptic medication. We conclude that structural and functional frontal lobe deficits in JME patients have to be interpreted with care. One reason for a variation between different cohorts may be the genetic heterogeneity of the disease.

### COMMENTARY

In 1985, Janz first describe juvenile myoclonic epilepsy (JME) as a special syndrome within the primary generalized epilepsies that is characterized clinically by irregular myoclonic jerks of the shoulders and arms after awakening and defined electroencephalographically by bilateral synchronous, 4 to 6 per second spike-wave complexes (1). In that article, it was also noted that JME patients sometimes exhibit inadequate social behavior, emotional instability, and disinhibition. Such behaviors might be explained by deficits in executive functions, which are dependent on the frontal lobes. Several studies have demonstrated abnormalities in executive functions among patients with JME, although considerable individual variability has been observed and abnormalities in cognitive functions that are beyond those supported by the frontal lobes also have been noted (2–6). Further, despite normal clinical MRIs among patients with JME, several studies using advanced imaging techniques have demonstrated subtle abnormalities in the frontal lobe structures, although there is variance in which frontal structures are involved and in whether the abnormality is associated with an increase or decrease in volume (7–12). In addition, brain regions outside the frontal lobes have also been found to be abnormal in some studies. For example, decreases in thalamic volumes and abnormalities in the white matter tracks connecting the thalamic and frontal regions have been reported (12,13). Interestingly, thalamic and frontal volumes have been shown to be significantly related to abnormalities in executive functioning among JME patients (6).

Based on a review of the literature and their study of 19 JME patients and 20 matched controls, Roebing et al. concluded that structural and behavioral deficits in JME patients need to be interpreted with caution because of the genetic heterogeneity of the disease. Although JME is one of the most common and best described epilepsy syndromes, it is not a single disease, which is obvious from the facts that several different genetic mutations have been linked to JME (14) and these mutations only explain the etiology for a fraction of patients with JME. The variability in underlying etiology may produce differences in subtypes of JME despite the overall clinical similarities. This theory may account for the variance across studies as well as the marked individual patient variability in neuropsychological and imaging results. From a clinical perspective, cognitive and personality abnormalities seen in some JME patients cannot be generalized to all JME patients. While the exact incidence of personality disorder in JME is uncertain, it appears to occur in only a minority of patients (15). From a research perspective, it is important to consider possible contributing factors, such as underlying etiologies, severity of disease, and differences in methodology, that may contribute to the observed variability.

As an example of subtype variability, de Araújo Filho et al. found significant volume reductions in thalamic and increases in mesiofrontal and frontobasal regions as well as a significant reduction of *N*-acetyl-aspartate/creatinine (NAA/Cr) ratio in the frontal lobes of JME patients with a personality disorder, but not in JME patients without psychiatric disorders (12,16). Another example of subtype variability is seen in a study by Lin et al., in which significant increases in gray matter volumes were found in the frontal lobes of the JME group overall compared to controls, but the investigation also revealed increased gray

matter volumes in the visual cortices and reduced volumes in the left hippocampus and left inferior frontal regions of JME patients who exhibited photosensitivity but not of JME patients without photosensitivity (17).

Roebeling et al. point out that neuropsychological deficits in JME may be due in part to the effects of antiepileptic drugs, which is an important issue to consider in assessing cognitive studies that involve patients with epilepsy. Although Roebeling et al. did not find frontal gray matter abnormalities or deficits on a working memory fMRI task, they did find abnormalities on two tasks (i.e., semantic and verbal memory) that are related to frontal lobe function. The observed deficits on these tasks are unlikely to have been affected in isolation by antiepileptic drugs without affecting other cognitive measures. Further, valproate is the antiepileptic drug most commonly used for JME, and the only noted neuropsychological abnormality related to its use in this study was verbal memory.

Roebeling et al. also concluded that structural and functional frontal lobe defects do not represent a prominent or common finding in JME. As noted before, it is important not to generalize the cognitive and personality abnormalities seen in some JME patients to all JME patients. Nevertheless, findings of structural abnormalities, especially in the frontal lobes, have been demonstrated in most studies employing advanced imaging techniques in this population. Similarly, the presence of impairments in executive frontal lobe functions is apparently frequent enough to be present in most JME studies of cognitive function. Future research might seek to understand the relationship of structural and functional findings to the different mechanisms underlying the etiology of JME subtypes.

by Kimford J. Meador, MD

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