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COMMENTARY

Neuroimaging by Voxel-Based Morphometry: Possible Approach to Finding the Correlation between Brain Structural Changes and Fatigue Severity in Patients with Multiple Sclerosis

In this issue of the *American Journal of Neuroradiology*, Riccitelli et al[1] report that findings in patients with multiple sclerosis (MS) and fatigue may correlate with atrophy of the primary sensorimotor area. This article helps us understand the clinical-pathologic correlation in patients with MS and fatigue.

MS is a chronic inflammatory demyelinating disease of the central nervous system with an unpredictable course and an unknown pathogenesis. It is considered one of the most common neurologic disorders affecting young adults. The clinical manifestations of MS are diverse. Fatigue is one of the most common and disabling symptoms among patients with MS, interfering with and considerably limiting daily social life and work.[2] The perception of fatigue is subjective and difficult to define; therefore, no exact definition has been made until now. To date, neither biologic nor neuroimaging markers have been found for fatigue. Fatigue in patients with MS is different from fatigue in a healthy population, and its pathophysiology and etiology are poorly understood. Both peripheral and central mechanisms may exist.[3] "Peripheral fatigue" could be an appropriate term for muscle fatigability due to disorders of muscle and the neuromuscular junctions. Objective reduction in motor power in muscle fatigability can be measured. However, the subjective sense of fatigue is essentially perceived at the level of the central nervous system—that is, it is a central fatigue.[4] Central fatigue, however, is not simply a sense of physical exhaustion; it also has an important cognitive component (mental fatigue). Cognitive impairment in central fatigue is common in patients with MS.

Many researchers have found that the cerebral volume in patients with MS shows significant decrease in many areas, such as deep gray matter, whole brain volume, and so forth. However, until now, few have tried to explain the structural changes in patients with MS and fatigue. In their article, Riccitelli et al[1] provide useful information regarding a possible approach to assessing patients with MS and fatigue in neuroimaging. They used a whole-brain voxelwise analysis to assess the patterns of regional distribution of lesions and found atrophy of the left central sulcus and precentral gyrus in patients with fatigue. Thus, the primary sensorimotor area might be an important component of the central neural system that regulates sensations of fatigue in patients with MS.

Although the number of overall patients reported here is relatively small, it does give us a glimpse into what neuroimaging techniques are being tried for this disease. Riccitelli et al[1] presented an interesting prospective case series of the application of voxel-based morphometry (VBM) for patients with MS and fatigue. As we know, VBM is an analysis method of brain structure. Studies with VBM have been performed by many researchers on a number of different populations, including patients with schizophrenia, autism, dyslexia, attention deficit disorder, Alzheimer disease, and so forth.[5-9]

Many structures and functions of the brain are asymmetric. For example, Albanese et al[10] have demonstrated a leftward structural asymmetry for the anterior language regions (lateralization of language function). This study by Riccitelli et al[1] showed that findings in patients with MS and fatigue may correlate with atrophy of the left central sulcus and precentral gyrus; this correlation suggests that lateralization may exist in these patients. It will be a very important discovery by these authors if it is true.

However, the study of Riccitelli et al[1] has several limitations. First, the authors made a number of restrictions for selecting patients. In fact, in daily medical work, patients with MS and fatigue who have complex findings will require more in-depth study. Second, the Fatigue Severity Scale is a subjective questionnaire that failed to regard fatigue as a multidimensional state with cognitive, physical, and psychological components. With self-assessment questionnaires, certainty about a true change is difficult, especially when symptom severity fluctuates greatly (regression to mean effect). Questionnaire-based surveys can also introduce bias into a study population because of the participants' knowledge that they are being studied (the Hawthorne effect).[4] Furthermore, more recently, tensor-based morphometry (TBM) has been shown to provide methodologic improvements over VBM. Jacobian determinant (JD) is one of the major TBM metrics that can directly measure tissue growth and atrophy.[11] The main advantage of TBM over VBM is that the former can be applied directly on the JDs of deformation fields without the need for tissue segmentation.[12.]

Riccitelli et al[1] do make a useful contribution to the literature in reporting their unique clinical experience with this disease, even though I do not think the small patient cohort reported here is sufficient to support the contention that findings in patients with MS and fatigue correlate with the atrophy of the primary sensorimotor area. This research is very useful to members of the neuroimaging community encountering patients who have this disease.

In the future, the study of MS will be deeper and wider, with new advanced methodologies. The combination of multimodality neuroimaging in 1 study will encourage using this combination in the study of other diseases, as inspired by this article.

References

1. Riccitelli G, Rocca MA, Forn C, et al. **Voxel-wise assessment of the regional distribution of damage in the brain from sclerosis patients with fatigue.** *AJNR Am J Neuroradiol* 2011;32:784–79
2. Krupp LB. **Fatigue in multiple sclerosis: definition, pathophysiology and treatment.** *CNS Drugs* 2003;17:225–34
3. Kos D, Kerckhofs E, Nagels G, et al. **Origin of fatigue in multiple sclerosis: review of the literature.** *Neurorehabil Neural Repair* 2008;22:91–100
4. Chaudhuri A, Behan PO. **Fatigue in neurological disorders.** *Lancet* 2004; 363:978–88
5. Wright IC, McGuire PK, Poline JB, et al. **A voxel-based method for the statis-**

tical analysis of gray and white matter density applied to schizophrenia. *NeuroImage* 1995;2:244–52
6. Abell F, Krams M, Ashburner J, et al. **The neuroanatomy of autism: A voxel based whole brain analysis of structural scans.** *NeuroReport* 1999;10:1647–51
7. Silani G, Frith U, Demonet JF, et al. **Brain abnormalities underlying altered activation in dyslexia: a voxel based morphometry study.** *Brain* 2005;128:2453–61
8. Yang P, Wang PN, Chuang KH, et al. **Absence of gender effect on children with attention-deficit/hyperactivity disorder as assessed by optimized voxel-based morphometry.** *Psychiatry Res* 2008;164:245–53
9. Baron JC, Chételat G, Desgranges B, et al. **In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease.** *NeuroImage* 2001;14:298–309
10. Albanese E, Merlo A, Albanese A, et al. **Anterior speech region. Asymmetry and weight-surface correlation.** *Arch Neurol* 1989;46:307–10
11. Chung MK, Dalton KM, Davidson RJ**. Tensor-based cortical surface morphometry via weighted spherical harmonic representation.** *IEEE Trans Med Imaging* 2008;27:1143–51
12. Tao G, Datta S, He R, et al. **Deep gray matter atrophy in multiple sclerosis: a tensor based morphometry**. *J Neurol Sci* 2009;282:39–46

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