New insights into the neural basis of functional movement disorders

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Functional movement disorders (FMDs) encompass a broad range of abnormal movements (e.g., tremor, dystonia, myoclonus, and parkinsonism) that are clinically inconsistent with known neurologic diseases. Although they account for 16% of new referrals to neurology clinics,[1] the pathophysiology of FMDs is poorly understood. In addition, FMDs represent a serious challenge for clinicians in terms of diagnosis and management. One of the key clinical features of FMDs is that the abnormal movements can be eliminated by distraction maneuvers.[2] Susceptibility to distraction is typical of voluntary movements, and yet patients with FMDs report that the movements are not under their control. This discrepancy between behavioral findings and patient reports may indicate that the symptoms are feigned or that there is a disruption in the brain processes related to self-agency, the subjective sense of controlling one's actions. A behavioral analogue of self-agency may be alexithymia (impaired ability to read one's own emotional state), which is also found among those with FMDs.[3]

Modern neuroimaging techniques provide a means to study the function of the brain in vivo. In this issue of *Neurology*, Maurer et al.[4] used resting-state fMRI to compare the connectivity of the right temporoparietal junction (rTPJ) between 35 patients with clinically definite FMDs and 35 age- and sex-matched controls. The rTPJ processes and compares the predicted and actual sensory consequences of action.[5] In FMDs, it is hypothesized that a mismatch between these signals may lead to abnormal brain activity in the rTPJ and the perception that voluntary movements are involuntary. After controlling for age, sex, anxiety, depression, and trauma, patients with FMDs had reduced functional connectivity (FC) between the rTPJ and several other brain regions including the right sensorimotor cortex, right insula, bilateral supplementary motor areas, and cerebellar vermis. Consistent with these findings, a previous task-based functional MRI (fMRI) study of 8 patients with functional tremor showed that the rTPJ had reduced activation and FC with sensorimotor and limbic regions during functional tremor, compared with mimicked (or feigned) tremor.[6] Taken together, this work provides strong evidence that there is a disruption of the self-agency network in patients with FMDs.

It is important to recognize, however, that the relationship between self-agency and rTPJ connectivity needs to be assessed directly. Moreover, the findings do not provide insight into what may have triggered the abnormal FC and movements. Historically, psychological trauma was considered the likely trigger of FMDs. Patients in the current study exhibited increased FC between the rTPJ and the left insula with increasing levels of childhood emotional trauma. While anxiety, depression, physical trauma, and sexual trauma were comparable between groups, emotional trauma nearly reached significance in the patients with FMDs ($p = 0.08$). To assess the effect of childhood emotional trauma on rTPJ connectivity, patients could be subdivided into 2 groups based on their level of emotional trauma (i.e., low and high). Another potential trigger, which was not examined, is physical injury. Recent work has shown that 61% of patients have abnormal scores on psychological tests,[7] while approximately 80% report that a physical injury preceded the onset of the abnormal movements.[8] Another limitation is that some patients were taking CNS-acting medications (antidepressants). The authors addressed this issue by comparing FC between medicated and unmedicated patients, and showed that the main findings were unchanged. Nevertheless, future work should have patients withdraw from CNS-acting medications prior to imaging, though the timing of withdrawal might add another variable.

The current study has several strengths. It is the first to study FMDs using resting-state fMRI, a technique that measures the level of spontaneous blood oxygenation level–dependent co-activation of different brain regions while at rest, and thus provides insight into the FC of the brain irrespective of task or task performance. Importantly, a control seed was placed in the posterior cingulate of the default mode network. No between-group differences were observed, indicating that the findings in the rTPJ cannot be explained by an overall disruption of FC

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in FMDs. The groups were adequate in size, age- and sex-matched, and well-characterized in terms of anxiety, depression, and childhood trauma. Moreover, the clinical variables were controlled for in the neuroimaging analyses. The symptoms in the patient group were heterogeneous, consistent with those observed in neurology clinics,[1] and therefore provide a general model with which to understand FMDs. An important next step will be to investigate whether there are differences in FC among FMD phenotypes.

Overall, the study by Maurer et al. represents an important step forward in our understanding of FMDs. The finding that the self-agency network is functionally disrupted at rest in FMDs provides further support that the symptoms are not feigned, and suggests that approaches to increase a patient's self-agency or awareness including motor reprogramming may be the key to lasting relief of FMDs. Improving self-agency would bypass issues of alexithymia by focusing on movement and therefore be more pragmatic and feasible.

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