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Letter to the Editor

The experience of fatigue in the brain

Chronic fatigue syndrome (CFS) is a disabling disorder that is marked by persistent or relapsing fatigue (Fukuda *et al.* 1994). CFS has often been linked to a disturbance in the central nervous system. In line with this hypothesis, previous studies have identified both functional (de Lange *et al.* 2004; Lange *et al.* 2005; Caseras *et al.* 2006; Tanaka *et al.* 2006; Cook *et al.* 2007) and structural (Okada *et al.* 2004; de Lange *et al.* 2005) alterations in the brain of CFS patients (for a review, see e.g. Cho *et al.* 2006; Prins *et al.* 2006).

Caseras *et al.* (2008) contribute to the growing literature of functional cerebral changes in CFS patients by using a novel fatigue provocation procedure. They measured cerebral activity, using fMRI, while CFS patients and healthy control subjects had to imagine fatigue-provoking events (e.g. 'imagine yourself doing your shopping and carrying home heavy bags'). To enhance the vividness of the imagination, participants concurrently watched video clips depicting the to-be-imagined event, shown from a first-person perspective. An anxiety-provoking condition was added to the experiment as a control for any non-specific emotional effects on brain activation.

The authors observed larger activity in the medial parietal cortex and precuneus in CFS patients during the fatigue-provocation task. Recent functional imaging findings in healthy subjects suggest a role for this area in imagery, episodic memory retrieval and self-processing operations like first-person perspective taking and experience of agency (Cavanna & Trimble, 2006). As such, the larger activity in the precuneus in CFS patients during fatigue provocation could well reflect the more vivid capability of CFS patients to imagine themselves in a fatiguing situation, as well as the greater identification that CFS patients experience with fatigue-inducing events.

Fatigue provocation did not only result in areas showing larger brain activity in CFS patients. Interestingly, CFS patients exhibited lower cerebral activity in the dorsolateral prefrontal cortex during the fatigue-provocation task. An earlier study, looking at brain morphology in CFS, found a reduction of grey matter in this cortical area (Okada *et al.* 2004). The dorsolateral prefrontal cortex is essential for the implementation of executive functions like selecting and

initiating behaviour, as has been demonstrated by experimental work from neuropsychology, functional imaging in humans, as well as lesion and single-cell recording studies in the monkey (Miller & Cohen, 2001). Lesions in lateral prefrontal cortex often lead to significant reductions in the generation of appropriate goal-directed voluntary behaviour (Jacobsen, 1935; Goldman-Rakic, 1987; Passingham, 1993), which become clinically manifest as apathy (Levy & Dubois, 2006). As such, there is converging evidence for combined functional and structural alterations in the lateral prefrontal cortex of CFS patients.

Although the study of Caseras and colleagues (2008) shows an interesting difference between CFS patients and healthy controls in the experience of fatigue, the relationship between causes and symptoms is many to one, and it therefore remains an open question whether this difference is specific to CFS. Moreover, it will be important for future studies to assess the dynamics of these functional differences. A recent study in our laboratory showed that the grey-matter volume reduction in the lateral prefrontal cortex could be partly reversed by successful cognitive behavioural therapy (de Lange *et al.* 2008). It would be interesting to see if the functional changes observed by Caseras and colleagues would follow a similar pattern as a function of disease recovery. Future longitudinal studies will be extremely helpful to address these important questions.

Declaration of Interest

None.

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