Neuroimaging in chronic fatigue syndrome

The link between viral infection, the brain, and fatiguing illnesses has a long history. This combination forced itself on the medical imagination after events in Austria in the winter of 1916–17. A virulent form of influenza was noted, characteristically, to produce lethargy and later, to leave a host of neurological deficits in its wake. By the spring of 1918 several English cases of encephalitis lethargica had been reported and in the next year the disease was notifiable. The peak of the epidemic occurred in 1924 in the United Kingdom, at which time the Board of Control reported that many cases had been admitted to hospital with psychiatric disturbances.1 Hence the notion that apparent psychiatric illnesses may be misdiagnosed manifestations of a postinfectious cerebral disease began; it refuses to disappear.2

The symptoms of chronic fatigue syndrome suggest many a disorder of the CNS. Indeed the term “myalgic encephalomyelitis”, favoured by some, implies a disease process involving the muscles, brain, and spinal cord. Although closely identified with a postviral aetiology,1 epidemiological studies suggest that this connection is at most weak,1,6 and the incidence of chronic fatigue syndrome is not increased after viral meningitis compared with non-CNS viral infections.2 Despite the severity and disabling nature of the symptoms in chronic fatigue syndrome, clinical findings tend to be non-specific and routine investigations have a low yield of abnormalities. Furthermore, there are strong associations between the syndrome and psychiatric disorders, most typically depressive illness.3 Mental fatigue and complaints of cognitive dysfunction are core symptoms of chronic fatigue syndrome, and attention has recently moved away from the muscles, the original site of investigation, to the brain. Neuroimaging has thus become a major component of chronic fatigue syndrome research.

Magnetic resonance imaging studies
White matter changes (leukoaraiosis)4 seen on MRI in normal subjects range from small, punctate foci (thought to be related to widening of the perivascular spaces, vascular ectasia, atrophic perivascular demyelination, and cystic and non-cystic infarcts) to larger deep confluent areas possibly reflecting demyelination, spongiosis, or focal infarcts. Such lesions are uncommon in normal subjects under the age of 45,10 but become increasingly prevalent with age,11–13 the presence of vascular disorders such as hypertension, and also in some dementias.14–16 They have also become a focus of interest in affective disorders, with studies reporting deep white matter lesions in some patients.17–19 Although the cognitive consequences of such lesions are unclear, studies have reported an association with speed of information processing in both healthy elderly subjects18 and patients with hypertensive and cerebrovascular disorders.20 Similarly, patients with major depression with such abnormalities are more likely to have cognitive dysfunction and increased admissions to hospital.19,21 As speed of information processing is one of the more consistent neuropsychological findings in patients with chronic fatigue syndrome,22 the status of changes in white matter in chronic fatigue syndrome is of particular interest.

The first MRI studies of a chronic fatigue-like syndrome described two types of focal hyperintensity on T2 weighted scans in the white matter: punctate foci in the upper centrum semiovale and the high parasagittal convolutional tracts and, less often, patchy areas deep in the frontal lobes.22 Multiple punctate foci of T2 high signal in the high convexity subcortical region were reported in a larger subsequent series from the same group.23 These abnormalities were evident in 78% of patients compared with 21% of controls and the authors concluded that the findings were suggestive of CNS inflammation with perivascular cellular infiltrate and/or a reactive demyelination of the surrounding white matter. However, selection criteria for those undergoing MRI (144 of 259 subjects) were not described and it is probable that greater disability and the presence of neurological symptoms were influential. It is also likely that other neurological conditions were mislabelled as chronic fatigue syndrome, as up to 15% of those undergoing MRI had seizures, ataxia, or paresis which are not features of the syndrome.24 Furthermore, cases and controls were scanned at different sites.

Subsequent studies have not replicated these findings. The same group reported hyperintense white matter foci in periventricular, subcortical, and centrum semiovale areas in a further small tertiary care sample of patients, but not at levels significantly different from controls.25 Studies restricted to younger patients with chronic fatigue syndrome reported subcortical hyperintensities much less often.21,27 In addition, three of the eight patients with abnormal scans in one of these studies subsequently developed symptoms suggestive of other medical diagnoses, including multiple sclerosis.27 Our study was the only one to use controls with depressive illness, and whereas no significant group differences were found, white matter
lesions tended to be more prevalent in the depressed patients and were associated with evidence of current intellectual underfunctioning.21 No other studies have investigated both white matter hyperintensities and neuropsychological functioning in chronic fatigue syndrome.

Overall, these studies suggest that no abnormality evident on MRI is characteristic of chronic fatigue syndrome. By contrast, MRI appearances in other conditions, particularly in relation to distribution of lesions, are well recognised. Demyelination due to inflammatory disorders typically causes multifocal white matter lesions, which are recurrent in multiple sclerosis, monophasic in acute disseminated encephalomyelitis, extensive in progressive multifocal leukoencephalopathy, and classically involving the pons or corpus callosum in myelinolysis.28 Similarly, other inflammatory vascular or encephalopathic conditions produce characteristic appearances29 30 whereas encephalomyelitis usually produces both changes in grey matter and white matter lesions which are evident on MRI. In studies which have shown an excess of white matter lesions in chronic fatigue syndrome, it is unclear whether the findings are related to age, misdiagnosis of neurological disorders, or the presence of major depression. Despite the presence of these confounding variables, a quantitative summary of the most rigorous data31 26 27 suggests that there is no significant increase in white matter lesions in chronic fatigue syndrome (OR 2·1, 95% CI 0·92–4·85; 19/90 v. 10/89).

### Functional neuroimaging in chronic fatigue syndrome

Given the paucity of abnormal findings on MRI, researchers have begun to explore whether CNS dysfunction can be shown in chronic fatigue syndrome by functional neuroimaging. As with structural imaging studies, much of this work has sought to establish a diagnostic test for chronic fatigue syndrome, rather than examining the relations between cerebral blood flow and clinical findings. All the studies have assessed resting regional cerebral blood flow, most using 99mTc-hexamethylpropyleneamine oxime (99mTc-HMPAO) single photon emission computed tomography (SPECT).

The first investigations, with healthy age matched control groups for comparison, suggested mild generalised brain hypoperfusion in chronic fatigue syndrome, most commonly in the frontal lobes bilaterally but also in the basal ganglia,32 thalamus, and brainstem.32 Other researchers have described more localised abnormalities, including temporal asymmetry,33 hypoperfusion of the hypothalamus and pons,34 and of the right frontal, temporal, and occipital cortex.35 The reliance of these studies on relative measures of perfusion is a common problem for all studies in SPECT, as it assumes that the reference region is unaffected by the condition of interest. For example, blood flow in the cerebellum, which is often used as a reference region, varies with cognitive activity36 37 and may be abnormal in depression.38 Using whole brain blood flow as a reference might be a more conservative approach; when this technique was used in studies of chronic fatigue syndrome, no specific abnormalities were found.39 40

Although there are discrepancies in the medical literature about cerebral blood flow in major depressive illness, a consensus exists for the finding of frontal hypoperfusion,39 41 42 which is consistent with pathophysiological models of the disorder. Anxiety disorders also lead to clear changes in cerebral blood flow.31 34 43 Most SPECT studies in chronic fatigue syndrome have taken no account of psychopathology and must therefore be interpreted with caution. When patients with major depression have been used as a control group, no consistent differences were found between the two groups.35 44 45

The finding of brainstem hypoperfusion in chronic fatigue syndrome is novel,47 but in the study concerned other regions were not analysed, despite global hypoperfusion on preliminary qualitative analysis. A multivariate approach to show whether brainstem regional blood flow was reduced over and above this global change was not used and thus the specificity of this finding is in doubt. Few centres examine brainstem perfusion, and a structure of this size lies at the spatial resolution limit of SPECT.48 Defining a brainstem region of interest involves the risk of incorporating the surrounding CSF spaces, which would lower the apparent count density. As such definition is often manual it is prone to bias. The physiological manifestations of brainstem hypoperfusion would be difficult to predict, but certainly abnormalities in the level of consciousness, abnormal eye movements, and other “brainstem signs”, are conspicuously absent in patients with chronic fatigue syndrome, as indeed are any resting neurological signs.

Such results suggest that as with MRI, there is no pattern of abnormalities in regional cerebral blood flow which is characteristic of chronic fatigue syndrome, let alone employable as a diagnostic test.49 There is also little consistency between the abnormal findings reported with the two techniques46 48 and to date, no studies have been able to correlate neuroimaging abnormalities with clinical findings in chronic fatigue syndrome.

### Implications for future studies

Thus far, neuroimaging studies in chronic fatigue syndrome have been subject to several shortcomings. Few seem to have been hypothesis led. Rather than attempting to link clinical findings with possible pathophysiological mechanisms, most have been exploratory in nature, seeking abnormalities which are diagnostic of the condition. Although recent work has used patients with chronic fatigue syndrome who meet certain diagnostic criteria guidelines, these do not reflect the apparently heterogeneous nature of the condition, particularly with regard to psychiatric comorbidity and the most recent studies have consequently included patients with depressive illness as controls. The use of instrumentation with higher resolution for functional imaging, coregistration of functional with structural images, and semiquantitative methods of analysis should facilitate research in this area. In addition, the cerebellum should probably be abandoned as a reference region. All functional imaging studies in chronic fatigue syndrome to date have been performed in the resting state. Activation studies using cognitively demanding tasks may provide a more fruitful line of enquiry, particularly as some performance deficits in chronic fatigue syndrome emerge on tasks requiring sustained mental effort. Such studies might also aid our understanding of the phenomenon of fatigue itself by looking at this symptom across diagnostic boundaries.

### Conclusion

Researchers have to apply Occam’s razor to chronic fatigue syndrome. As around two thirds of patients with chronic fatigue syndrome meet diagnostic criteria for depression or anxiety related disorders,4 any abnormality found with neuroimaging in patients with chronic fatigue syndrome must be shown to be distinct from that expected in patients with these psychiatric disorders as well as normal controls. This is difficult, as the range of features evident in the normal population, and those seen in
depression and anxiety, have not yet been well defined. It is therefore premature to claim unique neuroimaging abnormalities in the chronic fatigue syndrome, particularly in the context of the heady adversarial atmosphere which surrounds research in this area.

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