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EDITORIAL

Is the chronic fatigue syndrome best understood as a primary disturbance of the sense of effort?[1]

Chronic fatigue syndrome (CFS) is characterized by severe and prolonged fatigue, affecting both physical and mental functioning, exacerbated by relatively minor exertion (Fukuda *et al*. 1994). A variety of other symptoms such as impaired concentration and memory, disturbed sleep, depressed mood and anxiety are also often present. Alongside this emerging consensus describing the clinical features of chronic fatigue, controversy has raged as to its aetiology, particularly the relative importance of viruses and other infectious agents, the contribution of neuromuscular abnormalities and whether the association with psychiatric disorders is primary or secondary.

In our view much of this argument has been spurious. Psychiatrists, by applying their prevailing methods of clinical description, have contributed to the reliability with which the condition can be identified and the understanding that it may be precipitated by a number of physical (including infectious) and psychosocial stressors (Bruce-Jones *et al*. 1994; Cope *et al*. 1994; Wessely *et al*. 1995) and maintained by other factors, such as (untreated) psychiatric disorder and avoidance of exercise (Gold *et al*. 1990; Sharpe *et al*. 1992; Lawrie & Pelosi, 1994; Wilson *et al*. 1994). For their part, neurologists have sought to implicate viruses directly (Behan *et al*. 1993) or to exclude major peripheral nervous system disease (Edwards *et al*. 1993) with conventional electromyographic and histological methods. The present consensus is probably that peripheral nervous system disease as conventionally understood is absent in CFS.

Running through this debate is a historical polarization between psychiatric explanations (often viewed as mental, non-physical constructs) and physical explanations (real disease). Never was Descartes error (Damasio, 1995) more prominent. We believe that CFS should be regarded as an authentic condition that requires the unifying approach of modern neuroscience to be placed at the heart of attempts to understand it.

THE HYPOTHESIS

We are impressed that patients' reports of fatigue and muscle weakness are complemented by neurophysiological investigations that have consistently demonstrated normal muscular strength but an increased perception of effort on both isometric contraction (Lloyd *et al*. 1991; Kent-Braun *et al*. 1993) and isotonic exercise (Riley *et al*. 1990; Gibson *et al*. 1993; Sisto *et al*. 1996). The sense of effort is an important concept for motor physiology. It appears to originate as a computation of central motor commands against afferent measures of movement and contraction in the nervous system (Goodwin *et al*. 1972*a*). An increased perception of effort can arise as a mismatch between the efferent outflow and afferent feedback of motor activity (Goodwin *et al*. 1972*b*; McCloskey *et al*. 1974; McCloskey & Prochazka, 1994) and has an undeniable subjective validity under experimental conditions. Effort is also used to describe the experience of active thought as well as active muscle contraction. The theory that higher cognitive function involves monitoring of delegated motor and computational modules by a 'supervisory attentional system' (Shallice, 1988) supposes comparisons between intended and achieved task completion. However, it has not explicitly included the consciousness of effort for the cognitive domain. We can see no reason why

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not. Indeed, we believe that only a careful attempt to articulate the subjective experience of patients with observation of motor and cognitive function can capture what is essential to chronic fatigue as a clinical entity.

In the motor domain, increased effort occurs in CFS in the absence of muscle weakness. There is, however, submaximal muscular contraction as detected by interpolated twitch (Stokes *et al*. 1988) or superimposed tetanic stimuli (Kent-Braun *et al*. 1993) during prolonged exercise. It would be in keeping with the more sceptical accounts of CFS to attribute these effects to lack of motivation. But, why is there an increased sensation of effort and evidence from recording of heart rate to suggest an excessive central activation (Riley *et al*. 1990; Lloyd *et al*. 1991) in the early stages of exercise? Heart rate only falls later in activation (Riley *et al*. 1990; Gibson *et al*. 1993). We need more evidence on the effects of the common antecedents of CFS upon motor processes. Subjects with brain lesions that limit motor capacity report that they also have to make a greater effort to concentrate on movement sequences (Brodal, 1972) and preliminary evidence of gait abnormalities in CFS (Boda *et al*. 1995) may support the view that there are an excess of errors in the execution and appreciation of movement. We predict that patients with CFS may have to devote more attention to both motor output and somatosensory feedback during exertion, leading to a greater perception of effort and a reduced tolerance of activity. A switch from automatic to supervised processing could occur as a result of transient disturbance of higher executive function by any disease that impairs brain function and may be compounded by a lack of appropriate practice of skilled activity.

We should perhaps explicitly state that we are not implicating 'abnormal illness behaviour', 'somatization' or even symptom misperception in this proposal. These vague concepts are at best re-descriptions of the patients' problems and at worst deny their subjective reality. They also suggest the cause before defining the nature of the condition. Rather, we postulate that excessive fatigue is due to a requirement for increased effort, accompanied by its percept.

Disturbed sense of effort as central to fatigue can also be integrated with published findings of neuropsychological impairment in CFS. The information processing deficits of CFS are most specific on tests of attention and memory: such as digit span (DeLuca *et al*. 1993; McDonald *et al*. 1993), proactive inhibition (Sandman *et al*. 1993), paced auditory serial addition (DeLuca *et al*. 1993, 1995) and paired associates (Grafman *et al*. 1993; McDonald *et al*. 1993; Sandman *et al*. 1993) – particularly where greater demands are made on sustained attention. Many neuropsychologists are comfortable with a qualitative distinction between effortful and automatic cognitive processing (Shifrin & Schneider, 1977; Hasher & Zachs, 1979; Roy-Byrne *et al*. 1986). The evidence to support a greater impairment of effortful tasks has been provided most specifically by Joyce *et al*. (1996) for a community series of patients with CFS. Deficits in effortful neuropsychological processing may result from a reduction in working memory capacity (cf. Baddely, 1992) or a greater operational demand to control and monitor cognitive processes.

Objective impairments of cognitive function are particularly impressive evidence for a brain-based disturbance of higher nervous function. It is a striking fact that the conditions most commonly antecedent to CFS, as well as CFS itself, seem to show such abnormality. A number of viral infections, including the common cold and influenza, can cause psychomotor performance impairments, even after the resolution of initial symptoms (Smith *et al*. 1989); depressive illnesses are associated with motor and cognitive deficits (Cohen *et al*. 1982; Roy-Byrne *et al*. 1986; Austin *et al*. 1992); and failures of attention and concentration may also be seen in patients with somatoform disorders (Miller, 1984). In infections these effects may be mediated by cytokines such as interferon, which have direct effects upon neurones (Hickie & Lloyd, 1995). The consequences of a prolonged period of illness requiring adaptation to a changed cognitive capacity are unknown. It is possible that the strategies individuals consciously or unconsciously adopt under these circumstances may worsen their subjective and objective problems. These cognitive (and motor) difficulties may provide pathways that, alone or in combination, account for some of the potential routes to a complaint of chronic fatigue.

The requirement for increased effort on muscular and cognitive tasks may also be compatible

with reports of neuro-endocrine and neuro-imaging abnormalities in CFS. These studies suggest a centrally mediated failure in the regulation of the hypothalamic–pituitary–adrenal axis (see Cleare & Wessely, 1996 for review), and widespread reductions in regional cerebral blood flow (rCBF) that are most consistently replicated in frontal cortex (Ichise *et al.* 1992; Schwartz *et al.* 1993; Goldstein *et al.* 1995). It is of considerable interest that frontal areas are where one would expect a convergence of representations of the motor pathways, the neuro-endocrine axis and the somatic inputs contributing to affective states. For example, the evaluation of aversive stimuli seems to involve the anterior cingulate and pre-frontal cortex (Jones *et al.* 1991; Derbyshire *et al.* 1994).

IMPLICATIONS FOR TREATMENT AND RESEARCH

Existing psychological theories have emphasized both physical deconditioning and emotional difficulties to explain the persistence of CFS (Wessely *et al.* 1989; Surawy *et al.* 1995). There has been a tendency thereby to redefine the subjective complaints of patients. This may contribute both to poor compliance with psychiatric treatment offered and even frank hostility to those who offer it. A clearer acceptance of the core problem of increased effort as a focus both for scientific understanding and the development of treatments appears to have inherent advantages.

Existing theories have generated treatments nevertheless. It has been empirically established that the clinical course of CFS can be modified by cognitive-behavioural therapy. This approach has aimed to correct the reduced physical fitness resulting from excessive rest and 'dysfunctional attitudes to exercise' (Sharpe *et al.* 1996). It is interesting that the benefit continues to accrue after stopping formal treatment, an unusual pattern of improvement for cognitive psychotherapy. It suggests that we do not yet understand the critical component of the treatment package.

The research agenda that results from our hypothesis broadly divides into studies clarifying the role of a sense of effort in motor and cognitive tasks in CFS, and intervention studies specifically to test the effects of modifying attentional strategies in motor and cognitive domains. It is obvious that comparisons will also have to be made between patients with CFS and those with affective disorder. Neurophysiological studies of the responses to both isometric and isotonic exercise should determine whether ratings of effort, and their physiological concomitants of increases in blood pressure and heart rate, correlate with subjective reports of fatigue and objective performance. Neuropsychological measures should verify that performance worsens disproportionately as the overall load on working memory increases and is also accompanied by a subjective experience of increasing effort. A dissociation should also be apparent between effortful and automatic tasks, independent of varying difficulty. Intervention studies could be even more critical in defining what adds value to a treatment package. Explicit modification of feedback in motor tasks could aim to re-educate subjects for automatic performance in the motor domain; a parallel approach to cognitive function might be feasible where it poses the major clinical problem. There is already an important indication that the sensation of respiratory effort can be reduced by simple distraction in subjects with chronic obstructive airways disease, resulting in improved exercise tolerance (Thornby *et al.* 1995).

CONCLUSION

Progress in identifying the essential pathophysiological features of CFS has been hindered by a dualistic approach to psychiatric and neurological disorders. Percepts like effort, fatigue and pain may be traditionally viewed as inherently subjective but deserve an understanding informed by integrative neuroscience. The argument developed here seeks nothing less for the disorder currently described as CFS. If it proves to have heuristic value, it will improve our understanding and management of a disabling condition of considerable public health importance.

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