

## Loss of brain gray matter in ME patients

By Dr Neil Abbot, MERGE

There is no doubt that central nervous system symptoms are part of the ME spectrum - as many members of the 25% Group already know! Indeed, they are as characteristic as the post-exercise malaise, myalgia or the myriad of other symptoms that people experience. They were discussed in the famous review by Acheson in 1959, and, half a century later, they form a key element of the Canadian definition (2003) which insists that patients must have at least two of a list of six "neurological/cognitive manifestations", including impairment of concentration and short-term memory, difficulty with information processing, and disorientation or confusion.

To date, no-one has established for certain what causes the cognitive dysfunction in ME, though a variety of structural and functional studies - including SPECT imaging and MRI scans - have been conducted. The jury is still out on the meaning of these reports, however, and it is entirely possible that well-conducted studies might yet be able to provide diagnostic information in place of the present deduction or guesswork about what might be going on in the brain.

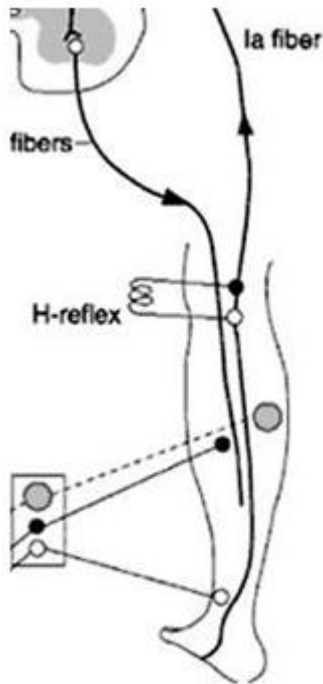
Recently, there have been two very interesting reports. One by de Lange in the journal, *Neuroimage*, found a significant 8% reduction in brain gray matter volume compared with healthy controls. The reductions were related to level of physical activity in the ME patients but not in the control group, and importantly were unrelated to age or duration of illness. The authors comment that their results "corroborate and complement previous studies that observed cerebral abnormalities associated with CFS" Importantly, these results accord another recent study by Okada (2004) in Aichi, Japan: this research group reported an average 11.8% reduction in gray-matter volume in the bilateral prefrontal cortex, a volume reduction which paralleled the severity of the fatigue of the patients.



Why should gray matter be reduced in ME? Grey matter, so named because it looks grey to the naked eye, refers to the areas of the brain that are mainly composed of the heads of nerve cells. De Lange et al speculate that reduced gray matter volume might be the "cause" of the illness and the ensuing physical inactivity. They comment that the fact that the volume reduction is not related to the length of time patients have been ill makes it unlikely that the reduced physical activity causes the gray matter reduction. Alternatively, oxidative stress may be involved: the finding from animal work that metabolically active gray matter of the brain appears more susceptible to oxidative stress than white matter, and is the likely primary target of oxidative stress at all ages, seems to accord with the number of reports linking ME with raised levels of oxidative stress in the tissues.

The truth is that whether gray matter reduction is a primary feature of ME, related to the underlying pathophysiology, or a finding secondary to other processes remains to be discovered. But the report of reduced gray matter by two separate research groups is interesting, more so because (unusually) both research groups have found correlations between loss of gray matter and patients' symptoms.

### New muscle investigation from MERGE



Historically, one of the cardinal signs of ME was marked muscle “fatigability” or loss of power, often in response to quite minor degrees of exercise. Muscle cramps, twitching and extreme muscle tenderness were also common findings. Today, how many ME patients have had a proper clinical examination of their affected muscles? Very few, in fact, but patient reports suggest that observable muscle abnormalities might be more common than is often supposed, and there is some evidence in the modern literature of anomalies in the muscles and nerves of patient. For example, muscle fatigue has been shown to produce alterations in muscle membrane excitability in ME patients, possibly associated with increased muscle oxidative stress (Jammes et al, 2005).

Building on their ongoing investigation of pain in ME patients, Dr Les Wood and Dr Lorna Paul at Glasgow Caledonian University - with their research team of Lindsay Day and Gillian Sutherland - have designed a new study of how exercise and fatigue can affect muscle activity. They have obtained funding from MERGE to look at how nerves control the calf muscles in the leg and what happens to this control after exercise. To do this, they stimulate one of the nerves in the back of the leg behind the knee using a short, non-painful electric shock and at the same time record what happens to the muscle when this occurs. They do this about ten times initially and then, after a short warm-up period, they ask the patient to undertake a short exercise designed to fatigue the calf muscles. This exercise involves pointing the toes to push as hard as possible against a footplate which records the force, and the patient does this for ten seconds followed by ten seconds rest and then repeats the test up to a total of twenty times.

As Dr Wood explains, “What we’re doing is investigating the effects of fatiguing contractions on the excitability of spinal motoneurone pools using the Hoffmann reflex (H-reflex) as a tool to measure this. Following this exercise, we stimulate the nerve again to observe any effects of the exercise on nerve control. This nerve stimulation will be repeated at several time intervals (initially every ten minutes) for up to four hours after the exercise has finished, and we invited the patient to come back to the lab for a short time the next day to repeat the nerve stimulation”.

From this initial investigation of the influence of delayed recovery on “reflex excitability”, the researchers hope to gain information on the status of spinal motoneurons in subjects with ME/CFS during the recovery phase following fatigue. The findings may lead to a large programme of research on the muscle and nerve function of a large group of ME patients.