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Letter to the Editor

Response to 'Localization of white-matter lesions and effect of vascular risk factors in late-onset major depression'

Recently, Dalby and colleagues published an interesting paper on the associations of localization, number and volume of deep white-matter lesions (DWMLs) with late-onset depression, using a case-control design in which they compared 22 patients with late-onset major depression to 22 healthy controls (Dalby *et al*. 2009). The authors found a relationship between DWML localization and late-onset depression, whereas no associations of DWML number and volume with late-onset depression were found. We read this paper with great interest, and although their findings could be of importance, we have a number of considerations when interpreting the findings.

First, DWMLs were identified on axial FLAIR images (matrix 224 × 256, slice thickness 5 mm) and manually labelled by one trained neuroradiologist. When axially viewed, deep lesions may appear to be present on MRI. However, when sagittal and coronal orientations are viewed, many of these lesions are actually contiguous with the ventricular lining and may therefore be incorrectly classified as 'deep' (DeCarli *et al*. 2005). Moreover, volume estimations from manually labelled WMLs have a lower reproducibility and objectivity than estimations from automated segmentation programmes, and often lead to a relative volume overestimation. When WMLs are visually labelled, all hyperintensities are given the same probability of being lesion volumes, since no distinctions are made in hyperintensity range. In addition, less hyperintense voxels around and within lesions are also counted as WML volume, which is likely to result in greater WML volumes than probabilistically estimated volumes. The aforementioned situations could result in a relative overestimation of DWML volume, which is in agreement with the high number of individuals displaying DWMLs in Dalby *et al*.'s study sample (17/22 patients, 21/22 controls). The authors did not report the median volume of DWMLs in patients and controls, but when we calculated this from their Figure 1, it was approximately 0.4 ml for patients and 0.5 ml for controls. These volumes are quite high, given the relatively young age and low prevalence of vascular risk factors in this population. Recently, we reported that volumetrically assessed median DWML volume was 0.4 ml in a large sample of patients with symptomatic atherosclerotic disease (mean age 58 ± 10 years), while they had more vascular risk factors than Dalby *et al*.'s study sample (Geerlings *et al*. 2009). Another study, in patients with evidence of vascular disease or at high risk of developing vascular disease of considerably older age (mean age 75 ± 3 years), found a median DWML volume of 0.5 ml (Versluis *et al*. 2006).

Second, because of the relatively small sample size, patients with extremely high or low values of DWML volume seem to distort the findings. In Figure 1, three patients with extremely high values are seen in the control group. When these patients are left out, the median volume seems to decrease to 0.18 ml. Further, in the patient group three outliers are seen with low values. Exclusion of these outliers seems to increase median DWML volume to 0.53 ml. A significant difference in WML volume between depressed and control subjects could have been present if these outliers were excluded from the analyses. Hence, it would have been preferable to use a larger sample size.

Third, when control subjects are recruited through advertisement, it is important to take the possibility of selection bias into consideration. Since not all people have access to the source of the advertisement, some members of the population are less likely to be included than others, leading to a biased and unrepresentative sample. Self-selection can also play an important role in recruitment through advertisement. A participants' decision to participate may be correlated with traits that affect the study, creating a non-representative control sample, thereby inducing incomparability between patients and controls.

Finally, the last hypothesis tested by the authors was that vascular risk factors have a significant effect on WML load. Most previous studies found that vascular risk factors, including hypertension and diabetes mellitus, are significantly associated with WML load. Dalby *et al*. did not find a significant effect of these variables on WML load. This may be a result of matching the depressed patients with control subjects for age, gender and vascular risk factors. A consequence of matching is that these factors can no longer be studied as a determinant of the outcome, because all variation is 'matched away'. However, a significant difference was found in social class between depressed and control subjects. Unfortunately, the authors did not adjust for the difference in socioeconomic class, whereas such an adjustment might have influenced the results.

Declaration of Interest

None.

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Letter to the Editor

Plausible explanations for neurocognitive deficits in ME/CFS, aggravation of neurocognitive impairment induced by exertion

We read the review by Cockshell & Mathias (2010) with great interest and compliment the authors for their thorough review of cognitive deficits in Chronic Fatigue Syndrome (CFS). As noted by Thomas & Smith (2009), cognitive impairments can be identified if the appropriate tests and measures are used. However, we would like to make two comments.

First, many studies have established organic aberrations which, at least partially, could account for the neurocognitive deficits seen in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Many aberrations in brain structures and functions have been established in ME/CFS, like hypoperfusion and hypometabolism of brain regions of interest, impaired cerebral oxygenation during exercise, SPECT scan abnormalities in the cerebral cortex, small discrete lesions in the subcortex, a reduction in grey matter, and immunological abnormalities and aberrant proteins in spinal fluid (Lange *et al*. 2005; Chen *et al*. 2008; Twisk & Maes, 2009). In ME/CFS brain activity is significantly more diffuse (Chen *et al*. 2008), possibly as a compensation mechanism (Lange *et al*. 2005).

Hypoperfusion and hypometabolism are plausible explanations for the 'brain fog' often reported by ME/CFS patients. Moreover, a correlation between neurological abnormalities and neurocognitive functioning has been established (Lange *et al*. 2005; Chen *et al*. 2008).

Second, exercise and graded exercise therapy (GET), proposed as a treatment for ME/CFS, are likely to aggravate the cognitive complaints in ME/CFS. The average increase of the prefrontal cortical volume due to cognitive behavioural therapy/GET (CBT/GET), mentioned by Cockshell & Mathias (2010), is very modest (+4.8 ml, S.E. = 2.3 ml, difference in grey-matter volume before intervention: −38.8 ml). The grey-matter volume even declined in a substantial subpopulation.

Inflammation, immunosuppression, immune dysfunction, oxidative and nitrosative stress, mitochondrial dysfunction, apoptosis, infections, channelopathy and a blunted stress response are key pathways in ME/CFS (Twisk & Maes, 2009), as has been confirmed by various gene expression studies.

Since exertion and GET increase inflammation, oxidative and nitrosative stress, and channelopathy, it is not surprising that exercise has a negative impact on the pre-existing cognitive impairments, in large subgroups of patients (Twisk & Maes, 2009).

Several studies show that neurocognitive problems of many ME/CFS patients are aggravated by exercise, e.g. cognitive processing is impaired 24 hours after physically demanding exercise; exertion has a negative effect on simple reaction time and choice reaction time; fatigue-inducing activities cause altered central nervous system signals, which control voluntary muscles; and exertion has a negative impact on perfusion of the left prefrontal lobe and cerebral