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LETTER TO THE EDITOR

Reply: Change in grey matter volume cannot be assumed to be due to cognitive behavioural therapy

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Sir, We thank Tom Kindlon for his letter, in which he raises several important issues. We will respond to all the issues in the same order as they appear in his letter.

First, Tom Kindlon points out that cognitive behavioural therapy (CBT) is not a panacea for the chronic fatigue syndrome (CFS). It should be obvious from all previous meta-analyses that CBT does not lead to a full recovery in all CFS patients (while the exact numbers on improvement rates depend on a host of experimental factors like the exact type of therapy given, inclusion criteria of the study, as well as other factors such as the patient's self efficacy, social support and physical activity pattern). Nevertheless, it should also be obvious from these meta-studies that psychotherapeutic interventions like graded exercise therapy and CBT interventions are the only interventions that have shown reliable, replicable and relatively robust improvements in health status in CFS, compared wtih all other interventions that have been investigated to date.

The second point of Tom Kindlon is that we should have used objective measures to quantify improvement in health status rather than questionnaires as the latter may simply reflect changes in response tendency of the CFS patients. We share the author's preference for objective measures, which is why all the reported significant brain–behaviour relations in our manuscript in fact pertain to objective, quantitative measures [see e.g. Fig. 4 of de Lange *et al*. (2008)]. The significant relationship between behavioural improvements and increase in grey matter volume (GMV) was constituted by the choice reaction time task (Vercoulen *et al*., 1998) and the digit symbol substitution test of the Wechsler adult intelligence scale (WAIS-dst) (Wechsler, 1981), two objective psychophysical tasks that are often used as measures of information processing speed (Chiaravalloti *et al*., 2003). Moreover, improvements in general physical activity, quantified by objective actigraphic measurements (Vercoulen *et al*., 1997; van der Werf *et al*., 2000) for a 2-week period both at baseline and follow-up, showed a trend of significant relationship with the GMV increase.

Lastly, the author points out that our study, for lack of control group, has not proven that the increase in GMV is specifically due to CBT, rather than spontaneous recovery. We agree with the author that the lack of patient control group limits the scope of our inferences, as has already been acknowledged both in the manuscript and in the reply to Dr Bramsen. We would like to point out that the improvement rate of the sample in our study far exceeded the improvement rate seen with passive support groups or a waiting list condition (Prins *et al*., 2001). But crucially, the aim of our study was not to test whether CBT is an effective intervention for CFS, as has been the topic of previous studies (Whiting *et al*., 2001; Chambers *et al*., 2006), but rather to investigate whether there was a relationship between behavioural improvements following CBT in CFS and changes in brain morphology. Our data clearly indicate that there are changes in brain morphology that are contingent upon behavioural improvements following CBT.

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