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## LETTER TO THE EDITOR

Reply to: can CBT substantially change grey matter volume in chronic fatigue syndrome?

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doi: 10.1093/brain/awn208

Received and Accepted August 1, 2008

Sir, We thank Dr Bramsen for her interest in our recently published article (de Lange *et al.* 2008). In this article, we report on an increase in prefrontal grey matter volume following cognitive behavioural therapy (CBT) in a group of patients suffering from the chronic fatigue syndrome (CFS).

Dr Bramsen raises two points of criticism. First, she questions the lack of a control group of patients receiving no treatment or a different treatment. While this limitation was already emphasized in the discussion section of de Lange *et al.* (2008), it remains unclear how the observed behavioral and cerebral changes could be accounted for by generic and CBT-independent factors. Dr Bramsen wonders whether the reported behavioural improvements are really the result of CBT, or whether they could be due to natural course or lifestyle changes, while the underlying disease process is not influenced by CBT. A large body of evidence suggests that this is not the case: there is overwhelming evidence in the literature from several carefully conducted randomized controlled trials (RCT) that demonstrate the specific efficacy of CBT for CFS (e.g. Sharpe *et al.* 1996; Deale *et al.* 1997; Prins *et al.* 2001). It was beyond the scope of this study to disprove that treatments other than CBT would have resulted in the same—or even better—results, simply because this possibility has already been tested and rejected (Whiting *et al.* 2001; Chambers *et al.* 2006).

The second point of criticism raised is that the structural changes in the brain are small, comprising <1% of the total brain volume. Dr Bramsen argues that, although statistically significant, these changes are unlikely to be clinically relevant. This argument is more an intuition than a scientific argument. Given the limited knowledge of

structural plasticity in the adult human brain, it seems arbitrary to set an *a priori* threshold for clinical relevance. More importantly however, Dr Bramsen neglects the fact that the reported increase in grey matter volume was largely regionally specific, confined to left and right lateral prefrontal cortex [see Fig. 3 of de Lange *et al.* (2008)]. The increase in grey matter volume might appear numerically modest when expressed in terms of *whole-brain* grey matter volume. Yet, when relating the change to a more specific anatomical structure (the lateral prefrontal cortex), the increase in grey matter volume was on average 8%. Nevertheless, we prefer to focus on whole-brain grey matter volume as a dependent measure, as it is a reliable, sensitive and unbiased measure of overall cerebral morphology (Good *et al.* 2001; Chard *et al.* 2002).

In summary, while our study did not compare the efficacy of CBT in bringing about the behavioural and brain changes with other treatments or no treatment, there is an overwhelming amount of evidence from the literature that shows the specific efficacy of CBT. The size of the structural changes should naturally be interpreted in relation to the dependent measure used. Finally, we agree with Dr Bramsen that our results do open a wide array of new questions, like: ‘What is the long-term time course of these structural brain changes?’ and ‘Can successful CBT also lead to structural brain changes in other psychopathologies, e.g. depression?’ These exciting research questions will hopefully be the topic of future studies.

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