REPLY

Early life stress and HPA axis changes in CFS

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We thank Filip Van Den Eede and Greta Moorkens for their comments (Neuroendocrine correlates of childhood trauma in CFS *Nat. Rev. Endocrinol.* **8**, doi:10.1038/nrendo.2011.153-c1)¹ on our published Review (Hypothalamic–pituitary–adrenal axis dysfunction in chronic fatigue syndrome. *Nat. Rev. Endocrinol.* **8**, 22–32; 2012).² We would like to reply as follows.

First, they assert that our statement that “mean saliva cortisol levels of those [CFS patients] without early-life stress as well as those with early-life stress were significantly lower [after 0.5 mg dexamethasone] than those of healthy controls” (page 26) is incorrect, as is our reference in our Table 4 to “intermediate” post-dexamethasone cortisol in those with early life stress compared to those without early life stress and controls. However, referring to Table 3 of their study³ shows that mean saliva cortisol levels post-dexamethasone in patients with CFS without early life stress (24 ng/100 ml) as well as in those with early life stress (49.8 ng/100 ml) were lower than those of healthy controls (80.9 ng/100 ml) and reported to be statistically significant using Kruskal–Wallis testing across the three groups, and when both patient groups were combined; this was the basis of our assertions on page 26 and in Table 4. However, we acknowledge that post-hoc testing using the Dunn test was reported to show no specific difference between those with early life stress and controls, although the power of such a post-hoc test in just 11 participants with early life stress is of course limited, and no actual details of these test statistics were given in their paper to allow further evaluation.

Similar considerations apply to our statement in our Table 3 that there was “significantly decreased mean AUC total [cortisol] post DEX and post CRH”. Data³ in their Table 3 do clearly show this: again, the three group comparison using Kruskal–Wallis testing is reported to be significant. However,

in relation to our Table 3, we do acknowledge a typographical error and, in keeping with the above, agree that it should have read “patients without early-life stress had lower mean cortisol post DEX and lower AUC total post DEX plus CRH than both controls and patients with early-life stress”. We cannot find any further statistical comparisons in their 2007 article.⁴

Essentially, the data of Van Den Eede *et al.*^{3,4} are in keeping with other studies providing now consistent evidence for heightened negative feedback and increased glucocorticoid receptor function in CFS. We agree that more research is needed to clarify the effect of adverse experiences early in life on this and other changes to the hypothalamic–pituitary–adrenal (HPA) axis in CFS. Indeed, one of the main conclusions of our Review was that our understanding of factors contributing to HPA dysfunction remains incomplete. Therefore, that there remains disagreement between studies^{3,5} is perhaps not surprising. The effect of adverse early life experiences on HPA axis activity may depend on their nature, severity, duration and age of exposure. There may also be a switch from a period of hyper-activation to a period of hypo-activation of the HPA axis.^{6–8} Nevertheless, there is accumulating evidence that in adult healthy individuals without any psychopathology such adverse events early in life lead not only to lower daily cortisol secretion and lower cortisol responses to stress tests^{9–11} but also to increased DNA methylation of key enzymes controlling the activity of the stress system.^{12,13}

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Competing interests

The authors declare no competing interests.

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