Correspondence

Pituitary in psychosis

Pariante *et al* (2004) conclude that patients with first-episode psychosis have a larger pituitary volume and those with chronic schizophrenia a smaller pituitary volume in comparison with the controls. However, there are a number of factors that limit this conclusion.

First, normal variation in pituitary volume: a large degree of variation is observed in the morphology of anterior and posterior pituitary in healthy individuals (Fujisawa *et al*, 1987). Moreover, the variations may occur in the same individual if the measurements are repeated after an interval (Brooks *et al*, 1989). Therefore, conclusions based on a single measurement may be unreliable and at least two or three measurements should have been performed for better accuracy.

Second, effect of gender and age: men tend to have smaller pituitaries, as mentioned by Pariante *et al*, and the pituitary size decreases with age (Brooks *et al*, 1989). In the study by Pariante *et al* the schizophrenia group contained a significantly larger number of men and significantly older people compared with the control group. These differences could be partially responsible for the smaller pituitary size observed in chronic schizophrenia.

Third, failure to demonstrate the hyperactivity of hypothalamic–pituitary–adrenal (HPA) axis: the correlation between HPA axis and pituitary volume is purely speculative and Pariante *et al* did not discuss the negative studies on the subject. Katona & Roth (1985) reported an abnormal dexamethasone suppression response in only 33% of patients (10 out of 30) with schizo-affective depression.

Fourth, failure to measure the adrenal gland size: adrenal gland hypertrophy has been shown to correlate with hyperactivity of the HPA axis in depression (Nemeroff *et al*, 1992). Pariante *et al* did not measure the adrenal gland size, probably as the study was not pre-planned and magnetic resonance imaging data obtained for another study were utilised. Measurement of adrenal gland size would have added more weight to the study findings.

Another comment worth mentioning is that hyperactivity of the HPA axis does not point to a specific diagnosis and occurs in a large number of conditions associated with stress. Therefore, this finding alone has a limited role in diagnosis of a particular condition.

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Author's reply: We welcome Dr Kumar's comments, drawing attention to some of the limitations of our study (Pariante *et al*, 2004). Even though some of these points had already been discussed in the paper, we think it is helpful to reply to all comments.

We agree that there is a large degree of variation in the morphology of the pituitary. For example, in our sample approximately half the subjects had a 'concave' pituitary, and a third had a 'flat' pituitary. However, we have minimised the influence of morphology on the volume measurement by tracing all coronal slices where the pituitary was visualised. Dr Kumar also refers to the paper by Brooks *et al* (1989) showing intra-individual changes in the brightness of the posterior bright signal, representing vasopressin released in the posterior lobe for fluids control. We did not analyse the brightness of the posterior bright signal, as we were not interested in the regulation of fluids control in our sample.

In our study there were significant differences in age and gender between the groups. By definition, it was impossible to have one single control that was comparable to the young first-episode participants as well as to the older individuals with established schizophrenia, for both age and gender distribution. However, we used two strategies to control for these confounders: first, gender and age (and whole-brain volume) were included as covariates in the analysis; second, the results obtained from this analysis were further corroborated by conducting separate tests comparing the clinical groups (first-episode and established) with selected control groups that had similar age and gender distribution. Both strategies led to the same results, thus demonstrating that the smaller pituitary volume in patients with established schizophrenia is not due to differences in age and gender distribution.

We agree that the association between increased pituitary volume and HPA axis hyperactivity is speculative, and we clearly stated this in our paper (see Limitations, p.10). Nevertheless, over 30 years ago Sachar *et al* (1970) found that patients experiencing a first-episode psychosis were more likely to present with HPA abnormalities, because of the distress associated with the 'dramatic and ego-dystonic' nature of this experience. Several studies have confirmed that patients who are in the acute phase of a psychotic disorder, with florid symptoms, newly hospitalised or unmedicated, have elevated HPA axis activity as shown by raised cortisol levels (Sachar *et al*, 1970), non-suppression of cortisol secretion by dexamethasone in dexamethasone suppression test and in the dexamethasone/corticotropin-releasing factor (CRF) test (Herz *et al*, 1985; Lammers *et al*, 1995), and elevated levels of CRF in the cerebrospinal fluid (Banki *et al*, 1987). Only patients who are clinically stable and receiving treatment tend to have a normal HPA axis (Ismail *et al*, 1998). Indeed,

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