Authors' reply: In our study we found that recent severe life events were associated with increased salivary cortisol but that depression was not. This is incompatible with the widely held theory that stress predisposes to depression through its effects on the hypothalamic–pituitary–adrenal (HPA) axis. Dr Moore hopes that those with more severe depression may have shown evidence of cortisol hypersecretion. Unfortunately for the stress–HPA theory of depression there is no such evidence – not even in the 9 out of 94 cases with ICD–10 severe depression. The median 23.00 h cortisol levels are identical for the non-depressed subjects and those with depression at all levels of ICD–10 severity. For the 09.00 h cortisol levels, the 'severe depression' group median is 7.5 compared with 7.0 for the controls, with interquartile ranges of 5.75 and 5 respectively (i.e. almost total overlap between the groups).

Although it has become dogma that cortisol secretion is increased in depression, increased cortisol secretion is only reliably recorded in severe and often psychotic depression in hospital in-patients. We suggest that this reflects a primary disorder of the HPA in patients with bipolar and psychotic illness, which is unlikely to be connected with psychosocial stress. Our findings indicate that most depression occurs with normal or slightly reduced cortisol secretion and this finding is already present in the literature. For example, Stokes *et al* (1984) found that only 15–20% of subjects with depression in the community had elevated plasma cortisol concentrations. It seems inescapable that sustained hypercortisolaemia is not how social adversity causes depression. However, there is evidence from our study that depression is associated with sensitisation of the HPA axis to chronic stress. Chronic stress occurred in many non-depressed subjects but had no effect on cortisol, whereas in subjects with depression cortisol was increased in those who were chronically stressed. Therefore, increased cortisol in those with chronic stress is due to the depression and not vice versa; it is a marker for brain vulnerability to depression and not the proximal cause of the depressed state. As the findings of Maes *et al* (1994) suggest, the profound stress of admission to a psychiatric hospital may be the factor that induces hypercortisolaemia in hospital studies of depression, since cortisol was not increased in community patients with equal levels of depression. Similarly, as Garland importantly points out, degree of stress may be the key factor in determining physical morbidity and mortality associated with depression; the interaction of stress with being depressed may be all-important in determining the physical and psychiatric outcome of depression.

Contrary to Garland's assertion, the dexfenfluramine results were not 'negative'; we found enhanced responses in the 'depressed' group. Perhaps he regards the failure to observe blunting in depression as a negative result. But our study is arguably the largest and best-controlled ever performed. Furthermore, exaggerated 5-HT_{2C} responses in depression have been observed in studies using 5-hydroxytryptophan challenge (Meltzer *et al*, 1984). Serotonin abnormalities, like the cortisol response to chronic stress, may be seen as effects of depression. As Cowen points out in his commentary (Cowen, 2002), life events appear to increase fenfluramine responses only in the 'depressed' group. Fenfluramine responses were in fact lower ($P<0.1$; Strickland *et al*, 2002: Fig. 1c) in the small number of depressed subjects without life-events. A small amount of serotonin release, induced by life events, playing onto supersensitive 5-HT_{2C} receptors together with subsensitive autoreceptors, could account for the exaggerated serotonin responses to life events in the 'depressed' group. If so, then biological vulnerability to depression could involve an underlying presynaptic impairment of serotonin function. On this interpretation, some of the symptoms of depression, such as anxiety, might still be mediated by unstable excessive stimulation of 5-HT_{2C} receptors together with impaired 5-HT_{1A} resilience mechanisms as suggested by Deakin & Graeff (1991). Dr Moore's suggestion that resistance to depression in the face of life events might be mediated by normal or enhanced serotonin responsiveness is compatible with this line of reasoning. However, his suggestion that life events act on a vulnerable serotonin system through cortisol responses is not compatible with our evidence – depression in the community is not associated with hypercortisolaemia.

Declaration of interest

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Non-right-handedness and schizophrenia

Sommer *et al* (2001: p. 349) found 'compelling evidence . . . for decreased cerebral dominance in schizophrenia', from a review of studies of handedness and other functional and anatomical asymmetries, consistent with the theory that schizophrenia is associated with an anomaly of the mechanisms of cerebral dominance (Crow, 1997), possibly a 'right-shift factor'. They suggested that reduced asymmetry may help identify risk for schizophrenia. Procopio (2001) welcomed the review but cautioned that the 'right shift' is only a hypothesis and that findings for asymmetry in twins demonstrate an important environmental component.

The Sommer *et al* review puts it beyond doubt, in my opinion, that asymmetries are reduced in schizophrenia but this needs careful interpretation. The right-shift theory (for review see Annett, 2002) suggests that the main agent of asymmetry is environmental, random accidents of early growth in bilaterally symmetrical creatures. Random accidents occur in monozygotic twins as individuals, just as in other individuals. What is interesting about humans is that several chance distributions

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