be obtained. Since the publication of our report, a post-mortem study by Crow and colleagues has been completed showing no significant change in total and sub-field volumes and neuronal density within the hippocampus of patients with schizophrenia (T. J. Crow, personal communication, 1999). Since lateral ventricular size may be expanding over time and cortical volume decreasing in patients with chronic schizophrenia (DeLisi, 1999), one has to account for why post-mortem studies of patients who have been ill for several years (at the 'end-stage' of illness) find little evidence for pathology of the hippocampus.

The first point that Wood *et al* raise is that we appeared to overlook two recent reviews in the literature that conclude that the hippocampus is reduced in schizophrenia bilaterally. Neither of these reviews, however, deals with the inconsistencies I raise above (they review MRI, but not post-mortem studies), or with the issue of measurement variability. The anatomical delineation of the hippocampus as it is visualised on MRI scans is difficult. Separation from the boundary of the parahippocampal gyrus may vary between observers, and the anterior and posterior boundaries are frequently difficult to define. In general, the thicker the MRI slice, the more inaccurate the measurements are likely to be. In fact, interrater reliability for measurements of these medial limbic structures is usually reported to be low. The temporal horns of the lateral ventricles are even more difficult to measure accurately, because of their irregular shape; in controls they are small and irregularly visualised. For these and the other reasons listed above, we conclude from our own review of the literature (in Table 1 of Razi *et al*, 1999) that the findings in the medial termporal lobes of patients with schizophrenia are inconsistent. Wood *et al* mention an additional problem of how one chooses to separate amygdala from hippocampus. However, this seems irrelevant to their argument since both reviews they cite conclude that both the amygdala and the hippocampus are reduced.

Wood *et al*, raise a second issue that suggests a lack of validity of our failure to find evidence for medial temporal lobe pathology in first-episode patients because it is present in other recent studies of first-episode schizophrenia. Although the number of subjects scanned at the first episode in our own study is small, this is unlikely to account for the discrepancy. Positive studies such as Hirayasu *et al* (1998) cited by Wood *et al* also studied a small cohort, particularly when considering that 12 of their 17 'first-episode' cases were ill at least six months prior to the initial hospitalisation and an another two were not scanned until a follow-up evaluation at 15 and 22 months. Thus, perhaps what accounts for the discrepancy is a problem with the term 'first-episode'. One assumes that by studying patients at the time of their first hospitalisation (usually also their first episode), they are being studied at the onset of the disorder. However, brain structural change and subtle behavioural symptoms could have been occurring for several years prior to the identification of the first episode (DeLisi, 1992). Thus, the timing of the development and ability to detect brain changes is likely to vary across small samples of patients.

Finally, the question was raised as to why measurement of total brain volume was obtained only on slices in which the medial temporal lobe structures were measured. This method was thought to be valid since the medial temporal lobe appears in only a small portion of the total number of slices covering the entire brain and it is likely that medial temporal lobe volumes are not linearly correlated with total brain volume. We also wanted to determine whether reduced total brain volume specifically within the region where the medial temporal lobe appears could account for our results. Thus, we thought the use of this partial volume would be a valid way to control for brain size in analyses. However, whether these measurements should be controlled for brain size at all, given the studies showing overall hemispheric volume reduction in schizophrenia, is a more important issue. In Razi *et al* (1999) the volumes of medial temporal lobe structures were compared with and without brain size as a covariate and the findings did not differ. In addition, a subsequent analysis was performed on the same data substituting the height of each individual for brain volume to eliminate the confound of overall brain volume reduction in schizophrenia, yet still controlling for the size of the individual. There were no differences in height among diagnostic subgroups and all previously significant results remained the same. Both hippocampus and parahippocampus were reduced in patients compared with controls ($F=6.7$, $P<0.002$ and $F=7.6$, $P<0.001$). The *post hoc* analyses show differences only in chronic, not in first-episode patients, and are as reported in Razi *et al* (1999).

I therefore conclude that the objections of Wood *et al* in no way negate the possibility that any observed reduction of the hippocampus seen on MRI in patients with schizophrenia could be due to a primary enlargement of lateral ventricles (the temporal horn of which interferes with measurements of hippocampus), and that this expansion of ventricular space continues sporadically through the chronic course of schizophrenia, to a greater extent on the left than the right and possibly in those with a poor course.

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Post-abortion mania

Sir: It has been suggested that the oestrogen decrease occurring after delivery plays an aetiological role in puerperal psychoses (Deuchar & Brockington, 1998). Acute psychosis following abortion is a very rare disorder (incidence 0–3/1000 induced abortions) (Brewer, 1977) and has been rarely documented. We describe the case of a woman who presented with psychotic mania following abortion.

Mrs A. experienced puerperal mania with psychotic features when she was 19,

21 and 27 years old (all pregnancies went to term). She became pregnant again at the age of 31 and since she was treated with numerous drugs with possible teratogenic effect, abortion was recommended. The early termination of this pregnancy was successfully achieved by aspiration alone during the tenth week. Abortion was immediately followed by a manic episode with psychotic features which resolved with conventional treatment. Mrs A. experienced a fifth pregnancy at the age of 33 (to term, Caesarean section) which was associated with a manic episode with psychotic features. At the age of 35 she experienced a sixth pregnancy which stopped spontaneously at the tenth week. This spontaneous abortion was followed by a manic state. At the age of 36 she experienced a seventh pregnancy (to term) which was followed by a manic episode with psychotic features. Delivery was followed by a marked decrease in peripheral oestrogen. Peripheral oestrogen crosses the blood–brain barrier and modulates various systems of neurotransmission, especially dopaminergic transmission (Fink *et al*, 1996), and the oestrogen decrease has been hypothesised as being a precipitating factor of puerperal psychosis in predisposed individuals (Deuchar & Brockington, 1998).

The occurrence of both puerperal psychotic mania and abortion-associated psychotic mania in the same person suggests an individual predisposition, and a single aetiological mechanism can be hypothesised: abortion (spontaneous or induced) during the first trimester is followed by a marked decrease in oestrogen levels (Blazar *et al*, 1980) and the termination of all seven pregnancies was simultaneously associated with both the occurrence of acute psychotic mania and a decrease in oestrogen levels consistent with a modification of the brain oestrogen environment. This suggests that the oestrogen withdrawal hypothesis may be relevant in psychoses occurring after pregnancies that are not going to term.

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Mirtazapine withdrawal causing hypomania

Sir: Although a number of studies have reported the development of hypomania following discontinuation of antidepressant therapy (e.g. Mirin *et al*, 1981; Hartmann, 1990; Landry & Roy, 1997), this has not yet been reported for the relatively new noradrenergic and specific serotonergic antidepressant, mirtazapine.

A 65-year-old woman was commenced on mirtazapine 30 mg nocte owing to symptoms of depressed mood with diurnal variation (worse in the morning), intermittent suicidal ideation, disrupted sleep pattern, poor concentration, lack of motivation and general anhedonia. Although she derived little benefit from the medication, she remained on it for a period of five weeks at which point of her own accord, she decided to discontinue it abruptly at a time when her suicidal ideation was particularly marked. Within two days of stopping the drug, she felt dramatically better and became quite elated and mildly disinhibited, with pressure of speech, increased energy levels and a reduced need for sleep. She adopted a youthful style of dress and demeanour and offered one of the authors small gifts. At no point during this time, however, did she develop flight of ideas or any psychotic symptoms. She continues to be mildly hypomanic six weeks after drug withdrawal.

This woman had a long history of recurrent anxiety and depressive episodes. She had previously suffered a mild degree of hypomania following commencement of paroxetine in July 1998 but there is no other history of hypomania. Prior to commencing mirtazapine, she had been treated unsuccessfully with sertraline in doses up to 100 mg daily (she was unwilling to increase the dose further because of side-effects and lack of efficacy). Although hypomania has been noted to have occurred following mirtazapine augmentation of sertraline (Soutullo *et al*, 1998), the symptoms of hypomania only occurred in this case immediately after discontinuation of the mirtazapine and the two drugs were never given concurrently.

Mechanisms proposed to explain this withdrawal phenomenon previously noted with other classes of antidepressant include 'cholinergic overdrive' (Dilsaver & Greden, 1984) and noradrenergic hyperactivity (Charney *et al*, 1982), although the true reason for its occurrence remains unclear. This further report of the same phenomenon with one of the newer classes of antidepressant serves to highlight the need for further research in this area.

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Drug therapy in treatment-resistant depression

Sir: We commend the study by Poirier & Boyer (1999), comparing the efficacy of venlafaxine and paroxetine in people with treatment-resistant depression as this is a difficult sub-population in which to conduct research. However, we were dismayed that there was no discussion as to why venlafaxine should be superior to paroxetine, a finding that is indeed supported by our clinical experience in managing people with treatment-resistant depression.

The majority of our referrals with treatment-resistant depression have usually been prescribed adequate doses of tricyclic antidepressants, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors during the course of their illness. It is our practice to use augmentation strategies,