reflect the inappropriateness of the control group.

In the Rey Auditory Verbal Learning Test, significantly lower scores on lists A1–A5 were taken to infer a reduction in verbal memory. However, there was no difference between patients and controls for lists A6 and A7. The percentage of words retained between trials A5 and A7 would provide a purer index of retention (Thompson *et al*, 2005) and would help to better interpret the data.

In the future, meta-analyses of existing data and studies involving assessment of cognitive function and neuroimaging in euthymic patients with bipolar disorder should help elucidate a profile of cognitive deficits and their underlying neurobiological bases.

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Authors' reply Certain aspects of methodology were left out of our paper owing to space constraints. Bharadwaj cites Ferrier & Thompson (2002) when questioning the exclusion criteria used in our study. Both are co-authors of our paper, which is a result of collaborative research between the Department of Psychiatry in New Delhi and Newcastle since 1998. Whenever possible, similar tests and criteria for euthymia have been used in both centres with occasional variations to respect cultural differences. Use of spouses and siblings as members of the control group was acceptable, as it brought together people of broadly similar backgrounds. Although this might have resulted in the inclusion of a limited number of controls who were at risk of developing bipolar disorder, it minimised differences between people with bipolar disorder and controls without greatly confounding our results.

For verification of euthymia participants were seen at least twice, separated by a minimum of 1 month, before they were tested. Clinical judgement of euthymia was reinforced by a Hamilton Rating Scale for Depression score <8 and a score <20 on Bech's modification of Beigel's Manic State Rating Scale on both occasions. The stability of mood during the intervening period was assessed clinically on a weekly basis. We were not aware of any Hindi version of the Structured Clinical Interview for DSM–III – patient version. The exclusion of other psychiatric morbidity was based on clinical interviews by two highly experienced psychiatrists, complemented by careful mapping of life charts using the techniques of Post *et al* (1998).

Soft neurological signs were assessed with the widely used modified Kolakowska battery. We are unsure whether the use of other batteries, such as the Cambridge Neurological Inventory, would substantially alter our findings. Involving a second rater would perhaps increase reliability but would extend the assessment time unreasonably.

Not surprisingly, soft signs were found in the control group, but only at about one-quarter of the severity seen in people with bipolar disorder. The maximum score on the modified Kolakowska battery was 45. The maximum score for controls was 9 whereas the mean for patients was 13.9. Control scores mainly comprised minimum scores on a few of the 15 items. In a subsequent article (further details available on request) we report high levels of soft signs in the youngest patients with bipolar disorder. There is no evidence that soft signs progress with age in bipolar disorder, whereas in controls there is significant ($P<0.01$) progression with age.

List A7 of the Rey Auditory Verbal Learning Test measures retention after 20 min. We have further analysed these data and found no difference between the groups.

We agree that 'duration of illness'; actually describes 'duration of illness episodes'. The actual mean duration of illness was 9.1 years (s.d.=6.0). Data concerning marital status and occupation were collected but were omitted for brevity. We did not wish to control for handedness or birth injuries as potential confounders as we regarded these differences to be part of the spectrum of people with bipolar disorder. We did not include those who had recently received electroconvulsive therapy ($\geqslant 6$ months). Finally, we would agree that there is a need for meta-analyses and have recently published such a study (Robinson *et al*, 2006).

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Delay in onset of action of antidepressants

In an important editorial, Mitchell (2006) marshalls evidence to show that we do not have to wait 2 weeks for antidepressants to work.

Why has it been so difficult so far to show that they work in the first few days? In addition to the reasons that Mitchell sets out, I should like to mention a further problem. If you analyse the results on a day-by-day basis, it is hard to obtain sufficient statistical power to distinguish the early response to the drug from the response to the placebo, since you have just the scores for that day.

In 1996 my colleagues and I published evidence that the fall in scores on the Hamilton Rating Scale for Depression followed an exponential decay curve with a correlation coefficient of 0.99 (Priest *et al*, 1996; Livingston & Clark, 1997). This observation corresponds with Mitchell's remarks on the steep fall in scores in the first 2 weeks. A comparison of the slope of the curve for the active drug with the placebo, using all of the data, gives a very sensitive way of testing for efficacy.

By plotting the log of the depression scores against time, a straight line is obtained. Thus the recovery from depression

is of one piece, with a smooth process throughout. The clear implication is that there is no delay in the onset of action, either of the active drug or of the placebo. By using the slope of the graph, one can use all of the trial results, not just those on a particular day. The statistical power is greatly increased and the distinction between drug and placebo enhanced.

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Author's reply I thank Professor Priest for further insights concerning the difficulty in obtaining sufficient statistical power to distinguish the early drug–placebo response. This is correct but the reason for the difficulty is mainly that the absolute difference between drug and placebo is initially small and when combined with typically low sample sizes the overall power to detect a true difference is insufficient. That said, if the aim of the study is to discover how early an effect is manifest there is no alternative to regular early measures.

Professor Priest then anticipates our next piece of work to which I previously eluded – examination of the trajectories of antidepressant response. He quite cleverly observes that a comparison of the slope of the response curves for the active drug and placebo is in effect a test of efficacy. It is also suggested that the response is often neither delayed nor steady but actually rapid (or perhaps more accurately 'accelerated'). Allow me to illustrate this point further (Fig. 1). The rate of change of those taking placebo is poor compared with a hypothetical antidepressant with a 'steady' or 'rapid' onset. A delayed onset, as so often suggested, is not illustrated, but I expect readers will be able to sketch their own view of the delayed trajectory. In fact several 'delayed' paths are possible, depending on whether there is a catch-up with the steady path and if so, when.

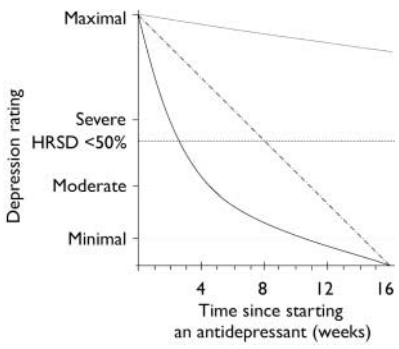

Fig. 1 Depression rating against time since starting hypothetical antidepressant with rapid (—) and steady (· - · -) onset. HRSD, Hamilton Rating Scale for Depression; · · · · · · · , placebo response.

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Primary agoraphobia as a specific phobia

The elegant study of 1920 participants from the Baltimore Epidemiologic Catchment Area programme concluded that 'the implied one-way causal relationship between spontaneous panic attacks and agoraphobia in DSM–IV appears incorrect' (Bienvenu *et al*, 2006). Bienvenu *et al* echo the arguments of many researchers, beginning with Marks (1987), that agoraphobia without panic attacks (primary agoraphobia) should be reinstated in DSM–V as a stand-alone diagnosis as in ICD–10.

It has been argued that evolutionary biological reasoning predicts the existence of a 'hard-wired' primary stand-alone agoraphobia, which should be classified with other specific phobias (Bracha, 2006). Specific phobias have been considered as conserved traits that enhanced survival during the human era of evolutionary adaptedness (Nesse, 1999; Bracha, 2006). Primary agoraphobia may similarly be traced back to the fact that humans relied on arboreality as a major escape response long after they diverged from chimpanzees. *Homo sapiens* expanded beyond its densely forested East-African indigenous niche into sparsely wooded habitats (savannahs and water-front dunes) only about 70 000 years ago. In sparsely wooded habitats, anxiety in wide-open spaces was arguably a survival-enhancing trait since opportunities for arboreal escape from large predators were limited (Bracha, 2006). These arguments may be relevant to psychiatric classification and contribute to the 'neuroscience research agenda to guide development of a pathophysiologically based classification system' emphasised in the research agenda for DSM–V (Kupfer *et al*, 2002).

If, as one of us (Bracha, 2006) has argued, the two types of agoraphobia have different modes of acquisition, there might be some clinical implications. Primary agoraphobia might, like other specific phobias, be especially amenable to virtual reality exposure treatment. In contrast, agoraphobia secondary to panic attacks can be classified in DSM–V and treated along with post-traumatic stress disorder (and other fear–memory–overconsolidation disorders, which are misclassified as specific phobias in DSM–IV–TR, e.g. hospital phobia, dentist phobia, dog phobia, bird phobia, and bat phobia).

Finally, contrary to myth, predictions based on brain evolution are eminently testable/falsifiable (Nesse, 1999). Some 30 such predictions are elaborated elsewhere (Bracha, 2006).

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