Sir, Recent publication of Whitwell et al. (2007) in Brain offers a useful addition to our understanding of dementia with Lewy bodies (DLB). In a very large n study, they offer the most definitive evidence yet published of what previous studies have been hinting at in recent years; this being that cortical atrophy, particularly when compared to Alzheimer’s disease (AD), is not a major feature of DLB. In contradistinction to a well-matched sample of AD patients, they found minimal cortical involvement in DLB and argued, very plausibly, that where atrophy was identified it could simply be a reflection of concomitant AD pathology. However, when discussing their findings with respect to visual hallucination they make the following comment:

“The specific structural locus of visual hallucinations is, however, unclear. Authors have suggested that deficits in the NBM (Perry and Perry, 1995; Josephs et al., 2006), or midbrain may be critical (Manford and Andermann, 1998; Josephs et al., 2006). Cortical regions have also been implicated (Imamura et al., 1999; Harding et al., 2002; Mori et al., 2006), although our study, and others, have failed to find widespread cortical atrophy in DLB (Middelkoop et al., 2001).

This passage suggests that damage to a ‘specific’ area is likely to cause hallucinations, yet I would propose that a dynamic interaction of regions, some damaged and some preserved, is at least as likely to be the culprit. To this end, it is the second sentence in the above excerpt that needs unpacking. To cursory inspection, this statement resembles many in the literature in suggesting that the results from different studies are in conflict. However, if one critically examines the evidence from the cited articles, a coherent hypothesis regarding visual hallucination in DLB may start to emerge. The key point is that while Middelkoop et al. (2001) and Whitwell et al., (2007) failed to find widespread cortical atrophy, Harding et al. (2002), Imamura et al. (1999) and Mori et al. (2006) did not actually study cortical atrophy. Harding et al. reported a post-mortem examination of histopathological markers in DLB and Parkinson’s with dementia (PDD) that sampled five cortical regions. The first point to note is that being post-mortem research, it is likely that case selection was biased towards more advanced disease stages. In spite of this they found only negligible numbers of Lewy bodies (LB) in the occipital cortex. When they compared hallucinators to non-hallucinators they found a greater density of LB in the parahippocampal gyrus but otherwise the cortical distribution of LB was similar between groups. Imamura et al., using positron emission tomography, found significant occipital glucose hypometabolism. Interestingly they contrasted hallucinators with non-hallucinators and found occipital hypometabolism was common to both groups but that hallucinators had relatively preserved parietal metabolism leading them to speculate that the imbalance may have been the critical factor. In passing, it is notable that physiological dysfunction as defined by either hypometabolism or hypoperfusion in the occipital lobes is a highly replicated finding in DLB (e.g. Okamura et al., 2001; Colloby et al., 2002; Pasquier et al., 2002; Gilman et al., 2005).

Taken together, these studies suggest that there is significant physiological shut-down of the occipital lobes in DLB and that this is highly unlikely due to local atrophy or the presence of Lewy bodies. This brings us to the study by Mori et al. (2006). The background to their report was that (i) DLB is associated with a cholinergic deficit and (ii) the clinical observation that visual hallucination in DLB usually responds well to cholinesterase inhibitors. They studied a cohort before and during donepezil therapy with SPECT. As expected, there was
a major attenuation of visual hallucination on therapy. When the SPECT data taken before and during therapy were contrasted, they found a significant but focal increase in occipital association cortex perfusion on donepezil.

In summary, there is now strong evidence for a dissociation between occipital lobe function (i.e. metabolism or perfusion measures) and local pathology in DLB. The observation that perfusion is, to some extent, restored with cholinesterase inhibitors suggests that loss of input from remote cholinergic nuclei may contribute to this physiological hypofunction. Interestingly, focal up-regulation of occipital muscarinic receptors has been reported in DLB and PDD (Colloby et al., 2006)—one might speculate that this is the response of preserved target neurons to loss of afferent cholinergic input.

In turn, it may be that relative occipital hypofunction, cholinergic-mediated or otherwise, is too simplistic an explanation for the genesis of hallucination and that a dynamic imbalance between occipital and other (e.g. parietal) cortical regions may be critical. In passing, it is notable that the posterior cortical atrophy (PCA) variant of AD is associated with significant occipito-parietal degeneration in which, unlike DLB, there is concordance between atrophy (Whitwell et al., 2007) and hypometabolism (Nestor et al., 2003). In contrast to DLB, visual hallucination is an unusual symptom in PCA offering, albeit circumstantial evidence that local occipital degeneration per se is not the critical determinant of visual hallucination. Overall, with some ‘joined-up’ analysis of differing investigational methods we may be approaching a more in-depth understanding of how the neurobiology of DLB translates into visual hallucination. At the very least, these observations have generated some potentially testable hypotheses.

References