Our study did not evidence whole-brain volume deficits in first-episode bipolar disorder compared with healthy controls. This may indicate that a progressive decrease of whole-brain volume occurs over the course of the disease, and might be detectable only when multi-episode or chronic cases are considered. This is confirmed by the correlation found between gray matter loss and duration of illness in the meta-regression performed by Arnone *et al*[1] and by the results of longitudinal studies demonstrating gray matter volume loss over time in the prefrontal cortex in young adults with bipolar disorder[3] or of cross-sectional comparisons between first- and multiple-episode bipolar disorder showing more severe brain abnormalities in patients with multiple episodes of illness.[4]

On the other hand, we did find a significant decrease of total white matter volume in first-episode bipolar disorder, while Arnone *et al*[1] failed to obtain the same finding in their analysis of a larger number of studies mainly conducted in patients with chronic illness. This may indicate that alterations in white matter normal growth may constitute early and primary abnormalities in bipolar disorder, consistent with some preliminary evidence of the association between patterns of disturbed structural white matter integrity in bipolar disorder and genetic liability for the illness.[5] In order to explain the lack of white matter volume reduction in chronic illness, it could be hypothesised either that other, more generalised brain changes may override white matter abnormalities over the course of the disease, or that white matter changes may be attenuated by treatment or, again, may be less sensitive to the later effects of ageing. Indirect support for this idea derives from the finding of smaller volumetric differences in the temporal lobes in bipolar disorder with increasing age, duration of illness and use of mood stabilisers,[1] the only discrete brain volume including white matter analysed in the meta-regressions performed by Arnone *et al*.

In conclusion, the finding of different brain abnormalities in chronic *v*. first-episode bipolar disorder supports the notion of different pathophysiological trajectories of specific brain morphological characteristics over the course of the disease and emphasises the need for further longitudinal studies aimed at addressing specifically the issue of the time of appearance and course of individual brain abnormalities in bipolar disorder, from which may derive a better understanding of the pathogenesis of the disease itself.


1 Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *Br J Psychiatry* 2009; **195**: 194–201.

2 Vita A, De Peri L, Sacchetti E. Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies. *Bipolar Disord* 2009; **11**: 807–14.

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5 Chaddock CA, Barker GJ, Marshall N, Schulze K, Hall MH, et al. White matter microstructural impairments and genetic liability to familial bipolar I disorder. *Br J Psychiatry* 2009; **194**: 527–34.



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**doi: 10.1192/bjp.196.3.245b**


**Author's reply:** We are grateful to Drs Vita, Peri and Sacchetti, who raise the very important point that morphometric abnormalities detectable in first-onset bipolar disorder appear different from those described in chronic patients. An observation which, as Vita *et al* suggest, may underpin important information about the pathogenesis of the disorder and would benefit from clarification emerging from longitudinal studies. Prompted by their meta-analysis[1] and our own work,[2] we have conducted further analyses by including only patients with first-episode bipolar disorder *v.* healthy controls. Despite methodological differences and different inclusion and exclusion criteria, we are in agreement with Vita *et al*. We found no evidence of whole-brain volume reduction in the first-episode patients *v.* healthy controls (effect size −0.23; 95% CI −0.47 to 0.002; $I^2 = 0$, $P = 0.51$; Egger's $P = 0.31$). This finding supports Vita *et al*'s hypothesis that whole-brain volume loss may be occurring with illness progression and/or its epiphenomena (e.g. number of episodes, pharmacological treatment). Similarly we found no evidence of gray matter loss (effect size −0.02; 95% CI −0.40 to 0.37; $I^2 = 0.02$, $P = 0.36$; Egger's $P = 0.16$) but significant white matter volumetric reduction in the first-episode patients *v.* healthy controls (effect size −0.45; 95% CI −0.85 to −0.06; $I^2 = 0.04$, $P = 0.35$; Egger's $P = 0.68$). These and other observations[3,4] support the possibility that white matter deficits have a particular relevance to the aetiology of bipolar disorder. However, the paucity of first-episode studies is reflected in the relatively wide confidence intervals around our estimates. Further studies of patients with first-episode bipolar disorder, as well as cohort and high-risk studies, are necessary if we are to improve our understanding of the role of structural changes in the pathogenesis of this condition.


1 Vita A, De Peri L, Sacchetti E. Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies. *Bipolar Disord* 2009; **11**: 807–14.

2 Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *Br J Psychiatry* 2009; **195**: 194–201.

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**doi: 10.1192/bjp.196.3.246**


## Evolution and psychiatry

If evolution is the missing half of a 'truly biological psychiatry',[1] the other half being biological reductionism, then value is out of the picture. But this cannot be. We do not deny the gains from biology or those that are to come (millions of people manage to live because of advances in this field). Nor are we pessimistic about the potential gains that evolution claims for mental healthcare. However, these two 'halves' do not make a whole. We understand the aspiration for a truly biological psychiatry: life would be easier. Biology (although a big part, or the major part of the picture) cannot (alas!) be the whole, and evolutionary theoretical considerations of disorder, natural function, design and the like cannot fill what is missing. The reason is that even if we accept a value-free account of naturally selected mechanisms, physical as well as mental, these must be considered within the spectrum of individual and social values. Fulford[2] explains why values are so feared. Other theorists who have considered



https://doi.org/10.1192/bjp.196.3.246 Published online by Cambridge University Press