

Letter to the Editor

Lithium and Increased Hippocampal Volume—More Tissue or More Water?

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Sir

I read Yucel *et al*'s (2007) *Bilateral Hippocampal Volume Increase in Patients with Bipolar Disorder and Short-Term Lithium Treatment* with interest, in hopes that they had addressed the possibility that their finding resulted from an effect of lithium on brain water homeostasis as well as from neuroprotective or neurotrophic effects. However, this possibility was not mentioned in the article, although there is much discussion of their hypothesis that the increase is a product of neurogenesis and neuroprotection occurring over an average of 30 days on lithium. Other investigators who have found a lithium-associated increase in cortical gray matter have at least acknowledged the possibility that increased tissue water could have contributed to their finding (Bearden *et al*, 2007; Moore *et al*, 2000; Sassi *et al*, 2002), although none has reported data to exclude a contribution of water.

There are reasons to consider that lithium-associated increases in brain volume can also be explained by increases in tissue water. Numerous case reports indicate that lithium treatment is associated with pseudotumor cerebri (idiopathic intracranial hypertension) (Saul *et al*, 1985). The pathophysiology of pseudotumor cerebri is not fully understood; however, increased brain water has been hypothesized to be a contributing factor (Gideon *et al*, 1995; Sorensen *et al*, 1989). There is also evidence from animal studies that chronic lithium administration can increase the tissue water content of particular brain regions. In our laboratory we found that rats fed a lithium-enriched diet for 5 weeks (but not 11 days) had increases in water content of 0.8% in cerebellum and 3.1% in hippocampus and frontal cortex, relative to rats fed regular food (Phatak *et al*, 2006). After Bonferroni correction, only the frontal cortex increase in water was statistically significant due to greater variance among hippocampal samples. One expla-

nation for the increased variance among hippocampal samples in our study was that we did not assay the entire hippocampus, and therefore hippocampal samples likely had varying amounts of gray and white matter. Frontal cortex samples were exclusively gray matter, because we had dissected away the underlying white matter. Gray and white matter normally differ in their water content—gray averaging 80% and white averaging 70% and may also differ in their ability to accommodate increases in tissue water. Of note, Yucel *et al* found a significant increase in hippocampal head volume, but not in body or tail volume of bipolar subjects on lithium. Investigators have found that the gray matter composition of the hippocampal head (pes hippocampi) is 10% higher than posterior portions of the hippocampus (Vermathen *et al*, 2000). This difference in tissue composition could be relevant to both neurotrophic and water homeostatic effects of lithium on the hippocampus.

Although lithium has well described neuroprotective and neurotrophic effects, which may be clinically relevant, insufficient attention has been paid to the possibility that lithium-associated increases in brain volume result from increases in tissue water. These volume increases should not be presumed to be a function of a neuroprotective or neurotrophic effect.

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