

Reply: Lithium and Increased Cortical Gray Matter—More Tissue or More Water?

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To the Editor:

We thank Dr. Regenold for his interest and comment on our recent article, in which we identified significantly increased gray matter (GM) density, particularly within the bilateral cingulate and paralimbic cortices, in lithium-treated patients with bipolar disorder, relative to healthy control subjects (1). Dr. Regenold voices some disappointment that we did not determine whether an increase in brain tissue water might have contributed to our findings. Although GM increases might, in part, reflect expansion of neuropil content, unfortunately brain imaging cannot confirm which cellular changes are occurring in living patients.

Although lithium's effects on body water homeostasis (2) are important to consider, the absence of any effect on white matter (WM) suggests that findings are unlikely to be accounted for by increased tissue hydration alone. Although tissue types might differ in their ability to accommodate increases in tissue water, one would not expect to see such dramatic differences in effect solely on the basis of differential accommodation of water (e.g., approximately 9% increase in total GM, approximately 0% in WM). Moreover, these effects are much larger than what we would expect to see on the basis of changes in hydration: even extreme dehydration results in a change in brain volume of < 1% (3). Nonetheless, it is important to note that changes in water content or related intracellular constituents might reflect changes relevant to the therapeutic mechanism of lithium, either directly or as an epiphenomenon. Increased water content is not a trivial explanation for the pattern of findings, because it reflects alterations in the intracellular milieu and thus might be an important marker, perhaps even of neurotrophic changes (4).

Here we did not test hypotheses related to brain tissue water, but further investigation with alternative methodologies might be able to elucidate the underlying physiology of our empirical findings. Magnetic resonance relaxometry, for example, can provide estimates of total water content and myelin water fraction in WM *in vivo*, on the basis of T2 relaxation time (5). However, to date relaxometric methods are more routinely used in disease states involving highly abnormal water content of brain tissue (6,7), and thus it is not clear that such methods can accurately quantify small changes in water content.

Diffusion tensor imaging (DTI) is a relatively new brain imaging methodology that collects information on the local geometry of water diffusion to assess WM microstructure (8). Although the current spatial and angular resolutions of DTI limit its utility for assessing water content in cortical GM, rapid technological advances suggest that DTI might soon become a useful tool for quantification of cortical tissue water.

We agree with Dr. Regenold that tissue hydration in lithium-treated patients warrants future study, such as determining whether and how rapidly such changes reverse after discontinuation of lithium treatment. We hope that this dialogue inspires other scientists in the field to pursue answers with translational research methods, to better understand the mechanisms underlying neuro-anatomic effects of lithium and other mood stabilizers.

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