

Ms Phillips and Dr Blier Reply

To the Editor: We thank Dr Maany for his comments regarding our article,¹ which documented an increased brain volume with sustained remission in patients with treatment-resistant depression. In his letter, Dr Maany asks us to speculate about the cellular basis that underlies the volume increases we observed in remitted patients. Proposed mechanisms that could contribute to increased brain volume among antidepressant-treated patients may include regeneration of neurons, increase in glial cell numbers, larger neuropil volume, more blood vessels, or less apoptosis. Since we did not measure any of these parameters directly, our discussion is purely speculative.

The brain region most often reported to exhibit volume reduction in depression is the hippocampus, where atrophic changes are generally purported to be associated with stress-induced neurotoxicity.² Hippocampal neurogenesis is necessary for mediating the response to antidepressant treatment,³ suggesting a mechanism that could drive volume recovery in this area. However, the existence and extent of human adult neurogenesis remain controversial, with some scientists even arguing against its presence in the human neocortex.⁴ Evidence of antidepressant-

induced increases in neural progenitor cells in humans has been limited to the dentate gyrus, which constitutes only 6% of the total volume of the human hippocampus. Given that the magnitude of adult neurogenesis in humans is probably too low to account for the volume changes observed within the hippocampus itself,⁵ and that the addition of new cells occurs in such a small portion of the brain, neurogenesis is unlikely to account for the degree of whole-brain volume change detected in our study or for the localization of the volume changes to the regions identified with voxel-based morphometry (orbitofrontal cortex, inferior frontal gyrus).¹

Recent research has demonstrated an association between neurogenesis and angiogenesis in the adult human dentate gyrus. Specifically, increased neural progenitor cell number and capillary volume observed with antidepressant treatment were found to correlate with larger dentate gyrus volume.⁶ While antidepressant treatments increase vascular endothelial growth factor expression and induce the proliferation of vascular endothelial cells in the hippocampus,⁷ it is not clear whether angiogenesis occurs elsewhere in the cortex in response to treatment and, thus, whether it could contribute to brain-volume increase in remitted patients.

Finally, some of the brain-volume increase may be accounted for by synaptogenesis, as antidepressants can reverse decreased synaptic connections caused by chronic stress. Recently, rapidly sprouting cortical pyramidal neurons were documented following acute ketamine infusion in the rat.⁸ Ketamine produces rapid antidepressant effects in patients with treatment-resistant depression. That ketamine also has faster effects on synaptic density relative to typical antidepressants suggests the importance of synaptic alterations on treatment response.⁹ This may provide a clue as to why brain-volume increase was seen only in patients who achieved sustained remission in our study despite all patients' receiving intensive pharmacotherapy throughout the follow-up period.

As for the potential correlation between brain atrophy and cortisol hypersecretion in nonremitted patients, we did not measure cortisol levels in our sample and thus cannot comment.

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