of astrocytic activation 5 weeks after ECT is additional robust evidence in favor of brain damage—not against it.

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Dr. Dwork and Colleagues Reply

TO THE EDITOR: Dr. Friedberg contends that our demonstration of increased immunoreactivity for glial fibrillary acidic protein after ECT in a nonhuman primate model indicates that ECT resulted in brain damage. Although glial fibrillary acidic protein can be increased with neuronal injury or cell death, it is also increased with a variety of other conditions not involving brain damage, including spreading depression (1) and subconvulsive transcranial magnetic stimulation (2). Our animals were sacrificed 11 weeks after the first treatment and 3 days after the last. Had neuronal injury occurred during the treatments, we would have seen histological evidence of both acute (e.g., vacuolation, eosinophilia, atrophy) and subacute (e.g., ballooned neurons, neuronophagia) damage to the neurons themselves. We saw neither.

The diffuse increase in glial fibrillary acidic protein immunoreactivity did not have the appearance of a response to injury. Reactive gliosis is histologically recognizable by several features. With hematoxylin and eosin stains, reactive astrocytes are large and eosinophilic, with processes that stand out from the neuropil. With immunohistochemical stains for glial fibrillary acidic protein, they appear large, distinct, and numerous. Even in a diffuse degenerative disease, there is usually evidence of focality within the affected structures, the areas of gliosis standing out in contrast to areas of relative sparing. None of these features was present in these animals.

Studies in rats have long shown hippocampal and cortical increases in glial fibrillary acidic protein immunoreactivity after ECT, despite the absence of even subtle evidence of neuronal damage (3). The reasons for this have not yet been determined, but upregulation of glial fibrillary acidic protein may be part of a neurogenic or neuroprotective mechanism involving increased levels of trophic factors, such as brain-derived neurotrophic factor and basic fibroblast growth factor (4). In the rat, in addition to the sharp increase in neurogenesis after ECT, there is an increase in angiogenesis throughout the dentate gyrus (5). Since cerebral blood vessels are commonly associated with glial foot processes that are strongly immunoreactive for glial fibrillary acidic protein, the increased immunoreactivity that we see in treated monkeys may be related to increased angiogenesis.

It is impossible to prove the negative, and we cannot rule out the possibility that the observed increase in glial fibrillary acidic protein immunoreactivity was due to neuronal injury. Although ECT, transcranial magnetic stimulation, and spreading depression can enhance glial fibrillary acidic protein immunoreactivity in rodents without evidence of neuronal injury, our report provided the first demonstration of this phenomenon in primates, whose astrocytes have important structural and functional differences from those of rodents (6). Although we have not detected neuronal abnormalities thus far, we plan to increase sensitivity by studying other markers, such as β-amyloid precursor protein, whose accumulation in axons is an early indicator of axonal injury. However, it has long been recognized that the short duration of seizures produced during ECT does not provide the minimum requirements necessary for neuronal injury (7, 8).

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