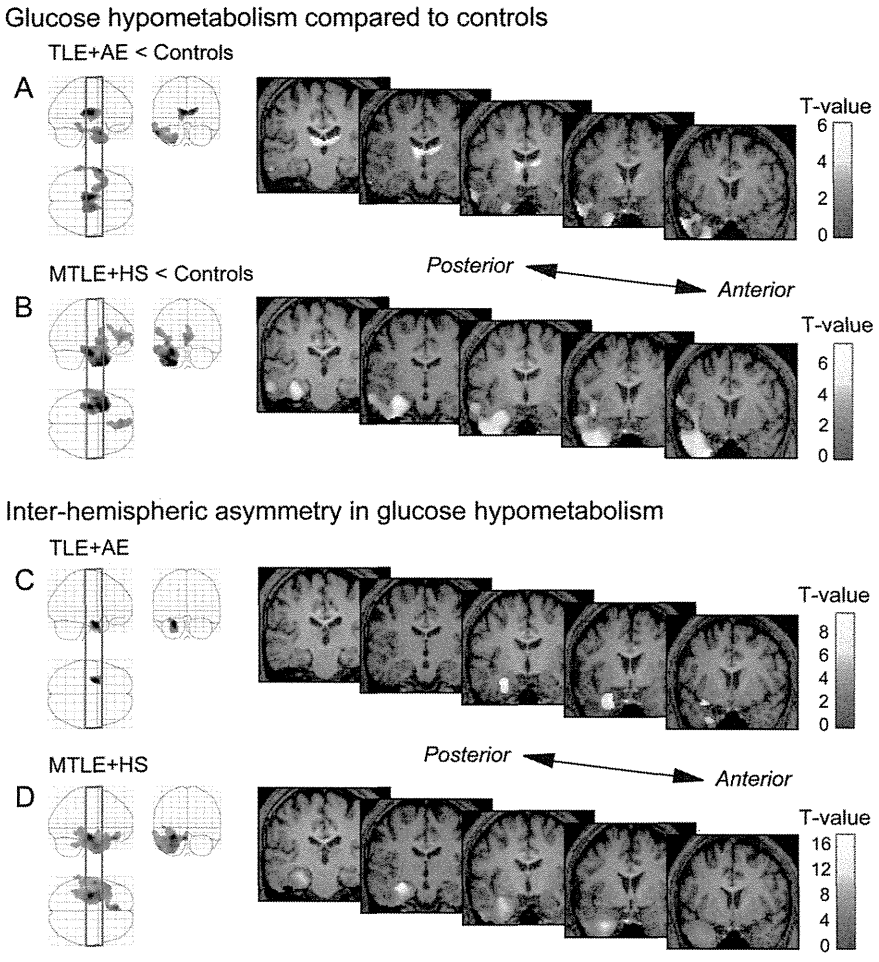

Fig 2. Brain regions showing glucose hypometabolism in the TLE + AE group and the MTLE + HS group superimposed on coronal images of a spatially normalized individual brain. Areas within red squares on the glass brains are displayed in the coronal view. (A, B) Brain regions showing significant glucose hypometabolism compared to age- and sex-matched controls for each patient group. Results are thresholded at voxel level of $P < .005$ and cluster-level corrected for multiple comparisons across the whole brain at $P < .05$. (C, D) Brain regions showing significant glucose hypometabolism compared to homologous brain regions in the contralateral hemisphere within each patient group. Results are thresholded at $P < .05$, FDR-corrected for multiple comparisons and extent threshold of 300 voxels.

Etiology of TLE + AE

The etiology of TLE + AE remains to be determined. This study has the potential limitation that a pathological specimen was examined from only 1 patient in the TLE + AE group. The morphologic or functional abnormalities of the amygdala have been discussed in patients with depression. As regarding the volume change, both increased and decreased amygdala volumes have been reported in patients with depression.[35,36] However, an increase in cerebral blood flow or glucose metabolism in the amygdala seems to be a common finding.[37] It is not congruent with glucose hypometabolism in the amygdala in patients with TLE + AE observed in this study. In addition, we excluded patients with clinically diagnosed depression for the present imaging study. Thus, the AE could not be attributed mainly to the concomitance of depression.

One possible cause of the AE is a mild form of a neuroinflammatory disorder. Neuroinflammatory processes have been reported to be one of the causes of adult-onset TLE.[38] Autoimmune-mediated encephalitis has been characterized in middle-aged patients with TLE, and some patients demonstrated a self-limited course.[38-40] Neuroinflammatory processes are consistent with the presence of mild gliosis observed upon pathological examination of a single patient in this study. However, in the present TLE + AE patients, no marked shrinkage or definite signal change of the amygdala in MRI, typical findings in the clinical course of patients with acute encephalitis, has been observed over the 2- to 5-year follow-up period.[7] Thus, a chronic and mild form of so-called focal encephalitis is a possible cause of the AE. Another possible cause of the AE may be genetic or developmental disorders such as hamartoma or focal cortical dysplasia, as reported in the previous study.[6,7,41] In adult-onset epilepsy, the developmental abnormality tends to be localized,[42] as it was in patients with TLE + AE in this study.

Further neuroimaging or neuropathological studies to clarify the etiology of TLE + AE are warranted.

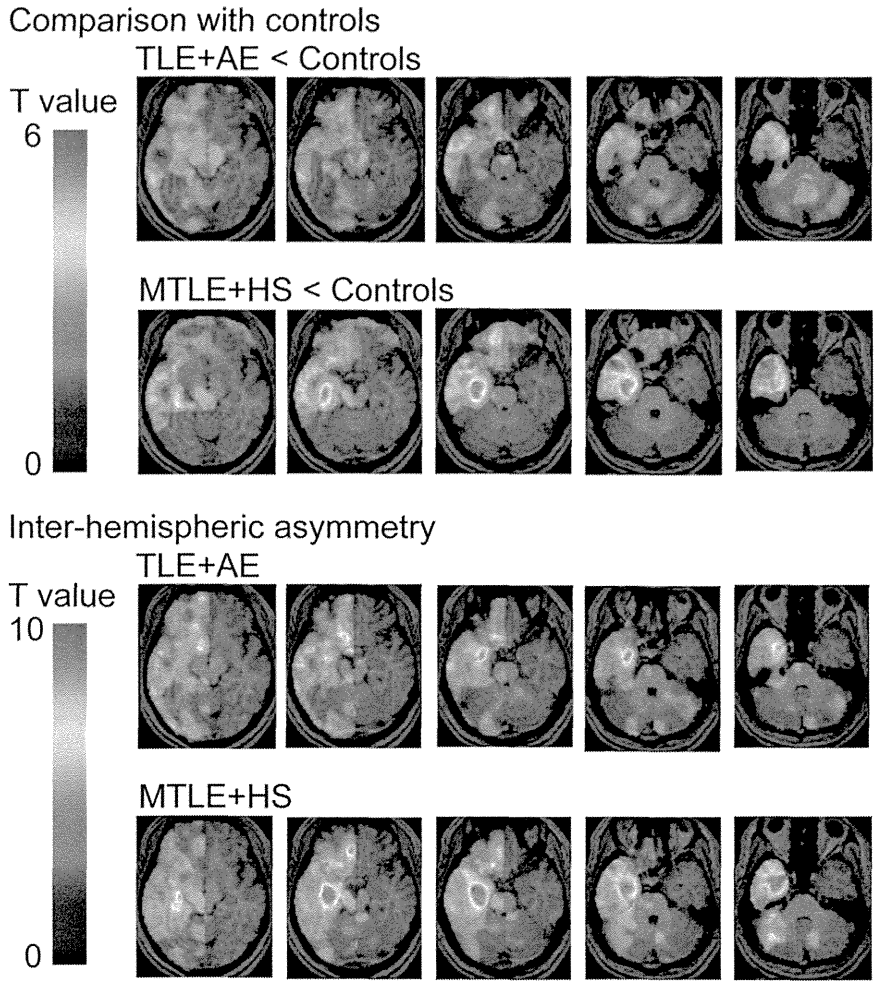

Fig 3. Unthresholded T-maps of glucose hypometabolism superimposed on axial images of a spatially normalized individual brain. The same results as in Figure 2 are displayed with no statistical threshold to preclude the effect of arbitrariness in the choice of statistical threshold and to clarify differences in the distribution of temporal lobe hypometabolism in each group. In the TLE with AE group, glucose hypometabolism is milder and more restricted in the anterior part of the mesial temporal lobe than in the TLE with HS group.

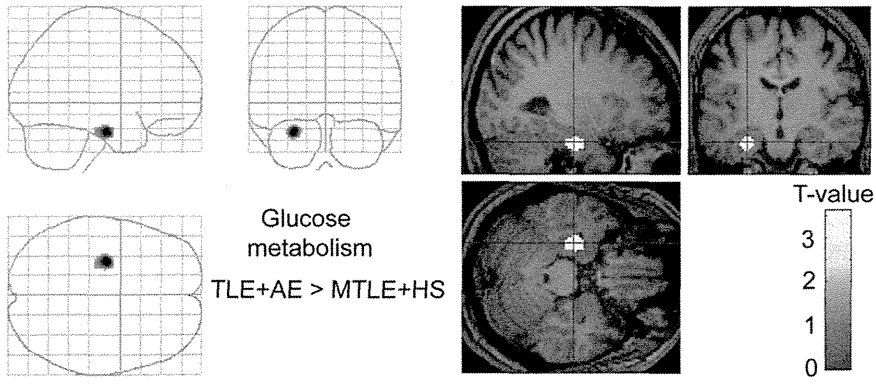

Fig 4. A brain region showing a decrease in glucose metabolism in the MTLE + HS group compared to the TLE + AE group. Adjustment for the potential confounders of age and sex was performed by including them as nuisance variables in the statistical model. Results are thresholded at voxel level of $P < .005$, uncorrected for multiple comparisons and extent threshold of 100 voxels. The finding indicates that glucose metabolism is relatively preserved in the hippocampus ipsilateral to the epileptic focus in the TLE + AE group compared to the MTLE + HS group. The reverse comparison did not detect decreased glucose hypometabolism in any brain regions in the TLE + AE group compared to the MTLE + HS group.

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