schizophrenia patients (3–5, 8, 12–15). In fact, our previous study in a smaller sample (N=68) of drug-naive first-episode schizophrenia patients also revealed decreased gray matter volume in the right temporal and anterior cingulate cortex (12). Several factors merit consideration in explaining the regionally greater gray matter volume seen in the present study relative to several previous studies. Differences in patient characteristics across studies may be important, as some other studies have also reported increased gray matter volume in schizophrenia, including a report of such effects in the orbital frontal gyrus and anterior cingulate cortex in a study of 169 patients (30). One patient characteristic that the present data suggest may be important is severity of negative symptoms. This sample had a higher proportion of patients with prominent negative symptoms (36%) than the sample in our previous study (12%) (12). The results of the present study indicate that patients without prominent negative symptoms have more regions with decreased volume, especially in right temporal regions, than patients with prominent negative symptoms close to the time of illness onset, which may partly explain the discrepancy with our previous findings (12). Second, as the patients in the present study were early in the course of illness (average illness duration=6.25 months), possible early-course neuronal pathology, such as preapoptotic osmotic changes or hypertrophy, could increase regional volumes (31). Progressive gray matter volume loss might be expected after antipsychotic treatment (6–10) or in relation to secondary factors or course of illness effects (6, 32), which could contribute to the absence of reported hypertrophy in previous studies of patients who had a longer duration of illness before MRI scans were obtained (11). Of note, anatomical and functional changes did not correlate with untreated illness duration or with positive symptoms, and the direct comparison between patients with long and short untreated illness durations revealed no significant differences. These findings suggest a relatively static or slowly evolving process of anatomical changes, which is consistent with a recent study of treated schizophrenia patients (33) in suggesting the absence of progressive loss of gray matter volume during the early illness course before treatment has begun. Thus, the structural and functional brain changes observed in first-episode patients may be associated with neurodevelopmental problems such as neuronal overgrowth or a deficit in normal pruning during neurogenesis, as suggested by previous studies (34, 35) or, alternatively, with early illness pathophysiology effects, possibilities that need to be examined in future studies following at-risk individuals. Third, this study had a large sample and may have had the statistical power to detect hypertrophic effects not reported frequently in previous studies. Finally, this study used VBM8, which provides a more optimized method of segmentation and normalization than the VBM2 method in the analysis of gray matter volume (12). Furthermore, with concern for potential influences of skull-stripping artifacts, especially in the orbital frontal gyrus where deskulling is difficult, we