**Appendix**

***Supplementary Appendix S1***

The National Institute of Mental Health (NIMH) childhood-onset schizophrenia (COS) study has been ongoing since 1990, with national recruitment of patients meeting DSM-IIIR/IV criteria for schizophrenia with the onset of psychosis before age 13. The COS sample is severely ill, as each patient is typically admitted after trying several antipsychotics with limited results. Our group analyzed our COS screening process and rating measures for the first 71 cases screened, concluding that a variety of developmental abnormalities can be found with childhood-onset psychosis outside of COS (McKenna *et al.*, 1994). Accurate diagnosis of schizophrenia in children and adolescents remains difficult, especially in distinguishing childhood-onset schizophrenia from other psychotic disorders or developmental disturbances.

Diagnosis is determined on the basis of extensive review. During the screening process, our group’s psychiatrists review referral materials, consisting of medical and academic records, and conduct a videotaped interview with the parents and child. They then administer the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (K-SADS-E) (Ambrosini *et al.*, 1989; Kaufman *et al.*, 1997) and portions of the Diagnostic Interview for Children and Adolescents-Parent Version (DICA-P) and Child Version (DICA-C) for disruptive disorders, substance abuse, and child psychosis (McKenna *et al.*, 1994). Based on the clinical interviews, best-estimate diagnoses are made for personality, Axis I, and developmental disorders (McKenna *et al.*, 1994).

Raters were trained with 10 interviews, using K-SADS-E, DICA-P, and DICA-C, with best-estimate diagnoses determined (McKenna *et al.*, 1994). Discussion would follow to resolve variability. Raters were also trained with 19 tapes to measure the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen & Olsen, 1982; Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen & Olsen, 1982; Andreasen, 1983). 19 tapes were scored, with supplementary discussion of 5 tapes (McKenna *et al.*, 1994).

After screening, patients are admitted for inpatient observation with a medication-washout period and drug-free observation in most cases. Inpatient observation can last several months, as patients are re-diagnosed with feedback from the clinical team and stabilized on a medication regimen before discharge. All patients, their parents, and full siblings are followed prospectively, with follow-up appointments at 2-year intervals.

***Supplementary Appendix S2***

The image files in DICOM (Digital Imaging and Communications in Medicine) format were transferred to a Linux workstation for analysis. Subcortical volumes were measured automatically with the FreeSurfer image analysis suite, which is documented and available online (http://surfer.nmr.mgh.harvard.edu/). Individual scans were inspected for significant artifacts or motion disturbances (N = 1 proband was excluded from analysis). The automated procedures for subcortical volumetric measurements of different brain structures have been standardized previously (Fischl *et al*., 2002; Fischl *et al*., 2004) and used in our COS study (Mattai *et al.*, 2011). This procedure automatically provides segments and labels for many brain structures and assigns a neuroanatomic label to each voxel in magnetic resonance imaging (MRI) volume on the basis or probabilistic information estimated automatically from a manually labeled training set (Mattai *et al.*, 2011). This processing includes motion correction and averaging of multiple volumetric T1-weighted images when more than one is available, removal of nonbrain tissue using a hybrid watershed/surface deformation procedure (Ségonne *et al*., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (includes the hippocampus for our interest, as well as the amygdala, caudate, putamen, and ventricles) (Fischl *et al*., 2002; Fischl *et al*., 2004), intensity normalization, tessellation of the gray-white matter boundary, automated topology correction (Fischl *et al*., 2001; Ségonne *et al*., 2007), and surface deformation following intensity gradients to optimally place the gray-white matter and gray matter/CSF borders at the location where the greatest shift in intensity defines the transition to the other tissue class.

The segmentation utilizes the following data to disambiguate labels: 1) the prior probability of a given tissue class at a specific atlas location, 2) the likelihood of the image intensity given the tissue class, and 3) the probability of the local spatial configuration of labels given the tissue class (Mattai *et al.*, 2011). This technique has previously compared in accuracy to manual labeling (Fischl *et al*., 2002) and has demonstrated good test-retest reliability across scanner manufacturers and field strengths (Han *et al*., 2006). However, all segmentations were visually inspected for accuracy prior to inclusion in the group analysis. Hippocampal volume was calculated in terms of left, right, and total as a sum of hippocampal volumes for each study participant.

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