Supporting Information

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SI Methods

Subjects. ***Discovery sample: TOP study.*** The Thematic Organized Psychosis study was launched in 2004 as a collaborative study involving the University of Oslo and all of the Hospitals in the Oslo region, funded by the University, Regional Health Authorities, and the Research Council of Norway.

A total of 287 subjects (aged 18–65 years, 35 ± 10.4 years; 48% males) had successful MRI scans and Affymetrix 6.0 genotyping. This included healthy control participants $n = 101$ (41 males, 60 females), a schizophrenia spectrum group $n = 80$ (33 males, 47 females), an affective spectrum group $n = 69$ (41 males, 28 females), and psychotic disorders not otherwise specified, $n = 37$ (20 males, 17 females). The analyses of rs930557 and rs41310927 were conducted using samples of $n = 210$ and $n = 225$, respectively. The differences in sample size were due to variation in genotyping rates associated with different technology.

The clinical participants were recruited continuously from psychiatric units (out-patient and in-patient) in four major hospitals in Oslo. Clinical assessment was carried out by trained psychiatrists and clinical psychologists. Diagnosis was based on the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth edition* (DSM-IV) Axis I disorders (SCID-I) (1). Diagnostic reliability was found satisfactory, with overall agreement for DSM-IV diagnostic categories of 82% with $\kappa = 0.77$ (95% CI: 0.60–0.94) (2). Information from follow-up visits was used to secure correct diagnoses.

The healthy control participants were randomly selected from national statistical records from the same catchment area and contacted by letter inviting them to participate. The study is part of the TOP Research initiative and was approved by the Regional Committee for Medical Research Ethics, the Norwegian Data Inspectorate, and Health Authority. All participants gave written informed consent.

Exclusion criteria for all groups were: hospitalized head injury, neurological disorder, mental retardation (IQ below 70), and age outside the age range of 18 to 60 years. The healthy control sample was screened with the Primary Care Evaluation of Mental Disorders (PRIME-MD) (3) and subjects were excluded if they or any of their close relatives had a lifetime history of a severe psychiatric disorder (schizophrenia, bipolar disorder, and major depression), if they had an unstable medical condition known to interfere with brain function (including hypothyroidism, uncontrolled hypertension, and diabetes), or substance abuse or dependency in the last 3 months. All cases and controls were Caucasians (subject ethnicity determined during the clinical interviews). About 90% of patients and about 86% of controls were ethnically Norwegian (i.e., the patient and both parents were born in Norway; the remaining subjects had one parent born in another northwestern European country).

Replication sample: ADNI study. ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60-million 5-year public-private partnership. Data used in this article were obtained from the home page of the Alzheimer's Disease Neuroimaging Initiative database at the LONI Web site (http://www.loni.ucla.edu/ADNI), published in 2007. The principal investigator (PI) of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. The ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from more than 50 sites across the United States and Canada. The ADNI has recruited 229 cognitively healthy older individuals to be followed up for 3 years, 398 people with amnestic mild cognitive impairment to be followed up for 3 years, and 192 people with early Alzheimer's disease to be followed up for 2 years. Up-to-date information is available from the home page of the ADNI-Info Web site at http://www.adni-info.org for 2009. The prospective research protocol, the ADNI project and sample, are described in McEvoy et al. (4). The ADNI general eligibility criteria are described in the ADNI Protocol Summary page of the ADNI-Info Web site at http://www.adni-info.org/index.php?option _com_content&task_view&id_9&Itemid _43 for 2009. Full details are available from the ADNI Protocol page of the ADNI-Info Web site at http://www.adni-info.org/images/stories/Documentation/adni_protocol_9_19_08.pdf, published on September 19, 2008.

MR Image Processing. The FreeSurfer 3.0.2 software package (http://surfer.nmr.mgh.harvard.edu) was used to create a three-dimensional model of the cortical surface for cortical thickness and cortical surface area measurements. This was done by using both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to construct representations of the gray/white matter boundary and pial surface (5–7). Cortical thickness measures were obtained by calculating the distance between those surfaces at numerous points (vertices) across the cortical mantle (8). Vertices were arranged in a triangular grid with ≈1-mm spacing, allowing for measures of cortical thickness at up to 160,000 points in each hemisphere. Topological defects in the gray/white matter boundary were manually fixed by laboratory assistants (listed under *Acknowledgments*). Maps were smoothed and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns (7). This procedure provides accurate matching of morphologically homologous cortical locations across subjects on the basis of each individual's anatomy while minimizing metric distortion. The maps thus produced are not restricted to the voxel resolution of the original images and are capable of detecting submillimeter differences between groups (8). Estimates of cortical area were obtained by computing the area of each triangle in a standardized, spherical atlas-space surface tessellation, when mapped into the individual subject space. This provides point-by-point estimates of the relative areal expansion or compression of each location in atlas space. In addition, the FreeSurfer software was used to obtain brain volume measurements and intracranial volume estimates. The brain volume measure was calculated as the sum of the volumes for all cortical and subcortical gray and white matter regions of interest (9).

1. First M, Spitzer R (1995) *Structured Clinical Interview for DSM-IV Axis I Disorders: Patient Edition (SCID-P), Version 2* (New York State Psychiatric Institute, Biometrics Research, New York, NY).
2. Birkenaes AB, et al. (2007) The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. *J Clin Psychiatry* 68:917–923.
3. Spitzer RL, et al. (1994) Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA* 272:1749–1756.
4. McEvoy LK, et al. Alzheimer's Disease Neuroimaging Initiative (2009) Alzheimer disease: quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment. *Radiology* 251(1):195–205.
5. Dale AM, Sereno MI (1993) Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction—A linear-approach. *J Cogn Neurosci* 5:162–176.
6. Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 9:179–194.

7. Fischl B, Sereno MI, Dale AM (1999) Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage* 9:195–207.
8. Fischl B, Dale AM (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA* 97:11050–11055.
9. Desikan RS, et al. (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31: 968–980.

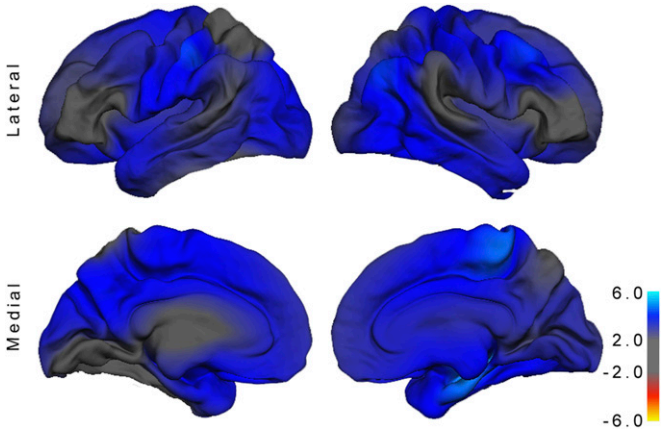

Fig. S1. Association of *MCPH1* SNP rs11779303 with cortical area in females. The maps show the distribution of −log *P*-values (sign indicating direction of effect per copy of minor allele) across the reconstructed cortical surface (i.e., blue denotes larger area with major allele vs. minor allele).

Other Supporting Information Files

Table S1 (DOC)
Table S2 (DOC)
Table S3 (DOC)