Supplementary Material for:
The Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) Consortium: A collaborative cognitive and neuroimaging genetics project

Sample Descriptions

CAMH — Center for Addiction and Mental Health

(Nazeri et al., 2013; Wheeler et al., 2014)

Recruitment. Patients and controls were recruited at the Center for Addiction and Mental Health (CAMH) in Toronto, Canada, via referrals, study registries, and advertisements. All clinical assessments occurred at CAMH and MRI scans were performed at a nearby general hospital in Toronto. Community-dwelling outpatients with schizophrenia were individually matched based on age, sex, handedness, and highest parental years of education to healthy controls. Controls form part of the Cognitive Genomics Consortium wave 2 (COGENT2) dataset (Trampush et al., 2017).

Inclusion/Exclusion Criteria. All participants were between 18 and 85 years of age. All participants received urine toxicology screens and anyone with current substance abuse or any history of substance dependence was excluded. Individuals with previous head trauma with loss of consciousness or neurological disorders were also excluded. For controls, a history of a primary psychotic disorder in first-degree relatives was also an exclusion criterion.

Clinical/Neuropsychological Assessment. All participants were interviewed by a psychiatrist and were administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1995b) to determine diagnosis and duration of illness. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and Clinical Global Impression Scale (CGI-S; Guy, 2000) were administered to further characterize illness symptoms. Burden of comorbid physical illness was measured by the Cumulative Illness Rating Scale for Geriatrics (Miller et al., 1992). Medication histories were initially recorded based on self-reports, and then verified either by the patient's treating psychiatrist or chart review. All participants underwent a battery of cognitive tests administered over approximately 1.5 hours. Premorbid IQ was measured using the Wechsler Test for Adult Reading (WTAR; Wechsler, 2001). The cognitive battery consisted of the subtests Digit Symbol Coding, Semantic Verbal Fluency, Digit Span, List Learning, Story Memory, and Figure Recall from the Repeated Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998), as well as the Trail Making Test-Part A and B (Reitan, 1958) and Controlled Oral Word Association Test (COWAT) of Phonemic Verbal Fluency (letters: F, A, S) (Reitan, 1985) to measure processing speed, University of Maryland Letter-Number Span (Gold et al., 1997) to measure verbal working memory, Stroop test to measure executive function (Stroop, 1935), Grooved Pegboard (Lafayette Instrument Company -- Trites, 1989) and Finger Tapping (Ruff and Parker, 1993) to assess psychomotor speed.

MRI Acquisition. T1-weighted structural scans (Echo Time [TE] = 5.3 ms; Inversion Time [TI] = 300 ms; Repetition Time [TR] = 12.3 ms; Flip angle = 20°; Field of View [FOV] = 20 cm; Spatial resolution = 0.78 x 0.78 x 1.5 mm; matrix = 256 x 256 mm; Slice acquisition direction = axial, AC-PC oblique) and Diffusion Tensor Imaging (TE = 85.5 ms; TR = 15000 ms; Flip angle = 90°; FOV = 33 cm; Spatial resolution = 2.6 x 2.6 x 2.6 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial, oblique; number of diffusion-encoding gradient directions = 23; number of b0 volumes = 2; b-value = 1000 s/mm^2) were acquired on a 1.5 Tesla General Electric (GE) Echospeed scanner using an 8-channel head coil.

Genotyping. DNA obtained from whole blood was genotyped on the Illumina OmniExpress array.

Ethics/Consent. The study was approved by the Research Ethics Board of CAMH and all participants provided informed written consent.

Acknowledgements. Data acquisition was supported by the Canadian Institutes of Health Research, Ontario Mental Health Foundation, the Brain and Behavior Research Foundation (formerly NARSAD), the Centre for Addiction and Mental Health (CAMH), and the CAMH Foundation through the Kimel Family, Koerner New Scientist Award, and Paul E Garfinkel New

Investigator Catalyst Award. The investigators acknowledge the assistance of David J. Rotenberg and Dr. Daniel Felsky.

CATIE — Clinical Antipsychotic Trials of Intervention Effectiveness
(Keefe et al., 2006; Lieberman, 2007; McClay et al., 2011; Stroup et al., 2003; Sullivan et al., 2008)

Recruitment. Patients were recruited from 57 clinical settings across the United States for a multiphase randomized controlled trial of antipsychotic medications, including the second-generation drugs, olanzapine, quetiapine, risperidone, and ziprasidone, compared with a midpotency first-generation drug, perphenazine. Patients were followed for up to 18 months. Patients who gave informed consent to participate in genetic studies are included in GENUS. Patients formed part of the Psychiatric Genomics Consortium Schizophrenia Working Group dataset (PGC Schizophrenia Working Group, 2014).

Inclusion/Exclusion Criteria. Eligible patients were 18 to 65 years of age; had received a diagnosis of schizophrenia (not schizoaffective disorder), as determined on the basis of the SCID; and were able to take oral antipsychotic medication, as determined by the study doctor. Patients were excluded if they had received a diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; had a history of serious adverse reactions to the proposed treatments; had had only one schizophrenic episode; had a history of treatment resistance, defined by the persistence of severe symptoms despite adequate trials of one of the proposed treatments or prior treatment with clozapine; were pregnant or breastfeeding; or had a serious and unstable medical condition. Patients with medical or psychiatric comorbidities those who require concomitant other medications are included. The patients who enroll in this study have chronic or recurrent schizophrenia. First episode patients and wholly treatment-refractory patients are excluded. First episode patients are excluded because of their high rates of response to antipsychotic medications at relatively low doses. Treatment-refractory patients are excluded because their severe illness may preclude detection of differential effectiveness that would be apparent in treatment-responsive patients.

Clinical/Neuropsychological Assessment. Schizophrenia patients were diagnosed using the SCID (First et al., 1994). Clinical rating scales include the PANSS (Kay et al., 1987), Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1992), and Clinical Global Impression Scale (CGI-S; Guy, 2000). Premorbid IQ was measured using the Reading subtest from the Wide Range Achievement Test, Third Edition (WRAT-3; Wilkinson, 1993). Processing speed was measured using the Wechsler Adult Intelligence Scale, Revised Version (WAIS-R) Digit Symbol subtest (Wechsler, 1981), Semantic Verbal Fluency (categories: animals, fruits, vegetables) (Benton and Hamsher, 1978), and COWAT Phonemic Verbal Fluency (letters: F, A, S) (Reitan, 1985); attention/vigilance was measured using the Continuous Performance Test-Identical Pairs version (CPT-IP; Cornblatt et al., 1988); spatial and verbal working memory were assessed using the computerized Spatial Delayed Response Task (Lyons-Warren et al., 2004) and University of Maryland Letter-Number Span (Gold et al., 1997), respectively. Verbal learning and memory was assessed with the Hopkins Verbal Learning Test (HVLT; Brandt, 1991). Executive function was assessed using the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) and the Mazes subtest from the Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1991). Grooved Pegboard (Lafayette Instrument Company -- Trites, 1989) was used to measure psychomotor speed and the Facial Emotion Discrimination Test (Kerr and Neale, 1993) measured social cognition.

MRI Acquisition. Not applicable.

Genotyping. DNA obtained from whole blood was genotyped on the Affymetrix 500K array and Perlegen's custom 164K chip. Genotype data are available from the NIMH Repository and Genomics Resource (http://www.nimhgenetics.org).

Ethics/Consent. All participants or their legal guardians gave written informed consent and the institutional review board at each site approved the study.

Acknowledgements. The principal investigators were Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., and Joseph P. McEvoy, M.D. The CATIE trial was funded by a grant from the National Institute of Mental Health (N01 MH900001) along with MH074027 (PI PF Sullivan). Genotyping was funded by Eli Lilly and Company.

Conflicts of interest. Dr. Sullivan reports receiving research funding from Eli Lilly in connection with the CATIE project. Dr. Stroup reports having received research funding from Eli Lilly and consulting fees from Janssen Pharmaceutica, GlaxoSmithKline, and Bristol-Myers Squibb. Dr. Lieberman reports having received research funding from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Pharmaceutica, and Pfizer and consulting and educational fees from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Novartis, Pfizer, and Solvay.

CIDAR/VA — Boston CIDAR Study / Veterans Affairs Healthcare System

(Clemm von Hohenberg et al., 2014; del Re et al., 2014; Kikinis et al., 2010; Kikinis et al., 2015; Pasternak et al., 2012; Quan et al., 2013; Seitz et al., 2016)

Recruitment. Participants were recruited through the Boston CIDAR study (www.bostoncidar.org) and the Veterans Affairs Healthcare System. The participants included in the GENUS dataset consisted of clinical high-risk individuals with prodromal symptoms who also have a family history of schizophrenia (included in the FHR group), individuals within the first episode of schizophrenia, and individuals with chronic schizophrenia, as well as group-matched healthy control participants. Patients and FHR participants were recruited by referrals from clinicians or through local hospitals and clinics, and controls were recruited through newspaper and website advertisements. Patient and control participants of European ancestry formed part of the Psychiatric Genomics Consortium Schizophrenia Working Group dataset (PGC Schizophrenia Working Group, 2014).

Inclusion/Exclusion Criteria. Exclusion criteria for controls included any current or past major DSM-IV-TR Axis I disorder, developmental disorders, psychiatric hospitalizations, prodromal symptoms, schizotypal or other Cluster A personality disorders, a first degree relative with psychosis, or current or past use of antipsychotics. Sleeping aids or anxiolytic agents for occasional use were acceptable, as well as other past psychotropic medication use if not within the prior 6 months. Exclusion criteria for all participants included sensory-motor handicaps, neurological disorders, medical illnesses that significantly impair neurocognitive function, diagnosis of intellectual disability (IQ<70), not fluent in English, DSM-IV substance abuse within the past month or dependence within the past 3 months, current suicidality, or history of electroconvulsive therapy for controls or electroconvulsive therapy within the past 5 years for patients. All first episode patients met DSM-IV-TR criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder, and none had more than one year of continuous antipsychotic treatment. Chronic patients met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder and had illness duration of at least five years. Inclusion criteria for clinical high-risk participants was predominantly presence of ‘late prodromal syndromes’ as classified by the Criteria of Prodromal States (Woods et al., 2001) based on the Scale of Prodromal Symptoms (Miller et al., 2003; Miller et al., 1999). Of the clinical high-risk participants, 14 participants fulfilled the GENUS definition of FHR. Controls were drawn from the same geographic bases with comparable age, gender, race and ethnicity, handedness, and parental socioeconomic status evaluated using the Hollingshead two-factor index (Hollingshead, 1975).

Clinical/Neuropsychological Assessment. Trained and skilled interviewers and neuropsychological testers conducted all clinical and cognitive assessments. DSM-IV diagnoses were based on interviews with the Structured Clinical Interview for DSM-IV-TR (SCID), Research Version (First et al., 2002b) and information from patient medical records. The Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) and the Scale for the Assessment

of Positive Symptoms (SAPS; Andreasen, 1984) were used to measure symptom severity. The Global Assessment of Functioning (GAF; American Psychiatric Association, 2000) and CGI-S (Guy, 2000) were used to measure overall functioning. Participants were administered a large neurocognitive test battery including tests estimating premorbid IQ (the Reading subtest from the Wide Range Achievement Test-4 (WRAT-4; Wilkinson and Robertson, 2006a) and current IQ (the Vocabulary and Block Design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). The Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding test (Keefe et al., 2008), the Trail Making Test-Part A (Reitan, 1958), and Semantic Verbal Fluency (MCCB Category Fluency; category: animals) (Benton and Hamsher, 1978; Kern et al., 2008; Nuechterlein et al., 2008) were used for processing speed; the Continuous Performance Test-Identical Pairs version (Cornblatt et al., 1988) was used to measure attention/vigilance; the Wechsler Memory Scale, Third Edition (WMS-III) Spatial Span subtest (Wechsler, 1997b) and University of Maryland Letter-Number Span (Gold et al., 1997) were used for assessing working memory. The 'vigilance', 'working memory' and 'working memory plus interference' measures from the Seidman Auditory Continuous Performance Test battery (Auditory CPT; (Seidman et al., 1998; Seidman et al., 2006). The Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt and Benedict, 1997) and the WMS-III Logical Memory subtest (Wechsler, 1997b) assessed verbal learning and memory. The Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997) assessed visual learning. Executive function was measured using the Mazes subtest of the Neuropsychological Assessment Battery (NAB; Stern and White, 2003) and the computerized WCST (Heaton, 2003; Heaton et al., 1993; Nestor et al., 1993). Finally, the Proverbs subtest from the Delis-Kaplan Executive Function System (D-KEFS; (Delis et al., 2001; Delis et al., 2004)) was administered to assess verbal ability, and Grooved Pegboard (Lafayette Instrument Company -- Trites, 1989) and Finger Tapping (Ruff and Parker, 1993) were administered to assess psychomotor speed. Social cognition was assessed using the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT; Mayer et al., 2003).

MRI Acquisition. T1-weighted structural scans of schizophrenia and age-gender-handedness matched controls were acquired at Brigham and Women's Hospital, Harvard University (TE = 3.0 ms; TI = 600 ms; TR = 7.8 ms; Flip angle = 10°; FOV = 25.6 cm; Spatial resolution = 1.0 x 1.0 x 1.0 mm; matrix = 256 x 256 mm; Slice acquisition direction = sagittal) and Diffusion Tensor Imaging (TE = 78 ms; TR = 17000 ms; Flip angle = 90°; FOV = 24 cm; Spatial resolution = 1.67 x 1.67 x 1.7 mm; matrix = 144 x 144 mm; Slice acquisition direction = axial, AC-PC; number of diffusion-encoding gradient directions = 51; number of b0 volumes = 8; b-value = 900 s/mm^2) were acquired on a 3 Tesla GE Signa HDxt Echospeed scanner using an 8-channel head coil.

T1-weighted structural scans of FHR participants and age-gender-handedness matched controls were acquired at Massachusetts General Hospital, Martinos Center, Harvard University, on a 3 Tesla Siemens Trio Tim scanner using a 32-channel head coil (TE = 3.48 ms; TI = 900 ms; TR = 2530 ms; Flip angle = 9°; FOV = 25.6 cm; Spatial resolution = 1.0 x 1.0 x 1.33 mm; matrix = 256 x 256 x 128 mm; Slice acquisition direction = sagittal) and Diffusion Tensor Imaging (TE = 84 ms; TR = 9400 ms; Flip angle = 90°; FOV = 25.6 cm; Spatial resolution = 2.0 x 2.0 x 2.0 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 60; number of b0 volumes = 10; b-value = 700 s/mm^2).

Genotyping. DNA was obtained from whole blood or saliva and genotyped on the Illumina OmniExpress array.

Ethics/Consent. The study was approved by the local IRB committees at Harvard Medical School, Beth Israel Deaconess Medical Center, Massachusetts General Hospital, Brigham and Women's Hospital and the Veteran Affairs Boston Healthcare System (Brockton campus). All study participants, or legal guardians for those under 18 years of age, gave written informed consent and received payment for participation.

Acknowledgements. Data acquisition was supported by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) under Award Numbers P50 MH080272 (RW

McCarley), U01MH081928 (LJ Seidman), R21MH106793 (Z Kikinis), and a NARSAD Young Investigator Award (Z Kikinis). Genotyping was funded by a Massachusetts General Hospital Executive Committee on Research Interim Support Fund award (TL Petryshen). The investigators thank all subjects for their participation in the study, the clinical and data management staff from the Boston CIDAR study and the Commonwealth Research Center (Dr. Matcheri Keshavan, Dr. Joanne Wojcik, Ann Cousins, Dr. Michelle Friedman-Yakoobian, Dr. Anthony J Giuliano, Andrea Gnong Granato, Lauren Gibson, Sarah Hornbach, Julia Schutt, Dr. Kristy Klein, Dr. Maria Hiraldo, Dr. Grace Francis, Corin Pilo, Rachael Serur, Grace Min, Alison Thomas, and Molly Franz), Tamara Tasoff, Dr. Beril Yaffe, and Danbee Kim for electrophysiology assistance (Harvard), and Kimberly Chambert (Broad Institute of MIT and Harvard), Patience Gallagher, Dr. Stephen Haddad, Brian Galloway, and Jenna Tarasoff (Massachusetts General Hospital) for genotyping assistance.

COGS-UK — Cognition in Schizophrenia, Cardiff University, UK

Recruitment. Patients were ascertained from psychiatric outpatient units, via voluntary mental health organizations and by public advert and entered the study following a telephone screening interview and confirmation of a clinical diagnosis of a non-affective psychosis by the treating clinical team. The sample consisted of white Caucasians, born in the UK and with British ancestry.

Inclusion/Exclusion Criteria. Patients were screened to exclude substance-induced psychotic disorder or psychosis due to a general medical condition. All patients were diagnosed with schizophrenia, schizophreniform or schizoaffective diagnoses.

Clinical/Neuropsychological Assessment. A semi-structured interview was administered to all patients by trained psychiatrists or psychologists. The comprehensive clinical phenotype battery included the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990)) sections on psychosis and affective symptoms, substance use, and family history as well as demographic details and a separate cognitive battery. Diagnosis was made according to DSM-IV criteria by experienced psychiatrists accessing the clinical interview data and case notes when appropriate. Clinical rating scales administered included SANS/SAPS (Andreasen, 1983, 1984), CDSS (Addington et al., 1992), and GAF (American Psychiatric Association, 1994). Premorbid IQ was estimated using the National Adult Reading Test (NART; (Nelson, 1982; Nelson and Willison, 1991)). Cognitive testing was performed using the MATRICS Consensus Cognitive Battery (MCCB; (Kern et al., 2008; Nuechterlein et al., 2008)). The MCCB evaluates seven domains of cognitive function including: speed of processing using the BACS Symbol Coding subtest (Keefe et al., 2008), Trail Making Test—Part A (Reitan, 1958), and Semantic Verbal Fluency (MCCB Category Fluency; category: animals) (Benton and Hamsher, 1978; Kern et al., 2008; Nuechterlein et al., 2008); attention using the Continuous Performance Test—Identical Pairs (CPT-IP; Cornblatt et al., 1988); working memory using the WMS-III Spatial Span subtest (Wechsler, 1997b) and University of Maryland Letter-Number Span (Gold et al., 1997) (spatial and letter-number span); verbal learning using the HVLT-R (Brandt and Benedict, 1997); visual learning using the BVMT-R (Benedict, 1997); reasoning and problem solving using the NAB Mazes subtest (Stern and White, 2003); and social cognition using the MSCEIT (Mayer et al., 2003). Finally, the D-KEFS Proverbs subtest (Delis et al., 2001; Delis et al., 2004) was administered to assess verbal ability.

MRI Acquisition. Not applicable.

Genotyping. DNA obtained from whole blood from a proportion of patients was genotyped on the Illumina Infinium OmniExpressExome-8 array.

Ethics/Consent. The UK Multi-center Research Ethics Committee (MREC) approved the study, as did relevant local research and development committees. All participants provided valid informed consent for the study.

Acknowledgements. The investigators wish to acknowledge Dr. Antonio F. Pardiñas and Amy Lynham for their assistance.

GAP — Genetics and Psychosis study

(O'Connor et al., 2013; Reis Marques et al., 2014; Theleritis et al., 2014; Vassos et al., 2017)

Recruitment. First episode psychosis patients were recruited as part of the National Institute of Health Research (NIHR) Biomedical Research Centre (BRC) Genetics and Psychosis study. Patients were approached if they appeared to meet DSM-IV criteria for schizophrenia or related disorder, or affective disorder with psychotic features and presented to one of 3 south London boroughs' geographical catchment area-based adult mental health services services of the South London and Maudsley NHS Foundation Trust (SLaM). During the same period a healthy control group was recruited from the local population living in the area and served by the SLaM Trust by means of internet and newspaper advertisements, and distribution of leaflets at train stations, shops and job centers. Particular attention was directed at attempting to obtain a control sample similar to the patient sample in age, gender, ethnicity, educational qualifications and employment status (Di Forti et al., 2009).

Inclusion/Exclusion Criteria. Between August 2008 and July 2011, patients aged between 18–65 years presenting for the first time to psychiatric services with a functional psychotic illness (ICD-10: F20-29, F30-34 excluding coding F1x.0 for acute intoxication; World Health Organization, 1992)). Inclusion criteria required that patients have 7 or more consecutive days of psychotic symptom(s) and were presenting to services for the first time with these symptoms. Patients were approached as soon as possible (up to 3 months after first contact). Exclusion criteria were: presence of an organic psychosis (i.e. known organic cause for psychosis), a moderate or severe developmental learning disability (as defined by ICD-10 F70-73), pregnancy, history of a medical or physiological cause of gonadal dysfunction (including hypothyroidism or other endocrine or metabolic disorder), vascular disorders, neurological disorders, antipsychotic treatment longer than 30 days (to minimize the effect of antipsychotics on BDNF levels), poor English fluency, and history of contact with health services for psychosis beyond the previous 6 months. Participants completed all measures within 6 months of first presentation with services. At 12 months after initial assessments, some research measures were repeated via clinical notes or face-to-face interview when available. Information about employment, relationships, living status and medication, was collected through interview with the patient and searching clinical records. Diagnosis was made according to DSM-IV criteria using the Operational Criteria (OPCRIT; McGuffin et al., 1991) based on the clinical notes for the month after first contact with psychiatric services for psychosis. Raters were experienced researchers who were extensively trained and demonstrated adequate inter-rater reliability on clinical and neuropsychological assessment. All diagnoses were carried out by qualified psychiatrists and clinical researchers, subject to comprehensive training and inter-rater reliability testing.

Clinical/Neuropsychological Assessment. Socio-demographic data (age, gender, self-reported ethnicity, level of education attainment) were collected using the Medical Research Council Social Scale (Mallett et al., 2002). Medication histories were completed using information from patients and electronic clinical records. The GAF (American Psychiatric Association, 1994) was used to rate both severity of symptoms and disability. Two separate ratings on the GAF were assigned based on dimensions of psychiatric symptoms and psychological, social and occupational function. To rate specific psychotic symptoms, scored on a clinical interview, the PANSS was used (Kay et al., 1987). Neuropsychological assessments included the following measures: premorbid IQ from the WTAR (Wechsler, 2001) or NART (Nelson, 1982; Nelson and Willison, 1991; Russell et al., 2000)); spatial and verbal working memory using the WMS-III Spatial Span subtest (Wechsler, 1997b) and the Digit Span subtest from the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997a)) and the Spatial Working Memory subtest from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, 2003a)); attention/processing speed using Trail Making Test—Part A (Reitan, 1958), WAIS-III Digit Symbol (Wechsler, 1997a), Semantic Verbal Fluency (categories: animals, body

parts, fruits) and Phonemic Verbal Fluency (letters F, A, S); verbal learning and memory was assessed using WMS-III Logical Memory (Wechsler, 1997b); visual memory using WMS-III Visual Reproduction; executive function was assessed using Trail Making Test—Part B (Reitan, 1958) and CANTAB Tower of London (Cambridge Cognition, 2003a). Additionally, the WAIS-III subtests Block Design, Matrix Reasoning, and Information, along with Digit Symbol and Digit Span were administered to allow for a calculation of total current IQ (Wechsler, 1997a).

MRI Acquisition. T1-weighted structural scans (TE = 2.85 ms; TI = 650 ms; TR = 6.99 ms; Flip angle = 8°; FOV = 26 cm; Spatial resolution = 1.0 x 1.0 x 1.2 mm; matrix = 256 x 256 mm; Slice acquisition direction = sagittal) and Diffusion Tensor Imaging (TE = 104.8 ms; TR = 15000 ms; Flip angle = 90°; FOV = 30.7 cm; Spatial resolution = 2.4 x 2.4 x 2.4 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 32; number of b0 volumes = 4; b-value = 1300 s/mm^2) were acquired on a 3 Tesla GE Signa HDx scanner using an 8-channel head coil.

Genotyping. DNA from a proportion of participants was extracted from blood or cheek swabs (80% and 20% of the participants, respectively) and genotyped on the Illumina HumanCore-24 Exome BeadChip.

Ethics/Consent. Ethical approval was obtained from the local research ethics committee. All study participants gave full informed consent. After hearing a complete description of the study and having the opportunity to ask questions, participants gave written informed consent.

Acknowledgements. The GAP study was supported by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Dr. Dazzan's research is also supported by the Medical Research Foundation. Dr. Reis-Marques and Dr. Dazzan's research is supported by NARSAD. Dr. Reinders is supported by the Netherlands Organization for Scientific Research (NWO-VENI grant no. 451-07-009). Genotyping and basic QC was supported by Guy's and St. Thomas Charity Grant No.R080529 (E Vassos) and the Psychiatry Research Trust (R Murray). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health". The investigators are grateful for the support of all GAP researchers and Principal Investigators for their contribution and support of the GAP study, and gratefully acknowledge the help of the Genetic & Psychosis and Physical Health & Substance Use in First Episode Psychosis study teams and participants, South London & Maudsley Mental Health NHS Trust. The investigators wish to specifically acknowledge Dr. Carmine M. Pariante, Dr. Kie Woo Nam, and Heather Taylor.

Conflicts of interest. Dr. Robin Murray has received honoraria for lectures from Janssen, AstraZeneca, Lilly, Novartis and Bristol-Myers Squibb.

IMH-SIGNRP — Institute of Mental Health, Singapore Imaging Genetics and Neuropsychological Research in Psychosis

(Ho et al., 2016; Kuswanto et al., 2015)

Recruitment. Chinese ethnicity patients diagnosed with DSM-IV schizophrenia were recruited from the Institute of Mental Health, Singapore. Age- and gender-matched healthy controls were recruited from the staff population at the hospital, as well as from the community by advertisements.

Inclusion/Exclusion Criteria. Participants with history of any significant neurological illnesses such as seizure disorder, head trauma, or cerebrovascular accident were excluded. No subject met DSM-IV criteria for alcohol or other substance abuse in the preceding 3 months. Patients were maintained on a stable dose of antipsychotic medication for at least two weeks prior to the recruitment and did not have their medications withdrawn for the purpose of the study. Healthy controls were deemed not to suffer from any Axis I psychiatric disorder and had no history of any major neurological, medical illnesses, substance abuse or psychotropic medication use.

Clinical/Neuropsychological Assessment. All diagnoses were made by a psychiatrist using information obtained from the existing medical records, clinical history, mental status examination, interviews with the patients and their significant family members, as well as the administration of SCID-I, Patient Version (SCID-I/P; First et al., 1994). Healthy controls were screened using the SCID-I, Non-Patient Version (SCID-I/NP; First et al., 2002a). Psychotic symptom levels were assessed using the PANSS (Kay et al., 1987). Premorbid IQ was assessed using the Reading subscale of the WRAT-3 (Wilkinson, 1993). The Symbol Coding, Category Instances (category: supermarket items), COWAT Phonemic Verbal Fluency (Reitan, 1985) (letters: F and S), Digit Sequencing, List Learning, and Tower of London (Shallice, 1982) subtests from the BACS (Keefe et al., 2004) were administered to assess attention/processing speed, verbal working memory, verbal learning and memory, and executive function, respectively.

MRI Acquisition. T1-weighted structural scans (TE = 3.3 ms; TI = 860 ms; TR = 7.2 ms; Flip angle = 8°; FOV = 23 cm; Spatial resolution = 0.9 x 0.9 x 0.9 mm; matrix = 256 x 256 mm; Slice acquisition direction = axial) and Diffusion Tensor Imaging (TE = 56 ms; TR = 3725 ms; Flip angle = 90°; FOV = 23 cm; Spatial resolution = 0.9 x 0.9 x 3.9 mm; matrix = 112 x 109 mm; Slice acquisition direction = axial, AC-PC; number of diffusion-encoding gradient directions = 15; number of b0 volumes = 1; b-value = 800 s/mm^2) were acquired on a 3 Tesla Philips Intera Achieva scanner using a SENSE 8-channel head coil.

Genotyping. DNA from a proportion of participants was obtained from whole blood and genotyped on one of three arrays: Illumina Human OmniZhongHua-8, Illumina Human1M-Duo, or Affymetrix 6.0.

Ethics/Consent. This study was approved by the Institutional Review Board of the Institute of Mental Health, Singapore, as well as the National Neuroscience Institute, Singapore. Participants gave written informed consent to participate in the study after a detailed explanation of the study procedure.

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IMH-STCRP — Institute of Mental Health, Singapore Translational and Clinical Research in Psychosis

(Lam et al., 2014)

Recruitment. Patients and healthy controls were recruited as part of the Singapore Translational and Clinical Research in Psychosis. Patients were recruited from rehabilitation centers, community care centers across the country, out-patient clinics and in-patient wards, under purview of the Institute of Mental Health, Singapore. Data collection was completed in approximately 3 years. Controls were from the Singapore Prospective Study Program and were randomly sampled from the Singapore population. Participants form part of the Psychiatric Genomics Consortium Schizophrenia Working Group dataset (PGC Schizophrenia Working Group, 2014).

Inclusion/Exclusion Criteria. Inclusion criteria were: Chinese ethnicity, to ensure a genetically homogeneous sample; and completion of a minimum of 6 years of primary school education. Additional exclusion criteria precluded all participants with significant history of substance abuse, clinically significant neurological disease or injury, color blindness, and healthy participants with first-degree relatives suffering from schizophrenia or other psychotic disorders.

Clinical/Neuropsychological Assessment. Clinical and neuropsychological evaluations were carried out by psychometricians. Schizophrenia patients fulfilled Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnostic criteria for schizophrenia based on the SCID-I (First et al., 2002b). Psychotic symptoms were assessed using the PANSS (Kay et al., 1987). Neuropsychological tests administered included the Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) as a measure of current IQ, Continuous Performance Tests-Identical Pairs (CPT-IP; Cornblatt et al., 1988) to measure attention/vigilance, 64-card WCST (WCST-64; Heaton et al., 1993) to measure executive function, Benton Judgment of Line Orientation Test (Benton et al., 1994) to measure visuospatial ability, and the BACS subtests Symbol Coding, Category Instances (categories: animals, fruits, vegetables), Digit Sequencing, List Learning, Tower of London, and Token Motor Task (Keefe et al., 2004; Keefe et al., 2008) to assess attention/processing speed, verbal working memory, verbal learning and memory, executive function, and psychomotor speed, respectively. Data including education, duration of illness, and medications were also collected.

MRI Acquisition. Not applicable.

Genotyping. DNA from a proportion of participants was obtained from whole blood and genotyped on the Illumina HumanOmniZhongHua-8 BeadChip.

Ethics/Consent. All participants consented to participate in research procedures prior to data collection. Consent procedures adhered to the guidelines specified by the National Healthcare Group Domain Specific Review Board's (domain A, NHG DSRB) requirements for human subject research.

Acknowledgements. Data acquisition was supported by the National Research Foundation Singapore under the National Medical Research Council Translational and Clinical Research Flagship Programme (grant no. NMRC/TCR/003/2008) for The Singapore Translational and Clinical Research in Psychosis, as well as research grants from the National Medical Research Council under the Centre Grant Programme (Institute of Mental Health, Singapore) (NMRC/CG/004/2013), the National Healthcare Group, Singapore (SIG/05004; SIG/05028), and the Singapore Bioimaging Consortium (RP C-009/2006).

KCL-MFS — King's College London - Maudsley Family Study

(Psychosis Endophenotypes International Consortium et al., 2014; Toulopoulou et al., 2004; Toulopoulou et al., 2003)

Recruitment. Patients and their relatives were drawn from a larger sample of the Maudsley Family Study (Frangou et al., 1997a,b; Griffiths et al., 1998). The relative group comprised mainly first-degree relatives and some second degree-relatives. The latter were second degree to the proband but they themselves had a first-degree relative with schizophrenia who either did not want to participate in this aspect of the Maudsley Family Study or was deceased. All offspring were adults. Families were recruited by referrals of psychiatric clinics and various other organizations across the United Kingdom. All patients, the vast majority of whom were outpatients, met DSM-III-R criteria for schizophrenia or schizoaffective disorder and were on antipsychotic medication at the time of the assessment. Among the non-psychotic relatives were seven individuals who had had a single episode of major depression, and the following had a lifetime diagnosis: 10 recurrent depressive disorder, three schizotypal personality disorder, and one of each of bulimia nervosa, alcohol dependency and social phobia. All relatives were well at the time of the neuropsychological assessment. Control participants were recruited from a set of controls obtained for previous studies conducted at the Institute of Psychiatry, King's College, London, from members of staff at the Institute of Psychiatry and the Bethlem and Maudsley Hospitals and via advertisements in the local newspapers. Some participants form part of the Psychiatric Genomics Consortium Schizophrenia Working Group dataset (PGC Schizophrenia Working Group, 2014).

Inclusion/Exclusion Criteria. All participants spoke English as their primary language. The normal control sample consisted of healthy participants with no personal or family history, up to second degree, of psychotic illness. The following exclusion criteria were used for all participants: head trauma resulting in loss of consciousness, drug or alcohol abuse during the 12 months before testing, organic brain disease, English as non-primary language and IQ<70. An additional exclusion criterion for relatives only was presence of psychosis that did not meet DSM-III-R criteria for schizophrenia or schizoaffective disorder.

Clinical/Neuropsychological Assessment. All patients and relatives were interviewed using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (Spitzer and Endicott, 1978). The data collected was later supplemented with information from case-notes and from other relatives to assign a lifetime DSM-III-R psychiatric diagnosis. Structured assessments of schizotypal personality disorder were completed using the paranoid/schizoid and schizotypal personality subscale of the Family Interview for Genetic Studies (Nurnberger et al., 1994) derived from a reliable informant. Psychotic symptoms were assessed using PANSS (Kay et al., 1987) and SANS/SAPS (Andreasen, 1983, 1984). Overall functioning was assessed using GAF (American Psychiatric Association, 1994). Current IQ was estimated using 8 subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS-R; Wechsler, 1981): Vocabulary, Comprehension, Information, Similarities, Block Design, Object Assembly, Picture Completion, and Picture Arrangement. Additionally, Vocabulary was used to estimate premorbid IQ. Processing speed was assessed using WAIS-R Digit Symbol and a computerized version of the Trail Making Test—Part A and B (Army Individual Test Battery, 1944; Reitan, 1958). Attention/vigilance was assessed using the CANTAB Rapid Visual Information Processing subtest. Verbal working memory was tested using the WAIS-R subtests Digit Span and Arithmetic. Spatial working memory was tested using the CANTAB Spatial Working Memory subtest (Cambridge Cognition, 2003a). Verbal and visual memory were assessed by the Wechsler Memory Scale–Revised (WMS-R) Logical Memory and Visual Reproduction subtests (Wechsler, 1987), respectively. Verbal and visual learning were measured using the WMS-R Paired Associate Learning and Visual Reproduction subtest, respectively.

MRI Acquisition. Not applicable.

Genotyping. DNA from a proportion of participants was obtained from whole blood or saliva and genotyped on the Affymetrix 6.0 array.

Ethics/Consent. The study was approved by the UK Multicenter Research Ethics Committee. All participants gave written informed consent before participating.

Acknowledgements. Support was provided by the European Community's Sixth Framework Programme through a Marie Curie Training Network (MRTN-CT-2006-035987) called the European Twin Study Network on Schizophrenia (EUTwinsS), NARSAD (through a Young Investigator Award to Dr. Toulopoulou), Wellcome Trust Research Training Fellowship (grant 064971 to Dr. Picchioni), Economic and Social Research Council/Medical Research Council and the Psychiatry Research Trust (PTA-037-27-0002); Deutsche Forschungsgemeinschaft (grant Et 31/2-1 to Dr. Ettinger), and Wellcome Trust Training Fellowship (ref 059007 to Dr. McDonald). The investigators acknowledge support from the Department of Health via the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health award to South London and Maudsley NHS Foundation Trust (SLaM) and the Institute of Psychiatry at King's College London. Principal funding for genotyping was provided by the Wellcome Trust, as part of the Wellcome Trust Case Control Consortium 2 project (Grant Nos. 085475/B/08/Z and 085475/Z/08/Z). Dr. Bramon was supported by a MRC New Investigator Award, a MRC Centenary Award, the National Institute of Health Research UK (post-doctoral fellowship), the Psychiatry Research Trust, the Schizophrenia Research Fund, a Brain and Behavior Research Foundation (NARSAD) Young Investigator Award, a Wellcome Trust Research Training Fellowship, and the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry Kings College London.

Conflicts of interest. Dr. Robin Murray has received honoraria for lectures from Janssen, AstraZeneca, Lilly, Novartis and Bristol-Myers Squibb. Dr. Picchioni has received travel awards from Pfizer, Janssen-Cilag, and Eli Lily and an educational grant from Janssen-Cilag.

KCL-MTS — King's College London - Maudsley Twin Study

(Owens et al., 2012; Owens et al., 2011a; Owens et al., 2011b; Psychosis Endophenotypes International Consortium et al., 2014; Toulopoulou et al., 2007)

Recruitment. Probands with schizophrenia were recruited nationally throughout the United Kingdom from National Health Service treatment centers through referrals by their treating psychiatrist. In the United Kingdom, the National Health Service is a comprehensive national treatment service funded centrally and free at the point of delivery for all aspects of health care. By virtue of its financial and organizational structure, it is hugely inclusive and as a consequence cares for most patients with schizophrenia, making it a very representative system from which to recruit. Control twins were recruited from a volunteer twin register held at the Institute of Psychiatry, London, England. Zygosity was determined by assessment of 12 highly polymorphic microsatellite markers and a standardized twin likeness questionnaire. Medication status was recorded at the time of the assessment, and age at first contact with psychiatric services was ascertained to serve as a proxy index of age at illness onset. In concordant pairs, both members fulfilled criteria for DSM-IV schizophrenia or schizoaffective disorder. In discordant pairs, one member was diagnosed with DSM-IV schizophrenia, whereas the co-twin was free of any psychotic illness. In control pairs, both members were free of personal or family history of psychosis or schizophrenia spectrum disorder. Some participants form part of the Psychiatric Genomics Consortium Schizophrenia Working Group dataset (PGC Schizophrenia Working Group, 2014).

Inclusion/Exclusion Criteria. Exclusion criteria applied to all groups were: <18 years of age, a history of a neurological disorder or systemic illness with known neurological complications, a history of significant head injury associated with loss of consciousness for more than 1 minute, and current harmful substance use or dependence (defined as within the last 12 months). No participant included in the study had a psychotic illness directly attributable to the harmful use of illicit substances.

Clinical/Neuropsychological Assessment. The DSM-IV diagnoses were made using the Schedule for Affective Disorders and Schizophrenia (SADS)–Lifetime Version (Spitzer and Endicott, 1978), supplemented by information from medical notes or by using the Structured Clinical Interview for DSM-IV (First et al., 1995a, b). Psychotic symptoms in the probands in the month before testing were assessed using PANSS (Kay et al., 1987) and/or SANS/SAPS (Andreasen, 1983, 1984), and overall functioning using GAF (American Psychiatric Association, 1994). The full UK version of the WAIS-III (WAIS-III-UK; Wechsler, 2005) was administered to all participants to assess current IQ, consisting of the following subtests: Vocabulary, Comprehension, Information, Similarities, Letter-Number Sequencing, Digit Span, Arithmetic, Digit Symbol, Block Design, Object Assembly, Picture Completion, and Picture Arrangement. Additionally, Vocabulary was used to estimate premorbid IQ. Furthermore, processing speed was assessed using a computerized version of the Trail Making Test—Part A and B (Army Individual Test Battery, 1944; Reitan, 1958), Semantic Verbal Fluency (categories: animals, fruits, body parts) (Benton and Hamsher, 1989) and COWAT Phonemic Verbal Fluency (letters: F, A, S) (Reitan, 1985). Attention/vigilance was assessed using the CANTAB Rapid Visual Information Processing subtest (Cambridge Cognition, 2003a). Verbal working memory was tested using the WAIS-R subtests Letter-Number Sequencing, Digit Span and Arithmetic. Spatial working memory was tested using the WMS-R Visual Memory Span subtest (Wechsler, 1987) and the CANTAB Spatial Working Memory subtest (Cambridge Cognition, 2003a). Verbal and visual memory were assessed by the WMS-R Logical Memory and Visual Reproduction subtests (Wechsler, 1987), respectively. Verbal and visual learning were measured using the WMS-R Paired Associate

Learning subtest and Visual Reproduction/Visual Paired Associates subtests, respectively (Wechsler, 1987). Executive processing was assessed by the CANTAB Intra-Extra Dimensional Set Shifting subtest (Cambridge Cognition, 2003a).

MRI Acquisition. T1-weighted structural scans (TE = 5.0 ms; TI = 450 ms; TR = 35 ms; Flip angle = 30°; FOV = 20 cm; Spatial resolution = 0.78 x 0.78 x 1.5 mm; matrix = 256 x 256 x 128 mm; Slice acquisition direction = coronal) and Diffusion Tensor Imaging (TE = 102 ms; TR = 15000 ms; Flip angle = n/a; FOV = 24 cm; Spatial resolution = 2.5 x 2.5 x 2.5 mm; matrix = 96 x 96 mm; Slice acquisition direction = axial, AC-PC; number of diffusion-encoding gradient directions = 64; number of b0 volumes = 7; b-value = 1300 s/mm^2) were acquired on a 1.5 Tesla GE Signa Advantage scanner using a circularly polarized (CP) head coil.

Genotyping. DNA from a proportion of participants was obtained from whole blood or saliva and genotyped on the Affymetrix 6.0 array.

Ethics/Consent. The study was approved by the UK Multicenter Research Ethics Committee. All participants gave written informed consent before participating.

Acknowledgements. Support was provided by the European Community's Sixth Framework Programme through a Marie Curie Training Network (MRTN-CT-2006-035987) called the European Twin Study Network on Schizophrenia (EUTwinsS), NARSAD (through a Young Investigator Award to Dr. Toulopoulou), Wellcome Trust Research Training Fellowship (grant 064971 to Dr. Picchioni), Economic and Social Research Council/Medical Research Council and the Psychiatry Research Trust (PTA-037-27-0002). The investigators acknowledge support from the Department of Health via the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health award to South London and Maudsley NHS Foundation Trust (SLaM) and the Institute of Psychiatry at King's College London. Principal funding for genotyping was provided by the Wellcome Trust, as part of the Wellcome Trust Case Control Consortium 2 project (Grant Nos. 085475/B/08/Z and 085475/Z/08/Z). Dr. Bramon was supported by a MRC New Investigator Award, a MRC Centenary Award, the National Institute of Health Research UK (post-doctoral fellowship), the Psychiatry Research Trust, the Schizophrenia Research Fund, a Brain and Behavior Research Foundation (NARSAD) Young Investigator Award, a Wellcome Trust Research Training Fellowship, and the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry Kings College London.

Conflicts of interest. Dr. Robin Murray has received honoraria for lectures from Janssen, AstraZeneca, Lilly, Novartis and Bristol-Myers Squibb. Dr. Picchioni has received travel awards from Pfizer, Janssen-Cilag, and Eli Lily and an educational grant from Janssen-Cilag.

L&R — Language and Risk in Schizophrenia

(Francis et al., 2012)

Recruitment. Individuals at familial high risk for schizophrenia (FHR) (age range of 19–32 years) with at least one first degree family member suffering from schizophrenia or schizoaffective disorder and one second or third degree relative with history of a psychosis, suicide, or psychiatric hospitalization were included in this study. Participants were recruited during 2009–2011 from throughout Massachusetts and other New England neighboring regions through brochures and advertisements and by networking through the National Alliance on Mental Illness. Controls with no family history of a psychosis in 1st, 2nd or 3rd degree relatives (age range of 20–32 years) were also recruited from the community via advertisements.

Inclusion/Exclusion Criteria. Participants with a DSM-IV diagnosis of any history of lifetime psychotic disorder were excluded. Additional exclusion factors were: English not the participant's native language, non-right-handedness, neurological illness, and IQ below 80.

Clinical/Neuropsychological Assessment. All participants were administered the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994). A family pedigree was drawn with information obtained from the participant. DSM-IV diagnoses (Axis I for major psychiatric illness

and Axis II for personality disorders) were made on all participants by a research psychiatrist using all available information collected during the interview. Schizotypal symptoms were measured using the Modified Structured Interview for Schizotypy (SIS; Kendler et al., 1989) from the DIGS. Data were acquired on 9 factors from the SIS (magical thinking, ideas of reference, illusions, suspiciousness, psychotic-like symptoms, restricted emotion, social isolation/ introversion, schizotypal social anxiety, and anger to slights). Participants were administered a large neurocognitive test battery including tests estimating premorbid IQ, i.e. the Reading subtest from the WRAT-4 (Wilkinson and Robertson, 2006a), and current IQ, i.e. the Vocabulary and Block Design subtest of the WASI (Wechsler, 1999). BACS Symbol Coding (Keefe et al., 2008), Trail Making Test—Part A (Reitan, 1958), and Semantic Verbal Fluency (MCCB Category Fluency; category: animals) (Benton and Hamsher, 1978; Kern et al., 2008; Nuechterlein et al., 2008) were used for processing speed; the CPT-IP (Cornblatt et al., 1988) was used to measure attention/vigilance; the WMS-III Spatial Span subtest (Wechsler, 1997b) and University of Maryland Letter-Number Span (Gold et al., 1997) were used for assessing working memory. The 'vigilance', 'working memory' and 'working memory plus interference' measures from the Seidman Auditory CPT (Seidman et al., 1998; Seidman et al., 2006). The HVLT-R (Brandt and Benedict, 1997) and the WMS-III Logical Memory subtest (Wechsler, 1997b) assessed verbal learning and memory. The BVMT-R (Benedict, 1997) assessed visual learning. Executive function was measured using NAB Mazes (Stern and White, 2003) and the computerized WCST (Heaton, 2003; Heaton et al., 1993; Nestor et al., 1993). The D-KEFS Proverbs subtest (Delis et al., 2001; Delis et al., 2004) was administered to assess verbal ability, and Grooved Pegboard (Lafayette Instrument Company -- Trites, 1989) and Finger Tapping (Ruff and Parker, 1993) were administered to assess motor control. Additionally, participants were administered verbal neuropsychological tests to test many aspects of linguistic functioning potentially associated with familial high-risk for schizophrenia, including: Abstract Reasoning (Delis et al., 2001), Woodcock-Johnson Passage Comprehension Test (Woodcock et al., 2001); Phonological Awareness derived from auditory stimuli: Elision and Blending Words subtests from the Comprehensive Test of Phonological Processing (Wagner et al., 1999); Phonological Awareness derived from visual stimuli including real words (WRAT-4 Reading subtest; Test of Word Reading Efficiency [TOWRE] Sight Word Efficiency**;** Woodcock**–**Johnson Letter Word Identification) and non-words (TOWRE Phonemic Decoding Efficiency; Woodcock-Johnson Word Attack) (Torgesen et al., 1999; Wilkinson and Robertson, 2006b; Woodcock et al., 2001).

MRI Acquisition. T1-weighted structural scans (TE = 3.48 ms; TI = 900 ms; TR = 15 ms; Flip angle = 9°; FOV = 25.6 cm; Spatial resolution = 1.0 x 1.0 x 1.0 mm; matrix = 256 x 256 mm; Slice acquisition direction = sagittal) and Diffusion Tensor Imaging (TE = 84 ms; TR = 8060 ms; Flip angle = 55°; FOV = 25.6 cm; Spatial resolution = 2.0 x 2.0 x 2.0 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 60; number of b0 volumes = 10; b-value = 700 s/mm^2) on a 3 Tesla Siemens Trio Tim scanner using a 32-channel head coil.

Genotyping. DNA was obtained from whole blood and genotyped on the Illumina Infinium PsychArray. Genotyping was funded by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) grant number R01MH092380 to T.L.P. supporting the GENUS Consortium.

Ethics/Consent. The study was approved by the Human Subjects Investigation Committee at Harvard Medical School, Beth Israel Deaconess Medical Center, Massachusetts Institute of Technology, Brigham and Women's Hospital, and Veterans Administration Boston Healthcare System, Brockton, Massachusetts. All participants provided written informed consent and were paid for their participation.

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MCIC — Mind Clinical Imaging Consortium
(Gollub et al., 2013)

Recruitment. Patients with schizophrenia and demographic, age and sex- matched healthy control participants were recruited for this study between July 2004 and July 2006 across four research sites—University of New Mexico, University of Minnesota, Massachusetts General Hospital, and University of Iowa. The final cohort for whom cognitive and/or MRI data are available includes 156 patients and 122 controls. However, the University of Iowa subsample (38 patients, 25 controls) is not included in the GENUS dataset, resulting in 118 patients and 97 controls included in the GENUS dataset. Participants form part of the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Schizophrenia Working Group dataset (van Erp et al., 2016).

Inclusion/Exclusion Criteria. Participants were excluded for reasons such as excessive motion during image acquisition, claustrophobia or discomfort during MRI scanning, or a determination of ineligibility based on screening exams and tests. All participants were between the ages of 18 and 60 and spoke English as their native language. To be included in the schizophrenia cohort, patients had to meet DSM-IV diagnostic criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder. Concerted effort was made to recruit patients early in the course of their illness and especially those who were antipsychotic drug naïve. The healthy control participants with no current or past history of psychiatric illness including substance abuse or dependence were matched within site to the patient cohort for age, sex, and parental education. Control participants who had not been diagnosed with any psychiatric disorders, but had been medicated with antidepressants, anti-anxiety medication or medication for sleep disturbance were included in the study, provided that the duration of their medication did not exceed 2 months of lifetime use and no medication was used within the 6 months preceding the baseline MRI scan. Control participants who met criteria for current or past history of substance abuse or dependence were excluded from the study. Patients were not excluded from the study unless criteria were met for current (i.e., within the past month) abuse or dependence except for 6 patients who were found to meet criteria for current abuse after the study data was collected. Both patients and controls were excluded if they had 1) an IQ less than 70 based on a standardized IQ test, 2) history of a head injury resulting in prolonged loss of consciousness, neurosurgical procedure, neurological disease, history of skull fracture, severe or disabling medical conditions, or 3) a contraindication for MRI scanning such as pregnancy, metal in body or head including implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, implanted TENS unit, or ventriculo-peritoneal shunt. Clinical teams at each site recruited the patients. Primary treating clinicians, not necessarily involved with the study, identified potential patients who met inclusion/ exclusion criteria and were competent to give informed consent. Healthy control participants were recruited from the community at each site through posters, brochures, newspapers, website advertisements, and institutional subject recruitment resources.

Clinical/Neuropsychological Assessment. Core demographic information collected includes age, handedness, height, weight, ethnicity, race, educational achievement, parental education, and socioeconomic status. A Structured Clinical Interview for DSM-IV Disorders, SCID-P for patients and SCID-NP for controls (First et al., 1995a, b), or the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992) were used to diagnose primary and co-morbid psychiatric disorders in controls and patients. Additionally, patients were interviewed with the SANS/SAPS (Andreasen, 1983, 1984) and the CDSS (Addington et al., 1992) to record symptoms and their current severity. Premorbid IQ and current IQ were measured using the Reading subtest of the WRAT-3 (Wilkinson, 1993), and the Block Design, Vocabulary, and Similarities subtests of the WAIS-III (Wechsler, 1997a), respectively. Trail Making Test—Part A and B (Reitan, 1958) measured processing speed. D-KEFS (Delis et al., 2001) assessed Semantic Verbal Fluency (categories: animals, fruits) and Phonemic Verbal Fluency (letters: F, A, S). The WAIS-III Letter-Number Sequencing subtest measured working memory. Verbal

memory and learning were assessed using the Wechsler Memory Scale—Third Edition (WMS-III) Logical Memory subtest (Wechsler, 1997b) and the HVLT-R (Brandt, 1991). The Benton Visual Retention Test (BVRT; Sivan, 1992) and the Face Recognition subtest of the WMS-III (Wechsler, 1997b) both measured visual memory. A computerized version of the Tower of London test (TOL; Shallice, 1982) was employed to measure planning and problem solving. The Grooved Pegboard Test (Ruff and Parker, 1993), and the California Computerized Assessment Package (CalCap; Miller, 1990), a computerized reaction time test, tested fine motor dexterity and speed. The Annett Scale of Hand Preference (Annett, 1970) provided a numeric measure of handedness.

MRI Acquisition. T1-weighted structural scans at Massachusetts General Hospital, Martinos Center (TE = 4.76 ms; TI = 300 ms; TR = 12.0 ms; Flip angle = 20°; FOV = 16 cm; Spatial resolution = 0.7 x 0.7 x 1.5 mm; matrix = 256 x 256 x 128 mm; Slice acquisition direction = axial, oblique) and Diffusion Tensor Imaging (TE = 80 ms; TR = 8900 ms; Flip angle = 90°; FOV = 16 cm; Spatial resolution = 2.0 x 2.0 x 2.0 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 60; number of b0 volumes = 10; b-value = 700 s/mm^2) were acquired on a 1.5 Tesla Siemens Sonata scanner using an 8-channel head coil. T1-weighted structural scans at the University of Minnesota (TE = 3.81 ms; TI = 1100 ms; TR = 2530 ms; Flip angle = 7°; FOV = 16 cm; Spatial resolution = 0.625 x 0.625 x 1.5 mm; matrix = 256 x 256 x 128 mm; Slice acquisition direction = coronal) and Diffusion Tensor Imaging (TE = 98 ms; TR = 11500 ms; Flip angle = 90°; FOV = 16 cm; Spatial resolution = 2.0 x 2.0 x 2.0 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 12; number of b0 volumes = 1; b-value = 1000 s/mm^2) were acquired on a 3.0 Tesla Siemens Trio Tim scanner using an 8-channel head coil. T1-weighted structural scans at the University of New Mexico (TE = 4.76 ms; TI = 300 ms; TR = 12.0 ms; Flip angle = 20°; FOV = 16 cm; Spatial resolution = 0.625 x 0.625 x 1.5 mm; matrix = 256 x 256 x 128 mm; Slice acquisition direction = coronal) and Diffusion Tensor Imaging (TE = 92 ms; TR = 10000 ms; Flip angle = 90°; FOV = 16 cm; Spatial resolution = 2.0 x 2.0 x 2.0 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 12; number of b0 volumes = 1; b-value = 1000 s/mm^2) were acquired on a 1.5 Tesla Siemens Sonata scanner using an 8-channel head coil.

Phenotype data are available from the Collaborative Informatics and Neuroimaging Suite (https://coins.mrn.org).

Genotyping. DNA was obtained from whole blood and genotyped on the Illumina HumanOmni1-Quad BeadChip.

Ethics/Consent. All participants provided informed consent to participate in the study. The study was approved by the human research committees at each site. In addition to informed consent, all patients successfully completed a questionnaire verifying that they understood the study procedures.

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MGH — Massachusetts General Hospital

(Ho et al., 2016; Holt et al., 2012; Linnman et al., 2013; Roffman et al., 2013; Roffman et al., 2011; Roffman et al., 2007; Roffman et al., 2008a; Roffman et al., 2008b)

Recruitment. Outpatients with schizophrenia were recruited from an urban community mental health center in Boston. Demographically matched healthy participants were recruited from the community by poster and website advertisements.

Inclusion/Exclusion Criteria. Participants were excluded if they had a history of substance abuse or dependence within the previous 6 months, a history of significant head injury, or neurologic illness. Healthy participants were screened to exclude a personal history of Axis I mental illness (First et al., 2002a) or a family history of schizophrenia-spectrum disorder. For all participants, exclusion criteria included severe medical illness, significant head trauma, neurologic illness, substance abuse during the past six months and contraindications for MRI scanning (e.g., implanted metal objects, claustrophobia, renal insufficiency). Patients had been maintained on stable doses of second generation antipsychotics for at least six weeks, with the exception of one patient taking prolixin, and three patients who were not taking any medications.

Clinical/Neuropsychological Assessment. Patient diagnoses were confirmed using the Structured Clinical Interview for DSM-IV-TR (First et al., 2002b). The healthy controls were without psychiatric disorders as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995b). Participants were also rated with the PANSS (Kay et al., 1987), Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) and Simpson–Angus Scale (Simpson and Angus, 1970), a measure of extrapyramidal symptoms. Tests were administered by one of four trained and certified raters. Premorbid IQ was estimated using the North American Adult Reading Test (NAART; Blair and Spreen, 1989). The WAIS—III (Wechsler, 1997a) was conducted to measure current IQ (all subtests [=13], except Symbol Search). Patients participated in a neurocognitive battery that included the CVLT (Delis et al., 1987), Semantic Verbal Fluency (category: animals) (Benton and Hamsher, 1989) and COWAT Phonemic Verbal Fluency (letters: F, A, S) (Reitan, 1985), WCST (Heaton et al., 1993), and Finger Tapping (Ruff and Parker, 1993).

MRI Acquisition. Subsample1: T1-weighted structural scans (TE = 1.54 ms, 3.36 ms; TI = 1100 ms; TR = 2200; Flip angle = 7°; FOV = 23 cm; Spatial resolution = 1.2 x 1.2 x 1.2 mm; matrix = 192 x 192 mm; Slice acquisition direction = sagittal) and Diffusion Tensor Imaging (TE = 85.0 ms; TR = 5980 ms; Flip angle = 90°; FOV = 22 cm; Spatial resolution = 1.375 x 1.375 x 3.0 mm; matrix = 160 x 160 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 6; number of b0 volumes = 1; b-value = 1000 s/mm^2) were acquired on a 3 Tesla Siemens Trio Tim scanner. Subsample 2: T1-weighted structural scans (TE = 3.39 ms; TI = 1100 ms; TR = 2530 ms; Flip angle = 7°; FOV = 25.6 cm; Spatial resolution = 1.0 x 1.0 x 1.3 mm; matrix = 256 x 256 mm; Slice acquisition direction = sagittal) were acquired on a 3 Tesla Siemens Trio Tim scanner using a 12-channel head coil.

Genotyping. DNA was obtained from whole blood or saliva and genotyped on the Illumina Infinium PsychArray. Genotyping was funded by the National Institute of Mental Health (NIMH) of

the National Institutes of Health (NIH) grant number R01MH092380 to T.L.P. supporting the GENUS Consortium.

Ethics/Consent. Study procedures were approved by the institutional review boards of Partners HealthCare and the Massachusetts Department of Mental Health. All participants provided written informed consent.

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NEFS — New England Family Study

(Buka et al., 2013; Goldstein et al., 2010; Goldstein et al., 2014; Seidman et al., 2013; Seidman et al., 2002)

Case and Control Recruitment. Participants were selected from the Boston and Providence cohorts of the Collaborative Perinatal Project (CPP), currently known as the New England Family Studies (NEFS). The CPP was initiated over 50 years ago to investigate prospectively the prenatal and familial antecedents of pediatric, neurological and psychological disorders of childhood (Niswander and Gordon, 1972). Approximately 17,000 pregnancies were followed in New England. Many types of assessments, including psychological examinations, were conducted on offspring up to 7 years of age, when the study officially ended in 1973. Ascertainment and assessment of the adult psychotic patients in NEFS were identified through a systemic follow-up of the entire NEFS cohort of the CPP. NEFS parents and offspring with a history of psychiatric hospitalization and/or possible psychotic and bipolar illness were identified from the following sources: (1) record linkages with public hospitals, mental health clinics, and the Massachusetts and Rhode Island Departments of Mental Health; (2) several follow-up and case-control studies nested within the larger NEFS cohort, involving direct interviews with approximately 20% of the cohort; and (3) reports from participants in these interview studies of a family member with a history of psychotic or bipolar symptoms or diagnosis. Controls were selected from families participating in the control arm of a NEFS high-risk study in which the control population was a random stratified sample of parents selected from the entire NEFS cohort, with no known history of psychosis or other major Axis I disorders. Thus, the NEFS sample of cases and controls is a representative community sample of subjects.

Inclusion/Exclusion Criteria. Adult offspring with major non-organic psychoses (including schizophrenia, schizoaffective disorder, delusional disorder, brief psychosis, psychosis NOS, bipolar disorder with psychotic features, and major depressive disorder with psychosis) within NEFS cohorts were identified approximately 30 years later through a two-stage diagnostic assessment procedure between 1996 and 2007. The investigators were blind to prior

assessments of these subjects during this follow-up. In the first stage, individuals with possible psychotic illness were identified through record linkages and from personal interviews. In the second stage, those who consented to participate in follow-up efforts were interviewed using the SCID (First et al., 1995b). Based on interview data and medical record review, trained PhD- and MD-level diagnosticians then completed best-estimate consensus diagnoses according to DSM-IV criteria for lifetime prevalence of psychotic and other psychiatric disorders. Exclusion criteria for all adult participants were a history of neurological disease, traumatic brain injury, medical illness or alcohol-related disease with documented cognitive sequelae, major sensory impairments (e.g. deafness), IQ<65 in adulthood or inability to understand the procedures, <6 years of formal education and severe substance abuse within the past 6 months. All psychoses cases were living in the community when assessed. Controls had to be free of any known lifetime history of psychosis or other major Axis I disorders. Furthermore, parents and grandparents, in addition to the parents' siblings, had to be free of any known lifetime history of psychosis, bipolar, schizotypal, recurrent MDD, suicide attempts or psychiatric hospitalizations. Siblings of the controls also had to be free of any lifetime history of psychosis or BD.

Family High Risk Sample Ascertainment: The study goal was to ascertain approximately 200 psychotic NEFS Generation-1 parents, half with schizophrenia and half with affective psychoses and a comparable group of normal control parents. Generation-1 parents were contacted between 1994 and 2002. Parents with a history of psychiatric treatment were identified by the following sources: (1) prior record review; (2) subsequent record linkages with private and public psychiatric treatment facilities in Rhode Island and Massachusetts; (3) information provided by mothers during the original study (e.g., psychiatric hospitalization at study enrollment; psychiatric treatment at the 7 year assessment; or history of treatment with antipsychotic medication); or (4) family member reports from recent follow-up studies with the NCPP cohort. Through these efforts, from a total pool of 26,928 G1 parents, we identified 859 persons with indications of potential psychosis. This represents a rate of approximately 3.2%-4.2% of the pool of parents we were able to review, which is consistent with current estimates of the lifetime prevalence of psychotic disorders. Of these parents, 755 were eligible for follow-up. Parents were considered eligible if at least one Generation-2 offspring was assessed after 4 months of age.

Control parents were selected to be comparable to parents with psychotic disorders based on the number of offspring enrolled in the CPP, patient status (public or private), parent's age, ethnicity (Caucasian or other), study site, and on the offspring's age, sex, and history of chronic hypoxia (given that we wanted to test for the interaction of genetic vulnerability and this obstetric condition). Eligible controls included all members of the CPP who were not identified as potential psychotic parents and whose records did not indicate a history of psychiatric treatment. Healthy control parents did not have spouses, parents, siblings, or any second-degree relatives with psychoses, recurrent MDD, suicide, or psychiatric hospitalizations.

Generation-1 Follow-Up and Psychiatric Assessment: Subjects were located through a variety of methods, including thorough searches of credit bureaus, address directories, death certificates, motor vehicle reports, and by home visits. The located subjects were invited to participate in a two-part interview. The first interview screened for potential psychoses and the second was a full diagnostic interview using the SCID (First et al., 1995b) and assessing Axis I diagnoses of any form of psychotic, major affective, and bipolar disorders; and substance abuse or dependence (alcohol and drug). The clinical interview was conducted by systematically trained M.A.-level clinical interviewers. Medical records were obtained with subject consent. Family history of psychiatric disorders was evaluated using the Family Interview for Genetic Studies (Maxwell, 1996). Expert diagnosticians (including J.G., L.S.) reviewed all of the information collected from both interviews and medical records, if available, to determine final best estimate diagnoses. If there was any evidence of mental illness in the spouse, we interviewed the spouse or searched for medical records if the spouse had passed away. Spouses' names were subjected to the linkage procedures used for the mothers.

Of the 755 eligible Generation-1 parents, 212 with confirmed DSM-IV psychotic disorders were identified, with 153 (72%) mothers and 59 (27%) fathers. The sample of 212 parents with psychosis and 132 non-psychotic parents had a total of 467 pregnancies: 167 offspring among affective parents, 114 offspring among SPS parents, and 186 offspring among non-psychotic parents. Of note, among the 344 final Generation-1 parents, there are six 'two parent families' in which both parents were diagnosed with some form of psychosis, resulting in a sample size of 338 unduplicated families. Of the 467 pregnancies, 22 (4.7%) resulted in an offspring who was stillborn, did not live past early childhood, was lost to follow-up before age 7, or was adopted/placed in foster care, and thus ineligible for this adult follow-up study. Of the 445 eligible Generation-2's, 428 (96.2%) were located of whom 344 (80.4%) were interviewed, for an overall interview rate of 77.3%. In addition to the 344 Generation-2's with diagnostic information from interviews, there were an additional six Generation-2's with a diagnostic summary from medical records from treatment facilities for a total of 350 Generation-2's with diagnostic information. This reflects a completed diagnostic rate of 78.7%.

Clinical/Neuropsychological Assessment. Trained and skilled M.A.-level interviewers and neuropsychological testers conducted all clinical and cognitive assessments. The SANS/SAPS (Andreasen, 1983, 1984)) were used to measure symptom severity. Participants were administered a large neurocognitive test battery including tests estimating premorbid IQ (the Reading subtest from the WRAT-3 (Wilkinson, 1993), and current IQ (the Vocabulary, Information, Comprehension, Block Design, Picture Arrangement, Digit Span and Digit Symbol subtests of the WAIS-R (Wechsler, 1974). The WAIS-R Digit Symbol Coding subtest (Wechsler, 1974) and COWAT Phonemic Verbal Fluency test (letters F, A, S) (Reitan, 1985) were used for measuring processing speed. The **'**vigilance**'**, **'**working memory**'** and **'**working memory plus interference**'** measures from the Seidman Auditory CPT (Seidman et al., 1998; Seidman et al., 2006) were used to measure attention/vigilance and verbal working memory, in addition to the WAIS-R Digit Span subtest for working memory assessment (Wechsler, 1974). The CVLT or CVLT-II (Delis et al., 1987, 2000) and the WMS-R or WMS-III Logical Memory subtest (Wechsler, 1987, 1997b) assessed verbal learning and memory. The WMS-III Faces subtest (Wechsler, 1997b) and the Rey-Osterrieth Complex Figure Test (Rey, 1964) assessed visual learning and memory. Executive function was measured using the WCST (Heaton et al., 1993) or the Stroop test (Stroop, 1935). Finally, the Rapid Automatized Naming test (Denckla and Rudel, 1974) was used to measure language ability.

MRI Acquisition. T1-weighted structural scans (TE = 3.31 ms; TI = 1000 ms; TR = 2730 ms; Flip angle = 7**°**; FOV = 25.6 cm; Spatial resolution = 1.0 x 1.0 x 1.33 mm; matrix = 256 x 256 mm; Slice acquisition direction = sagittal) and Diffusion Tensor Imaging (TE = 77-79 ms; TR = 7200 ms; Flip angle = 90**°**; FOV = 25.6 cm; Spatial resolution = 2.0 x 2.0 x 2.0 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 60; number of b0 volumes = 10; b-value = 700 s/mm^2) were acquired on a 1.5 Tesla Siemens Avanto scanner using a 4-channel head coil. For a second subsample, T1-weighted structural scans (TE = 3.39 ms; TI = 1000 ms; TR = 2730 ms; Flip angle = 7**°**; FOV = 25.6 cm; Spatial resolution = 1.0 x 1.0 x 1.33 mm; matrix = 256 x 256 mm; Slice acquisition direction = sagittal) and Diffusion Tensor Imaging (TE = 67 ms; TR = 9000 ms; Flip angle = 90**°**; FOV = 25.6 cm; Spatial resolution = 2.0 x 2.0 x 2.0 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 6; number of b0 volumes = 1; b-value = 600 s/mm^2) were acquired on a 1.5 Tesla Siemens Sonata scanner using a CP coil. A portion of T1-weighted structural scans were acquired also on a 1.5 Tesla Siemens Sonata scanner (TE = 4.3 ms; TI = 8 ms; TR = 11.8 ms; Flip angle = 8**°**; FOV = 25.6 cm; Spatial resolution = 1.0 x 1.0 x 1.5 mm; matrix = 256 x 256 mm; Slice acquisition direction = sagittal, CP head coil) or on a 1.5T GE Genesis Signa scanner (TE = 1.6 ms; TI = 300 ms; TR = 6.7 ms; Flip angle = 25**°**; FOV = 24 cm; Spatial resolution = 0.94 x 0.94 x 1.5 mm; matrix = 256 x 256 mm; Slice acquisition direction = sagittal, CP head coil). Given that NEFS is a long-term follow up study, in more recent years, T1-

weighted scans were acquired on a 3 Tesla Siemens Trio Tim scanner, using a 12-channel head coil (TE = 3.39 ms; TI = 1000 ms; TR = 2530 ms; Flip angle = 7°; FOV = 25.6 cm; Spatial resolution = 1.0 x 1.0 x 1.33 mm; matrix = 256 x 256 mm; Slice acquisition direction = sagittal) and Diffusion Tensor Imaging (TE = 83-84 ms, TR = 9400-9440 ms; Flip angle = 90°; FOV = 25.6 cm; Spatial resolution = 2.0 x 2.0 x 2.0 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 60; number of b0 volumes = 10; b-value = 700 s/mm^2).

Genotyping. DNA was obtained from whole blood or buffy coat and genotyped on the Illumina Infinium PsychArray. Genotyping was funded by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) grant number R01MH092380 to T.L.P. supporting the GENUS Consortium.

Ethics/Consent. Human subject research approval was granted by Institutional Review Boards at Harvard University, Partners Healthcare, Brown University and local psychiatric facilities. Written consent was obtained from all participants interviewed. Participants were compensated for their participation.

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PAGES — Phenomics and Genomics Sample
(Walters et al., 2010; Walters et al., 2013)

Recruitment. Clinically stable patients with a DSM-IV diagnosis of schizophrenia were ascertained from mental health services in the Munich area. Healthy control participants randomly selected from population registers from the Munich area were contacted by mail and invited to participate. The address, sex, and age of potential control participants were supplied by the municipal registration office, which enabled equal numbers of males and females and people of different ages (in decades) to be contacted. In patients, 68% were of German descent (all 4 grandparents born in Germany), and 32% were German white. All healthy control participants were of German descent (all 4 grandparents German). All patients and healthy control participants were unrelated. Some patients (62%) and healthy control participants (23%) form part of the SGENE-plus study (Stefansson et al., 2009). Some participants form part of the Psychiatric Genomics Consortium Schizophrenia Working Group dataset (PGC Schizophrenia Working Group, 2014). Controls form part of the Cognitive Genomics Consortium wave 1 (COGENT1) dataset (Lencz et al., 2014).

Inclusion/Exclusion Criteria. The inclusion criteria for patients were a diagnosis of schizophrenia (6-month symptom duration) and 18 to 80 years of age. Exclusion criteria were a history of head injury or neurological disease. Healthy control participants 18 to 65 years of age underwent an extensive screening process (Walters et al., 2010) to exclude those with neurological or psychotic disorders, those who had first-degree relatives with psychotic disorders, and those with lifetime exposure to psychiatric medication. In the case of healthy controls older than 60 years, the Mini-Mental State Examination (Folstein et al., 1983) was employed to exclude individuals with possible cognitive impairment. A neurologic examination was also conducted to exclude individuals with current central nervous system impairment.

Clinical/Neuropsychological Assessment. Detailed medical and psychiatric histories were collected, including data from a clinical interview using the SCID (First et al., 1995b) to evaluate lifetime Axis I and II diagnoses. The interviews were rated by four psychiatrists or one psychologist, and all measurements were independently rated by a senior researcher. Participants were also rated for symptoms using the PANSS (Kay et al., 1987). In addition, the Family History Assessment Module (Rice et al., 1995) was conducted to exclude psychotic disorders in first-degree relatives. Current IQ was measured by the full German WAIS-R (Tewes, 1991), consisting of 11 subtests: Vocabulary, Comprehension, Information, Digit Span, Arithmetic, Similarities, Block Design, Picture Completion, Picture Arrangement, Object Assembly, and Digit Symbol Coding. Additionally, Vocabulary was used to estimate premorbid IQ. All control participants completed the full WAIS-R assessment. All patients and 25% of control participants completed an extensive neuropsychological battery consisting of the WAIS-R and the following: Trail Making Test**—**Part A (Reitan, 1958), Semantic Verbal Fluency (categories: animals, food) (Benton and Hamsher, 1978), and Phonemic Verbal Fluency (letters: S and P) (Reitan, 1985) to assess attention/processing speed; Continuous Performance Test 3**–**7 Version (Nuechterlein and Asarnow, 2004) to assess attention/vigilance; WMS-R Spatial Span subtest (Härting et al., 2000; Wechsler, 1987) and a spatial n-back task (Callicott et al., 1998) to assess spatial working memory; Verbal Learning and Memory Test (Helmstaedter et al., 2001) or Verbaler Lerntest (Sturm and Willmes, 1999), and WMS-R Verbal Paired Associates subtest (Härting et al., 2000; Wechsler, 1987) to assess verbal learning and memory; WMS-R Logical Memory subtest (Härting et al., 2000; Wechsler, 1987) to assess episodic memory; WMS-R Figural Memory, Visual Reproduction, and Visual Paired Associates subtests (Härting et al., 2000; Wechsler, 1987) to assess visual learning and memory; and Trail Making Test-Part B (Reitan, 1958) and WCST (Heaton, 2003; Heaton et al., 1993) to assess executive function.

MRI Acquisition. Not applicable.

Genotyping. DNA from a proportion of participants was obtained from whole blood and genotyped on the Illumina OmniExpress array or Illumina HumanHap300 array.

Ethics/Consent All participants provided written informed consent in accordance with the relevant ethics approvals.

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PHRS — Pittsburgh High Risk Study

(Bhojraj et al., 2011; Bhojraj et al., 2009)

Recruitment. The study was conducted at the Western Psychiatric Institute and Clinic, Pittsburgh. First- or second-degree relatives of individuals diagnosed with schizophrenia and age- and gender-matched healthy comparison participants from an ongoing study at the University of Pittsburgh participated in this study. Relatives of patients with schizophrenia or schizoaffective disorder were recruited by approaching patients in the clinic and through advertisements. Controls were recruited through advertisements in the same community. The relatives and controls were included in the GENUS FHR and control groups, respectively.

Inclusion/Exclusion Criteria. Participants with an IQ<80, lifetime evidence of a psychotic disorder, exposure to antipsychotic medications or anti-depressant medications, substance use disorder within the last month, significant neurological or medical condition were excluded.

Clinical/Neuropsychological Assessment. Clinical assessments of all participants, and parental diagnoses of schizophrenia or schizoaffective disorder, used the SCID (First et al., 1995b) and were confirmed using consensus meetings led by senior diagnosticians. None of the relatives were diagnosed with psychotic or other psychiatric illnesses and none had received antipsychotic medications. In addition to the SCID, the Structured Interview for Prodromal Syndromes, including the Scale of Prodromal Symptoms, was administered (Miller et al., 2003). Current IQ was assessed using the Block Design, Matrix Reasoning, Vocabulary, and Similarities subtests from the WASI (Wechsler, 1999). Verbal fluency was assessed using the Multilingual Aphasia Examination (Benton and Hamsher, 1978) including a Phonemic Verbal Fluency task (number of words generated in 20 seconds (each) that start with the letter C, F, and L) (Reitan, 1985) and a Semantic Verbal Fluency task (categories: animals, fruits and vegetables) (Benton and Hamsher, 1978). The CPT-IP (Cornblatt et al., 1988), AX-CPT, Spatial Working Memory, Word List Memory, and Go-No-Go subtests from Cogtest (Sharma and Bilder, 2004; The Cognition Group, 2006) were used to assess attention/vigilance, attention, spatial working memory, verbal learning and memory, and executive functioning, respectively. The Penn Visual Object Learning Test (Glahn et al., 1997), the Computerized Finger Tapping Test (Coleman et al., 1997), and the Penn Emotion Recognition Test (Gur et al., 2002) from the Computerized Neurocognitive Battery (CNB; (Gur et al., 2010; Moore et al., 2015; Swagerman et al., 2016)) were used to assess visual learning, motor control, and social cognition, respectively. Further, the WCST (Heaton et al., 1993) was used to assess executive function.

MRI Acquisition. T1-weighted structural scans (TE = 5.0 ms; TR = 25 ms; Flip angle = 40°; FOV = 24 cm; Spatial resolution = 0.94 x 0.94 x 1.5 mm; matrix = 256 x 192 mm; Slice acquisition direction = coronal, AC-PC oblique) were acquired on a 1.5 Tesla GE Genesis Signa scanner using a circularly polarized head coil.

Genotyping. DNA was obtained from whole blood and genotyped on the Illumina Infinium PsychArray. Genotyping was funded by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) grant number R01MH092380 to T.L.P. supporting the GENUS Consortium.

Ethics/Consent. The study was approved by the University of Pittsburgh Institutional Review Board. All participants signed informed consent after the study was fully explained to them. For participants <18 years of age, the consent was provided by the parent or guardian, and the participants provided informed assent.

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TCD/NUIG — Trinity College Dublin and National University of Ireland, Galway
(Donohoe et al., 2009; O'Donovan et al., 2008; Walters et al., 2010; Walters et al., 2013)

Recruitment. Patients with schizophrenia were recruited from across Ireland. Comparison participants were recruited by local media advertisements. Some participants (~50%) form part of the Psychiatric Genomics Consortium Schizophrenia Working Group wave 2 dataset (PGC Schizophrenia Working Group, 2014). Some controls (~150) form part of the Cognitive Genomics Consortium wave 2 (COGENT2) dataset (Trampush et al., 2017). Some participants (~20%) form part of the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Schizophrenia Working Group dataset (van Erp et al., 2016).

Inclusion/Exclusion Criteria. Exclusion criteria were a history of head injury or neurological disease. The inclusion criteria required that participants had no history of substance abuse in the preceding 6 months based on self-report, and had no previous head injury with loss of consciousness or a history of seizures. Clinically stable patients with a DSM-IV diagnosis of schizophrenia were recruited from 5 sites across Ireland. Control participants were included only if they were aged 18 to 65 years and satisfied, based on clinical interview, the criteria of having no history of major mental health problems, intellectual disability, or a first-degree relative with a history of psychosis.

Clinical/Neuropsychological Assessment. Diagnosis was confirmed by trained psychiatrists using the SCID-I (First et al., 1995b). Additional diagnostic details and clinical sample characteristics ascertained at the time of interview included symptom severity as measured with SANS/SAPS (Andreasen, 1983, 1984) or PANSS (Kay et al., 1987), overall functioning using GAF (American Psychiatric Association, 1994), and medication dosage. Premorbid IQ was measured using the Wechsler Test of Adult Reading (Wechsler, 2001). Current IQ was measured using selected subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning) from the UK version of the WAIS-III (Wechsler, 2005). Speed of processing was assessed using the Trail Making Test**—**Part A and B (Reitan, 1958). Phonemic Verbal Fluency was assessed using the COWAT (Reitan, 1985) (number of words generated in 60 seconds that start on letter F, A and S). Attention/vigilance was measured using the 1-9 Continuous Performance Test (Gordon and Mettleman, 1987), or in a small subset using the three-letter condition of the CPT-IP (Cornblatt et al., 1988). Verbal working memory was measured using the Letter-Number Sequencing subtest from the Wechsler Memory Scale, Third Edition (WMS-III; Wechsler, 1997b) and spatial working memory using the Spatial Working Memory test from the CANTAB (Cambridge Cognition, 2003b) and a spatial n-back task (Callicott et al., 1998). Verbal learning and memory was assessed using the CVLT-II Short Form (Delis et al., 2000). Episodic memory was measured using the Logical Memory immediate and delayed tests from the WMS-III (Wechsler, 1997b). Visual learning and memory was assessed using the WMS-III Faces subtest (Wechsler, 1997b) and the CANTAB Paired Associates Learning subtest. Executive Functioning was assessed using the CANTAB Intra-Extra Dimensional Set Shifting subtest (Cambridge Cognition, 2003b) and the Sustained Attention to Response Task (Robertson et al., 1997). Finally, social cognition was measured using the Hinting Task (Versmissen et al., 2008) and Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001).

MRI Acquisition. For the subsample recruited from Trinity College Dublin, T1-weighted structural scans (TE = 3.8 ms; TR = 8.4 ms; Flip angle = 8°; FOV = 23 cm; Spatial resolution = 0.9 x 0.9 x 0.9 mm; matrix = 256 x 256 mm; Slice acquisition direction = axial) and Diffusion Tensor Imaging (TE = 52 ms; TR = 12445 ms; Flip angle = 90°; FOV = 22.4 cm; Spatial resolution = 1.75 x 1.75 x 2.2 mm; matrix = 128 x 128 mm; Slice acquisition direction = axial; number of

diffusion-encoding gradient directions = 15; number of b0 volumes = 1; b-value = 800 s/mm^2) were acquired on a 3 Tesla Philips Intera Achieva scanner at the Trinity College Institute for Neuroscience using a SENSE 8-channel head coil. For the subsample recruited from National University of Ireland Galway, T1-weighted structural scans (TE = 4.38 ms; TI = 600 ms; TR = 1140 ms; Flip angle = 15°; FOV = 23 cm; Spatial resolution = 0.45 x 0.45 x 0.9 mm; matrix = 512 x 512 mm; Slice acquisition direction = axial) were acquired on a 1.5 Tesla Siemens Magnetom Symphony scanner using a 4-channel head coil.

Genotyping. DNA from a proportion of participants was obtained from whole blood and genotyped on the Affymetrix 6.0 or Illumina HumanCore Exome arrays.

Ethics/Consent. Assessments of all patient and control participants were conducted in accordance with the relevant ethics committee approval from each participating site. All patients and controls were of Irish ancestry (4 grandparents born in Ireland), and all provided written informed consent.

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UMCU-SZ1 — University Medical Centre Utrecht, Schizophrenia study 1

(Hulshoff Pol et al., 2001; Terwisscha van Scheltinga et al., 2012; Terwisscha van Scheltinga et al., 2013a; Terwisscha van Scheltinga et al., 2013b)

Recruitment. Patients with schizophrenia or schizoaffective disorder were recruited from various outpatient and inpatient clinics; treatment setting was unrelated to age. Comparison control participants were matched with the patients for the socioeconomic status of their parents, which was expressed as the highest level of education completed by one parent. Participants form part of the Psychiatric Genomics Consortium Schizophrenia Working Group dataset (PGC Schizophrenia Working Group, 2014) and the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Schizophrenia Working Group dataset (van Erp et al., 2016).

Inclusion/Exclusion Criteria. All participants were between 16 and 70 years of age. Participants with a major medical or neurological illness, including past head trauma, hypertension, cardiac disease, diabetes mellitus, cerebrovascular disease, epilepsy, migraine, endocrine disorders, drug or alcohol dependence, or an IQ below 80 were excluded. Control participants had no history of psychiatric illness except for three participants who had a history of anxiety disorder, obsessive–compulsive disorder and adjustment disorder, respectively. None of the control participants had first-degree family members with psychotic illness.

Clinical/Neuropsychological Assessment. Clinical diagnosis was determined using the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992)) and the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978) and was assessed by two independent raters. Diagnostic consensus was achieved in the presence of a psychiatrist. The PANSS (Kay et al., 1987) and GAF (American Psychiatric Association, 1994) were used to measure symptom levels and overall functioning, respectively. Premorbid IQ was estimated using the Dutch version of the NART (Schmand et al., 1991). Current IQ was estimated with the Dutch version of the WAIS-III (Stinissen et al., 1970; Wechsler, 2000). Four out of 11 subtests of WAIS-III were used: Block Design, Comprehension, Vocabulary and Picture arrangement. Raw scores were multiplied by 11/4 to obtain an estimate of total IQ. Verbal fluency was assessed using the Multilingual Aphasia Examination (Benton and Hamsher, 1978) including a Phonemic Verbal Fluency task (number of words generated in 60 seconds that start on letter N, A and P) and a Semantic Verbal Fluency task (category: animals). Sustained visual attention and vigilance were assessed using the Continuous Performance Task-HQ (CPT A-X; Nuechterlein and Dawson, 1984)), with outcome parameters of reaction time and accuracy. Verbal learning

and memory was assessed with the CVLT (Delis et al., 1987). Episodic memory was assessed using the Logical Memory subtests from the Dutch WMS-R (Wechsler, 1987). Visual learning memory was assessed using the WMS-R Visual Reproduction subtests. Executive functioning was assessed using the Stroop test (Stroop, 1935).

MRI Acquisition. T1-weighted structural scans (TE = 4.6 ms; TR = 30 ms; Flip angle = 30°; FOV = 25.6 cm; Spatial resolution = 1.0 x 1.0 x 1.2 mm; matrix = 256 x 256 mm; Slice acquisition direction = coronal) were acquired on a 1.5 Tesla Philips NT Intera scanner using a 6-element SENSE receiver head coil.

Genotyping. DNA from a proportion of participants was obtained from whole blood and genotyped on the Illumina HumanHap550 or Illumina Infinium OmniExpressExome-8 arrays. Genotype data are available from the NIMH Repository and Genomics Resource (http://www.nimhgenetics.org).

Ethics/Consent. The study was approved by the Medical Ethical Committee of the University Medical Center Utrecht.

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UMCU-SZ2 — University Medical Centre Utrecht, Schizophrenia study 2

(Boos et al., 2013; Korver et al., 2012; Rais et al., 2012; Terwisscha van Scheltinga et al., 2013a)

Recruitment. Data pertain to baseline measures of a longitudinal study (GROUP) in the Netherlands and Belgium. In selected representative geographical areas, patients were identified through clinicians working in regional psychotic disorder services whose caseloads were screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services as either outpatients or in-patients were recruited for the study. Controls were selected through a system of random mailings to addresses in the catchment areas of the patients. Participants form part of the Psychiatric Genomics Consortium Schizophrenia Working Group dataset (PGC Schizophrenia Working Group, 2014).

Inclusion/Exclusion Criteria. Inclusion criteria for patients, siblings, and controls were: (1) age range of 16–50 years and (2) good command of the Dutch language. Patients had to meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for a non-affective psychotic disorder (American Psychiatric Association, 2000). Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree family member with a history of psychotic disorder.

Clinical/Neuropsychological Assessment. Diagnosis was assessed with the Comprehensive Assessment of Symptoms and History interview (CASH; Andreasen et al., 1992) or the Schedules for Clinical Assessment for Neuropsychiatry (SCAN) version 2.1 (Wing et al., 1990). The PANSS (Kay et al., 1987) and GAF (American Psychiatric Association, 1994) were used to measure symptom levels and overall functioning, respectively. Additionally, the Structured Interview for Schizotypy-Revised (SIS-R; Vollema and Ormel, 2000) and the CDSS (Addington et al., 1992) were administered. The cognitive assessment took between 90 and 120 min. The following subtests of the WAIS-III (Wechsler, 1997a) were assessed: Digit Symbol Coding as a measure of processing speed; Arithmetic as a measure of working memory; Information as a measure of acquired knowledge; and Block Design as a measure of reasoning and problem solving. Together, these 3 subtests were used to estimate Current IQ. Sustained visual attention and vigilance were assessed using the Continuous Performance Task-H-Q, a variation of the CPT A-X by Nuechterlein and Dawson, 1984), with outcome parameters of reaction time and accuracy. Verbal learning was assessed using the Auditory Verbal Learning Test (Brand and Jolles, 1985), with

outcome parameters of immediate recall (15-word list, three learning trials) and retention rate after 20 min. Set shifting ability was assessed using the Response Shifting Task, a modified version of the Competing Programs Task (Bilder et al., 1992; Nolan et al., 2004), with outcome parameters of reaction time and accuracy. The Degraded Facial Affect Recognition Task (van 't Wout et al., 2004) was used to assess recognition of neutral, happy, fearful and angry emotions. The Benton Face Recognition Task (Benton et al., 1983) was used to assess visuospatial discrimination of unfamiliar faces. The Hinting Task (Versmissen et al., 2008) was used to assess theory of mind.

MRI Acquisition. T1-weighted structural scans (TE = 4.6 ms; TR = 30 ms; Flip angle = 30°; FOV = 25.6 cm/70%; Spatial resolution = 1.0 x 1.0 x 1.2 mm; matrix = 256 x 256 mm; Slice acquisition direction = coronal) and Diffusion Tensor Imaging (TE = 88 ms, TR = 9822 ms; Flip angle = 90°; FOV = 24 cm; Spatial resolution = 2.0 x 2.0 x 2.0 mm; matrix = 128 x 96 mm; Slice acquisition direction = axial; number of diffusion-encoding gradient directions = 32; number of b0 volumes = 8; b-value = 1000 s/mm^2) were acquired on a 1.5 Tesla Philips Achieva scanner using a 6-element SENSE receiver head coil.

Genotyping. DNA from a proportion of participants was obtained from whole blood and genotyped on the Affymetrix 6.0, Illumina HumanHap550, or Illumina Infinium OmniExpressExome-8 arrays. Genotype data are available from the NIMH Repository and Genomics Resource (http://www.nimhgenetics.org).

Ethics/Consent. The study protocol was approved centrally by the Ethical Review Board of the University Medical Center Utrecht and subsequently by local review boards of each participating institute. All participants gave written informed consent in accordance with the committee's guidelines.

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ZHH — Zucker Hillside Hospital

(Lencz et al., 2014)

Recruitment. Healthy participants from the New York metropolitan area were recruited through advertisements, word of mouth, referrals, and study registries. Participants form part of the Cognitive Genomics Consortium wave 1 (COGENT1) dataset (Lencz et al., 2014).

Inclusion/Exclusion Criteria. Participants had no history of a current or past DSM-IV axis I major mood or psychotic disorder as assessed by structured diagnostic interview (First et al., 1995a). Other exclusion criteria included: intellectual or learning disability; significant medical illness that could affect brain structure; or lifetime exposure to psychiatric medication.

Clinical/Neuropsychological Assessment. Premorbid IQ was estimated using the WRAT-3 (Wilkinson, 1993). Further cognitive testing was performed using the MATRICS Consensus Cognitive Battery (MCCB) (Kern et al., 2008; Nuechterlein et al., 2008). Speed of processing was assessed using the BACS Symbol Coding subtest (Keefe et al., 2008), the WAIS-R Digit Symbol subtest (Wechsler, 1981), Trail Making Test**—**Part A and B (Reitan, 1958), Semantic Verbal Fluency (MCCB Category Fluency; category: animals) (Kern et al., 2008; Nuechterlein et al., 2008), and COWAT Phonemic Verbal Fluency (letters F, A, S) (Benton and Hamsher, 1978; Reitan, 1985); attention using the CPT-IP (Cornblatt et al., 1988); working memory using the WMS-III Spatial Span subtest (Wechsler, 1997b), University of Maryland Letter-Number Span (Gold et al., 1997), and the WAIS-R Digit Span subtest (Wechsler, 1981); verbal learning using the HVLT-R (Brandt and Benedict, 1997)); visual learning using the BVMT-R (Benedict, 1997); reasoning and problem solving using the WCST (Heaton et al., 1993) and NAB Mazes (Stern and White, 2003); and social cognition using the MSCEIT (Mayer et al., 2003).

MRI Acquisition. Not applicable.

Genotyping. DNA obtained from whole blood was genotyped on the Illumina OmniExpress array.

Ethics/Consent. This study was approved by the Institutional Review Board of the North Shore – Long Island Jewish Health System. Written informed consent was obtained from all participants.

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Supplementary Table 1. Description of the GENUS Consortium Sample Collection (subset with ge

Acronym	*Sample*	*Site*
CAMH	Centre for Addiction and Mental Health	Toronto, Canada
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness	Multi-site, USA
CIDAR/VA	Longwood Study of Psychosis consortium / VA Healthcare System	Boston, USA
COGS-UK	Cognition and Genetics in Schizophrenia & Bipolar Disorder	Cardiff, UK
GAP	Genetics and Psychosis First-Episode Study	London, UK
IMH-SIGNRP	Institute of Mental Health - Singapore Imaging Genetics and Neuropsychological Research in Psychosis	Singapore
IMH-STCRP	Institute of Mental Health - Singapore Translational and Clinical Research in Psychosis	Singapore
KCL-MFS	King's College London - Maudsley Family Study	London, UK
KCL-MTS	King's College London - Maudsley Twin Study	London, UK
L&R	Language and Risk in Schizophrenia	Boston, USA
MCIC	Mind Clinical Imaging Consortium	Multi-site, USA
MGH	Massachusetts General Hospital	Boston, USA
NEFS	New England Family Study	Boston, USA
PAGES	Phenomics and Genomics Sample	Munich, Germany
PHRS	Pittsburgh High Risk Study	Pittsburgh, USA
TCD/NUIG	Trinity College Dublin/ National University of Ireland, Galway	Multi-site, Ireland
UMCU-SZ1	University Medical Center Utrecht - Schizophrenia Study 1	Utrecht, Netherlands
UMCU-SZ2	University Medical Center Utrecht - Schizophrenia Study 2	Utrecht, Netherlands
ZHH	Zucker Hillside Hospital	New York, USA
Totals		

Data in this table are based on genotyped participants only.
All samples that acquired T1 MRI scans also acquired DTI scans except the PHRS and UMCU-SZ1
Population ancestry determined from genetic data (where available) or self report.
Eur = European-derived ancestry; FHR = familial high-risk.

notype data).

GWAS Array	*Neuropsychological data*				
	Patients (N)	*Controls (N)*	*FHR (N)*	*Male (%)*	*Eur (%)*
Illumina OmniExpress	90	107	0	54.8	76.1
Affymetrix 500K; Perlegen's custom 164K chip	741	0	0	73.6	54.7
Illumina OmniExpress	74	106	5	68.1	60.0
Illumina Infinium OmniExpressExome-8	529	0	0	60.7	97.3
Illumina HumanCore-24 Exome BeadChip	136	127	0	59.3	46.8
Illumina Human OmniZhongHua-8; Illumina Human1M-Duo; Affymetrix 6.0	104	3	0	51.4	0
Illumina HumanOmniZhongHua-8 BeadChip	419	956	0	53.0	0
Affymetrix 6.0	10	12	19	56.1	95.1
Affymetrix 6.0	18	65	5	35.2	100
Illumina Infinium PsychArray	0	30	41	36.6	74.7
Illumina HumanOmni1-Quad BeadChip	80	66	0	69.9	75.3
Illumina Infinium PsychArray	423	0	0	72.1	68.8
Illumina Infinium PsychArray	75	125	24	47.3	86.2
Illumina OmniExpress; Illumina HumanHap300	210	1,341	0	50.0	99.6
Illumina Infinium PsychArray	0	18	43	47.5	41.0
Affymetrix 6.0; Illumina HumanCore Exome	826	165	0	63.3	99.9
Illumina HumanHap550; Illumina Infinium OmniExpressExome-8	50	96	0	68.5	98.6
Illumina HumanHap550; Affymetrix 6.0; Illumina Infinium OmniExpressExome-8	189	115	168	58.7	97.5
Illumina OmniExpress	0	219	0	49.3	100
	3,974	3,551	305	56.6	72.2

y.
l scans except the PHRS and UMCU-SZ1
available) or self report.
.

T1-weighted structural MRI data				
Patients (N)	***Controls (N)***	***FHR (N)***	***Male (%)***	***Eur (%)***
89	115	0	55.4	76.5
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66	100	5	67.3	60.2
---	---	---	---	---
67	35	0	60.8	37.3
159	3	0	59.9	0
---	---	---	---	---
---	---	---	---	---
7	20	3	50.0	100
0	31	44	36.0	76.0
82	68	0	69.3	74.7
44	110	0	62.3	72.7
66	126	14	46.6	84.0
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0	11	33	45.5	45.5
134	189	0	54.5	99.7
74	101	0	69.7	98.3
154	103	151	58.8	97.6
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942	1,012	250	56.6	71.0

Supplementary Table 2. Clinical and demographic characteristics of the GENUS Consortium Sam

	Patients	
	N	**Mean ± SD (Range)**
Age (years)	4,101	39.8±12.1 (13-82)
Education Level (years)	3,740	12.2±2.5 (1-22)
Premorbid IQ	2,644	96.2±15.7 (44-145)
Current IQ	1,478	93.9±18.4 (47-155)
Illness Duration (years)	3,296	15.0±11.5 (<1-58)
Age at Onset (years)	3,278	24.5±8.3 (1-62)
Global Assessment of Functioning	1,396	60.4±15.7 (20-100)
PANSS Positive symptoms	2,507	16.7±7.3 (7-47)
PANSS Negative Symptoms	2,504	17.1±7.2 (7-42)
PANSS General Symptoms	2,510	32.7±12.0 (0-93)
SAPS Positive Symptoms	1,149	9.1±13.3 (0-121)
SANS Negative Symptoms	887	24.4±20.3 (0-103)
Antipsychotic dose – current CPZEQ	2,727	379.9±414.8 (0-5,000)
Antipsychotic dose – lifetime average CPZEQ	1,355	334.6±360.8 (0-3,125)
	N	**%**
Sex (male / female; % male)	2,721 / 1,381	66.3
Antipsychotic medication		
Atypical	1,691	48.2
Typical	350	10.0
Both Typical and Atypical	517	14.7
Naïve / None	375	10.7
Unknown Class	236	6.7
No information	338	9.6
Diagnosis		
Schizophrenia	3,321	81.0
Schizoaffective Disorder	340	8.3
Schizophreniform Disorder	67	1.6
Bipolar Psychosis	207	5.1
Other Psychosis	150	3.7
Psychosis Unknown Type	17	0.4
Ethnicity		
European	2,835	69.1
East Asian	624	15.2
African	454	11.1
American (Predominantly Latino)	138	3.4
South Asian	42	1
Mixed	11	0.3
Handedness (right / other; % right-handed)	1,508 / 151	90.1

Data in this table are based on genotyped participants only. CPZEQ = chlorpromazine 100 mg equivalent; df = deg

ple Collection (subset with genotype data).

Controls		Familial High Risk		*Statistic*	*df*
N	**Mean ± SD (Range)**	**N**	**Mean ± SD (Range)**		
3,851	40.3±16.1 (8-86)	306	27.2±8.9 (10-64)	F = 125.2	2, 8255
3,200	13.1±2.5 (6-26)	305	13.0±3.2 (3-20)	F = 101.0	2, 7242
1,060	107.7±10.8 (62-145)	70	104.4±16.8 (45-134)	F = 242.2	2, 3771
2,229	113.8±14.8 (71-161)	287	104.4±15.4 (58-152)	F = 668.9	2, 3991
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N	**%**	**N**	**%**		
1,935 / 1,916	50.2	133 / 173	43.5	χ^2 = 238.5	2
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				χ^2 = 451.2	10
2,703	70.2	264	86.3	---	---
982	25.5	1	0.3	---	---
111	2.9	35	11.4	---	---
28	0.7	3	1	---	---
26	0.7	3	1	---	---
1	0.1	0	0	---	---
1,816 / 194	90.3	272 / 21	92.8	χ^2 = 1.9	2

p
$<1x10^{-10}$
$<1x10^{-10}$
$<1x10^{-10}$
$<1x10^{-10}$

$<1x10^{-10}$

$<1x10^{-10}$

0.38

Supplementary Table 3. Sample size by neuropsychological test across GENUS Consortium samp

Domain	Attention / Processing Speed						
	Digit Symbol Coding			TMT-A	Verbal Fluency		
	BACS Symbol Coding*	WAIS Digit Symbol-Coding	RBANS Symbol Coding	TMT-A*	Semantic/ Category Fluency - Animals*	Semantic/ Category Fluency - Any	Phonemic/ Letter Fluency
CAMH			x	x	RBANS		COWAT
CATIE					x	x	COWAT
CIDAR/VA	x			x	MCCB	x	
COGS-UK	x			x	MCCB	x	
GAP		III		x	x	x	COWAT
IMH-SIGNRP	x					BACS	COWAT
IMH-STCRP	x				BACS	BACS	
KCL-MFS		R		x			
KCL-MTS		III-UK		x	x	x	COWAT
L&R	x			x	MCCB	x	
MCIC				x	D-KEFS	D-KEFS	D-KEFS
MGH		III			x	x	COWAT
NEFS		R					COWAT
PAGES		R-DE		x	x	x	x
PHRS					MAE	MAE	MAE
TCD/ NUIG				x			COWAT
UMCU-SZ1					MAE	MAE	MAE
UMCU-SZ2		III-NL					
ZHH	x			x	MCCB	x	COWAT
N Patients	1,470	1,909	116	1,549	3,139	3,414	2,626
N Controls	1,405	2,156	114	1,116	2,445	2,611	1,647
N FHR	50	346	0	196	247	247	229

N Total	2,925	4,411	230	2,861	5,831	6,272	4,502

*MATRICS test.

References for all neuropsychological tests are provided in the Supplemental Materials.

Abbreviations:128-P, 128-C = 128-card paper, computerized version; 64-P, 64-C = 64-card paper, computerized ve
Cognition in Schizophrenia; BVMT-R= Brief Visuospatial Memory Test-Revised; BVRT = Benton Visual Retention T
CMS = Children's Memory Scale; CNB = Computerized Neurocognitive Battery; CPT(-IP) = Continuous Performanc
version; D-KEFS = Delis–Kaplan Executive Function System; FHR = Familial High Risk; FigMem = Figural Memory
of Line Orientation; NAB = Neuropsychological Assessment Battery; NL = Dutch version; PAL = Paired Associates
Neuropsychological Status; RST = Response Shifting Task; RVIP = Rapid Visual Information Processing; SART = S
Cambridge; SWM = Spatial Working Memory; TOL = Tower of London; TMT-A, B = Trail Making Test Part A, B; UK
Paired Associates; VisRep = Visual Reproduction; VLMT = Verbal Learning and Memory Test; VLT = Verbaler Lern
Wechsler Intelligence Scale for Children; WMS = Wechsler Memory Scale; WAIS = Wechsler Adult Intelligence Sca

les (genotyped + ungenotyped).

Attention / Vigilance							
Continuous Performance							
CPT-IP*	ACPT	CANTAB RVIP	3-7 CPT	A-X CPT	1-9 CPT	H-Q CPT	X-Y CPT
x							
x	x						
x							
x							
			x				
			x				
x	x						
x							
	x						
			x				
x				x			
x					x		x
						x	
						x	
x							
2,337	122	44	201	0	83	246	85
1,410	256	74	411	22	60	198	42
119	83	21	0	66	0	211	0

3,866	461	139	612	88	143	655	127

rd paper, computerized version; ACPT = Auditory CPT; AVLT = Auditory Verbal Learning Test; BACS = Brief Assessment of
Benton Visual Retention Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; CFT = Complex Figure Tes
) = Continuous Performance Test (Identical Pairs); CVLT(-SF) = California Verbal Learning Test (Short Form); DE = German
FigMem = Figural Memory; HVLT = Hopkins Verbal Learning Test; IDED = Intra-Extra Dimensional Set Shifting; JOLO = Judgm
PAL = Paired Associates Learning; RAN = Rapid Automatized Naming; RBANS = Repeatable Battery for the Assessment of
ation Processing; SART = Sustained Attention to Response Task; SDRT = Spatial Delayed Response Task; SOC = Stockings o
Making Test Part A, B; UK = British version; UMD = University of Maryland; VisMemSpan = Visual Memory Span; VisPA = Vis
Test; VLT = Verbaler Lern Test; VOLT = Visual Object Learning Test; WASI = Wechsler Abbreviated Scale of Intelligence; WI
nsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test

Working Memory – verbal						Working Memory – n	
Letter-Number Span		Other				Spatial Span	
UMD Letter-Number Span*	WAIS Letter-Number Sequencing	RBANS Digit Span	WAIS/WMS Digit Span	BACS Digit Sequencing	WAIS/WMS Arithmetic	WMS-III Spatial Span*	WMS-R-UK Visual Memory Span
x		x					
x							
x						x	
x						x	
			III			x	
					x		
					x		
			R		R		
	III-UK		III-UK		III-UK		x
x						x	
	III						
	III		III		III		
			R				
			R-DE		R-DE		
	III						
					III-NL		
x			R			x	
1,734	1,168	565	115	637	1,001	1,024	73
468	616	1,075	141	1,889	1,752	429	181
49	30	0	0	114	314	50	26

2,251	1,814	1,640	256	2,640	3,067	1,503	280

BACS = Brief Assessment of
ery; CFT = Complex Figure Test;
(Short Form); DE = German
nal Set Shifting; JOLO = Judgment
Battery for the Assessment of
onse Task; SOC = Stockings of
ual Memory Span; VisPA = Visual
viated Scale of Intelligence; WISC =

Working Memory – non-verbal				Verbal Le			
Other				Word List Learning			
SDRT	CANTAB SWM	n-back	Cogtest SWM	HVLT*	CVLT	CVLT-SF	BACS
x				x			
				R			
				R			
		x					
							x
							x
		x					
		x					
				R			
				R			
					x		
					x / II		
			x				
		x	x			x	
					I-NL		
			x	R			
656	792	268	0	1,737	562	100	558
0	448	433	48	426	227	36	1,074
0	21	0	68	50	32	0	0

656	1,261	701	116	2,213	821	136	1,632

Verbal Learning & Memory

Word List Learning				Story Recall			Other
RBANS	AVLT	Cogtest WLMT	VLMT	WMS Logical Memory	CMS Logical Memory	RBANS Stories	WMS Verbal Paired Associates
x						x	
				III	x		
				III			
				R			R
				R-UK			R-UK
				III			
				III			
				R/ III			
			x	R-DE			R-DE
		x					
				III			
	x						
116	213	0	206	1,330	6	116	388
141	142	49	426	863	13	141	705
0	231	71	0	82	0	0	177

257	586	120	632	2,275	19	257	1,270

Visual Learning & Memory							
BVMT-R*	**RBANS Figure Recall**	**WMS Figural Memory**	**WMS Visual Reproduction**	**WMS Faces**	**BVRT**	**Rey CFT**	**WMS Visual Paired Associates**
		x					
x							
x							
			III				
			R				
			R-UK				R-UK
x							
			R	III	x		
				III		x	
		R-DE	R-DE				R-DE
				III			
			R-NL				
x							
897	115	206	655	712	112	32	279
328	140	427	950	458	95	116	608
48	0	0	228	25	0	31	26

1,273	255	633	1,833	1,195	207	179	913

		Reasoning / Problem					
		Planning					
CANTAB PAL	CNB VOLT	NAB Mazes*	WISC-III Mazes	BACS TOL	TOL	TOL-DE	CANTAB SOC
			x				
		x					
		x					
							x
				x			
				x			
		x					
					x		
						x	
	x						
x							
		x					
		x					
608	0	903	715	551	93	202	109
242	50	328	0	1,075	84	427	117
0	56	50	0	0	0	0	0

850	106	1,281	715	1,626	177	629	226

Reasoning / Problem Solving

Set Shifting + Planning	Cognitive Flexibility / Set Shifting			Response Inhibition			
TMT-B	WCST 64-Card	WCST 128-Card	CANTAB IDED	Stroop	RST	SART	Cogtest Go-No-Go
x				x			
	64-C						
	64-C						
x							
	64-P						
x			x				
x			x				
	64-C						
x							
	64-C	128-C					
		128-P		x			
x		128-C					
		128-P					x
x			x			x	
				x			
					x		
x	128-P			x			
836	1,001	375	522	201	194	513	0
1,408	132	703	285	404	129	182	49
145	57	77	21	0	209	0	70

2,389	1,190	1,155	828	605	532	695	119

Visuo-spatial Ability						
WAIS Block Design	**WAIS Matrix Reasoning**	**WAIS Object Assembly**	**WAIS Picture Arrangement**	**WAIS Picture Completion**	**RBANS JOLO**	**Benton JOLO**
					x	
WASI						
III	III					
	WASI					x
R		R	R	R		
III-UK		III-UK	III-UK	III-UK		
WASI						
III						
III	III	III	III	III		
R			R			
R-DE		R-DE	R-DE	R-DE		
III-R-UK	III-R-UK					
III-R-NL			III-R-NL			
III-NL						
2,260	1,149	311	456	330	116	417
2,744	1,385	1,340	1,607	1,347	141	1,012
522	0	0	33	0	0	0

5,526	2,534	1,651	2,096	1,677	257	1,429

		Verbal Ability				
RBANS Figure Copy	**Rey CFT Copy**	**WAIS Vocabulary**	**WAIS Comprehension**	**WAIS Information**	**WAIS Similarities**	**D-KEFS Proverbs**
x						
		WASI				x
				III		
		R	R	R	R	
		III-UK	III-UK	III-UK	III-UK	
		WASI				x
		III			III	
		III	III	III	III	
	x	R	R	R		
		R-DE	R-DE	R-DE	R-DE	
		III-R-UK			III-R-UK	
		III-R-NL	III-R-NL			
				III-NL		
116	32	1,754	456	1,027	1,140	66
140	116	2,425	1,607	1,645	1,935	128
0	33	285	33	233	253	48

256	181	4,464	2,096	2,905	3,328	242