Supplementary Methods

Participants

The two subject groups consisted of children with genetically confirmed 22q11.2DS, and an age, gender, ethnicity, and IQ matched group of subjects with idiopathic developmental disability (DD). The characteristics of the groups are presented in Supplementary Table 1.

FISH

Blood was collected from all subjects. The presence and extent of a 22q11.2 interstitial microdeletion were verified by two–color fluorescent in situ hybridization (FISH), with cosmid probes DO832 (COMT) and N48C12 (D22S264) specific for the proximal and distal deletion regions, respectively.

Genotyping

DNA was extracted from blood leukocytes by standard techniques (Puregene, Gentra, Minneapolis).

COMT: Three single–nucleotide polymorphisms (SNPs) were genotyped by PCR and restriction digestion. The Val108/158–Met polymorphism was determined by NlaIII digestion (NlaIII+: Met/COMT\textsuperscript{h}, NlaIII–: Val/COMT\textsuperscript{h}), SNP ID (rs)2097603 by HinDIII (HinDIII+: G, HinDIII–: A), and rs165599 by MspI (MspI+: G, MspI–: A); rs737865 (C/T) was genotyped by Pyrosequencing (Biotage AB, Uppsala, Sweden) as described.

PRODH: SNP rs450046 (PRODH2*1766) and rs372055 (PRODH2*1945) were genotyped by PCR and restriction digestion (rs450046 NciI+: G, Nci–: A; rs372055 PvuII+: C, PvuII–).
Psychiatric Evaluation

Psychiatric evaluation of psychotic symptoms was conducted by using a semi-structured interview, the Psychotic Disorders Supplement of the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime (K–SADS–PL). Subjects above the age of 18 years were also evaluated with the Structured Clinical Interview for DSM–IV Diagnoses (SCID). The evaluation was based on interviews with the child and his parents by a board certified child and adolescent psychiatrist followed by a consensus meeting of the principal investigator (A.L.R.) and the raters. The child psychiatrist also completed the Brief Psychiatric Rating Scale (BPRS), which is a widely used clinician-rating instrument consisting of 18 items and yielding a continuous measure of severity of psychotic symptoms. Although the scale was originally developed to be used in adults, it has been extensively used to evaluate psychosis in children and adolescents. In addition, we calculated a schizophrenia subscale score of the BPRS. This subscale excludes items not directly related to psychosis or schizophrenia. The items excluded were somatic concern, anxiety, guilt feelings, tension, and depressive mood. The same group differences were obtained when analyses were repeated with a schizophrenia subscale score of the BPRS that excluded items not directly related to psychosis or schizophrenia.

Cognitive Assessment

Cognitive assessment was conducted using the Wechsler Intelligence Scale for Children, 3rd edition (WISC III) for subjects 17 years and younger and the Wechsler Adult Intelligence Scale, 3rd edition (WAIS III) for subjects older than 17 years.
Language was assessed using the *Clinical Evaluation of Language Fundamentals–III*\(^1\). The tool is widely used for the identification, diagnosis, and follow–up evaluation of language disorders in school–age children and young adults. It yields receptive, expressive and total language composite scores. Each of the scores is transformed to standardized scores, with means of 100 and SD of 15, based on American population norms by age. This test has been widely used in studies of children with a variety of developmental disabilities, including 22q11.2DS\(^{14–16}\).

**MRI Protocol**

MR images were acquired with a GE–Signa 1.5 T scanner (General Electric, Milwaukee, WI) located at Stanford University. The semiautomated image–processing procedure has been described previously\(^17\). Briefly, image processing was conducted with the program *BrainImage* v5.x running on an Apple Macintosh G4 or G5 computer. Data processing steps included removal of non–brain tissues from the images, correction of equipment–related image artifacts, separation (segmentation) of tissue components (gray, white, and CSF), and positional normalization of the brain volume to make it parallel to the plane defined by the anterior commissure and the posterior commissure. For the present analysis, the prefrontal cortex was defined as all frontal cortical gray matter lying anterior to a coronal plane intersecting the most anterior point of the genu of the corpus callosum\(^{18, 19}\).

References for Supplementary Methods