The Genetic and Environmental Determinants of the Association Between Brain Abnormalities and Schizophrenia: The Schizophrenia Twins and Relatives Consortium

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Background: Structural brain abnormalities are consistently found in schizophrenia (Sz) and have been associated with the familial risk for the disorder. We aim to define the relative contributions of genetic and nongenetic factors to the association between structural brain abnormalities and Sz in a uniquely powered cohort (Schizophrenia Twins and Relatives consortium).

Methods: An international multicenter magnetic resonance imaging collaboration was set up to pool magnetic resonance imaging scans from twin pairs in Utrecht (The Netherlands), Helsinki (Finland), London (United Kingdom), and Jena (Germany). A sample of 684 subjects took part, consisting of monozygotic twins ($n = 410$, with 51 patients from concordant and 52 from discordant pairs) and dizygotic twins ($n = 274$, with 39 patients from discordant pairs). The additive genetic, common, and unique environmental contributions to the association between brain volumes and risk for Sz were estimated by structural equation modeling.

Results: The heritabilities of most brain volumes were significant and ranged between 52% (temporal cortical gray matter) and 76% (cerebrum). Heritability of cerebral gray matter did not reach significance (34%). Significant phenotypic correlations were found between Sz and reduced volumes of the cerebrum (−.22 [−.30/−.14]) and white matter (−.17 [−.25/−.09]) and increased volume of the third ventricle (.18 [.08/.28]). These were predominantly due to overlapping genetic effects (77%, 94%, and 83%, respectively).

Conclusions: Some of the genes that transmit the risk for Sz also influence cerebral (white matter) volume.

Key Words: Brain volumes, multicenter, phenotypic correlation, schizophrenia, sMRI, twins

Although the causes of schizophrenia (Sz) are not completely understood, the importance of genetic factors has been firmly established by family, twin, and adoption studies. There is evidence for a substantial genetic contribution to the etiology of Sz, with heritability estimates up to 85% (1,2). Over the last decade a large number of linkage and (genome-wide) association studies have been carried out (3–5). The genes thus far identified only explain a small part of the genetic risk for Sz, although many seem to be involved in neurodevelopmental processes (6–8). This suggests that some of the genetic risk leading to the development of Sz is expressed as abnormal brain development.

In fact, abnormal brain structure is one of the most robust biological features of Sz (9). Volume loss in the prefrontal lobes, thalamus, superior temporal cortex, and hippocampus have consistently been demonstrated with in vivo and postmortem approaches (10). It is well-known that brain volume (BV) is highly heritable (11,12) and that the brain abnormalities found in Sz cosegregate with the illness within families (13,14). Furthermore, twin probands have smaller whole BVs than their nonaffected co-twins, who in turn have smaller brains than healthy twins (15–17). Hulshoff Pol *et al.* (18) showed that smaller white matter volume reflects the expression of genetic risk, whereas less gray matter is related to environmental risk factors. Thus, family and twin studies to date suggest that some of the brain abnormalities in Sz can be attributed to the genes conferring risk for this disorder. Although several twin-studies have tried to quantify the relative contribution of genetic and nongenetic factors to these brain abnormalities, these studies have all been small (due to recruitment challenges) and lacked power, leading to unreliable estimates. Furthermore, for a phenotype or endophenotype to be useful in the search for disease-related genes, it should not only be heritable but also share genetic variance with the risk for the disorder. Few studies have tested for such pleiotropic effects. The STAR (Schizophrenia Twins and Relatives) consortium was established to address these methodological problems, combining brain imaging data from most of the available twin samples with Sz.

Although the need to pool twin samples to gain sufficient statistical power is not disputed, it is a great challenge to combine struc-

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tural magnetic resonance imaging (MRI) data, given the variability of magnetic resonance scanners and acquisition protocols between sites. The ADNI (Alzheimer's Disease Neuroimaging Initiative) (19) and BIRN (Biomedical Informatics Research Network) studies (20,21) developed useful recommendations on how best to conduct multicenter imaging protocols; however, in the present multicenter study, tuning of the MRI acquisition protocols was not possible because scans of the twin pairs were already acquired. Therefore, a group of calibration subjects was scanned at all participating research sites, with the same acquisition protocols the twins were scanned with. The image processing pipeline algorithm was optimized by tuning two calibration factors that separated gray matter, white matter, and cerebrospinal fluid. This resulted in comparable between-site volumes for whole brain, cerebral gray and white matter volume, cerebellum, and third and lateral ventricles across most sites (22) (see also Methods and Materials). Consequently, we are confident that using the calibration factors from this study in the processing of the MRI twin data resulted in a reliable and unique powered sample. We investigated the relative contribution of genetic and environmental influences on the association between Sz liability and BV.

Methods and Materials

Subjects

The STAR consortium pooled all twin samples with MRI brain scans, collected at the Institute of Psychiatry, London (United Kingdom), University of Helsinki, Helsinki (Finland, in collaboration with University of California, Los Angeles), University of Jena, Jena (Germany), Universitätskliniek Heidelberg, Heidelberg (Germany), and the University Medical Center Utrecht, Utrecht (UMCU, The Netherlands), to increase power for variance component analyses. All available MRI scans were collated within the Department of Psychiatry at the UMCU and processed with our processing pipeline (see following). Previously a calibration and data compatibility study concluded that the Heidelberg scans could not be reliably pooled with the other sites, due to low interscanner reliability (intraclass coefficients) of the gray and white matter volumes (22).

High-quality MRI scans were available for 684 individuals, including 142 patients with Sz and 542 unaffected individuals (cotwins and control twins). Mean age in the total sample was 37.97 years (SD = 11.31). Table 1 lists the numbers of included individuals as a function of disease state, site, age, and gender.

Information on recruitment and psychiatric assessment for each site is described in Supplement 1.

MRI Processing

Scans were acquired on Philips (Utrecht, The Netherlands; Jena, Germany), GE (London, United Kingdom), and Siemens (Munich, Germany) systems. Differences in scan acquisition between sites concerned, among others, scan orientation (coronal or sagittal) and voxel dimensions (see Table S1 in Supplement 1). The London twins were scanned at St. Georges Hospital ($n = 78$) and at the Maudsley hospital ($n = 54$) on identical 1.5-T GE Signa scanners with slightly different acquisition protocols (16). Six twins were scanned on both scanners. Intraclass correlation coefficient (ICC) estimates ranged from .84 (cerebral gray matter) to .95 (lateral ventricles).

Image processing of the brain scans from Utrecht, London, and Jena was done on the neuroimaging computer network of the Department of Psychiatry in Utrecht. The reproducibility of the segmentation process on scans from the Utrecht scanner was established with ICC (23) and were .96 or higher for all structures (24–26). The T1-weighted images were first put into Talairach orientation (no scaling) (27). If a T2-weighted image was available (Utrecht and London), an intracranial volume was automatically segmented from this image. After registration to the T1-weighted image with a mutual information maximization algorithm (28), this segment served as a mask for further segmentation steps. If no T2-weighted image was available, an intracranial mask was manually segmented from the T1-weighted image.

The T1-weighted images were corrected for scanner radiofrequency-field nonuniformity (29). Total brain segmentations were done automatically, with mathematical morphology operations, on the basis of thresholds obtained from the steepest slope of the gray matter peak in intensity histograms of the intracranial region (i.e., the cerebrospinal fluid/gray matter separation threshold is the position of the steepest slope multiplied by a calibrated factor [.73 for scans from all sites]). This has been validated before (22,25).

Cerebellum and lateral and third ventricular segmentations were carried out semi-automatically on the basis of histogram analyses followed by mathematical morphology operations on the T1-weighted image. Anatomic knowledge-based selection principles were used for these segmentations. All segments were checked and manually corrected if necessary.

Separation of cerebral gray and white matter was done by applying a single threshold to the voxels of the total brain in the T1-weighted image. For each image, the threshold was obtained automatically from the T1-weighted intensity histogram (25). We have previously shown (25) that a scaling factor has to be calibrated, because of the dependence of the shapes of the gray and white matter distributions on the acquisition parameters. It was calculated for Utrecht scans on the basis of a comparison in 80 scans, where the gray/white separation had been determined manually twice by three raters ($f_{gw} = .960$). For scans from London and Jena, the threshold factors for gray/white separation were optimized (22) (London: $f_{gw} = .980$; Jena: $f_{gw} = .970$).

Table 1. Number of Twins, Mean Age, and Gender Distribution of the Samples/Site

	Helsinki			Jena			London			Utrecht		
	n	Age (yrs)	Gender (F/M)	*n*	Age (yrs)	Gender (F/M)	*n*	Age (yrs)	Gender (F/M)	*n*	Age (yrs)	Gender (F/M)
MZ-Conc	13	42.31 (8.44)	6/7				38	35.26 (9.13)	9/29			
MZ-Disc Pt	14	47.93 (3.63)	8/6	11	34.46 (11.07)	6/5	14	30.71 (10.86)	4/10	13	37.52 (11.18)	6/7
Co-Twin	15	48.20 (5.36)	9/6	11	34.45 (11.07)	6/5	17	32.51 (12.92)	7/10	13	37.55 (11.15)	6/7
MZ-HC	48	47.77 (3.48)	22/26	16	34.98 (12.62)	8/8	53	36.43 (10.13)	20/33	134	33.99 (10.93)	66/68
DZ-Disc Pt	23	47.43 (5.03)	11/12				3	43.88 (17.24)	2/1	13	35.38 (11.04)	6/7
Co-Twin	23	48.30 (5.57)	12/11				3	43.88 (17.24)	2/1	13	35.23 (10.58)	6/7
DZ-HC	50	49.32 (4.68)	29/21				4	37.00 (13.86)	0/4	142	32.66 (10.35)	81/61

$N = 684$. Age given in years (SD).

Conc, concordant; Disc, discordant; DZ, dizygotic; F, female; HC, healthy control subjects; M, male; MZ, monozygotic; Pt, patient.