Cortical Mapping of Genotype–Phenotype Relationships in Schizophrenia

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Abstract: Although schizophrenia is highly heritable, the search for susceptibility genes has been challenging. The "endophenotype" approach is an alternative method for measuring phenotypic variation that may make it easier to identify susceptibility genes in the context of complexly inherited traits. Neuroimaging methods in particular offer a powerful way to bridge the neurobiology of genes and behavior. Such investigations may be further empowered by complementary strategies involving chromosomal abnormalities associated with schizophrenia, which can help to localize causative genes and better understand the genetic complexity of the illness. Here, we illustrate our use of these convergent approaches, with a focus on neuroimaging studies using novel computational brain mapping algorithms, to investigate genetic influences on brain structure in the development of psychosis. These studies provide compelling evidence that specific genetic loci suspected to predispose to schizophrenia may affect quantitative variation in neural indicators underlying the neurobehavioral phenotype, and illustrate how genetic-neuroimaging paradigms can improve our understanding of the pathogenesis of this highly disabling mental illness. *Hum Brain Mapp 28:519–532, 2007.*

Key words: psychosis; brain mapping; genetic; neuroanatomy; chromosome 22q11.2; velocardiofacial syndrome; twin study; DISC1

INTRODUCTION

Schizophrenia is one of the most chronic and debilitating of psychiatric syndromes and, with a lifetime prevalence of about 1%, it represents a major public health concern. Despite the very high heritability for this disorder [~80–85%; Cardno et al., 1999; McGuffin et al. 1984], the search for schizophrenia susceptibility genes has been slow to

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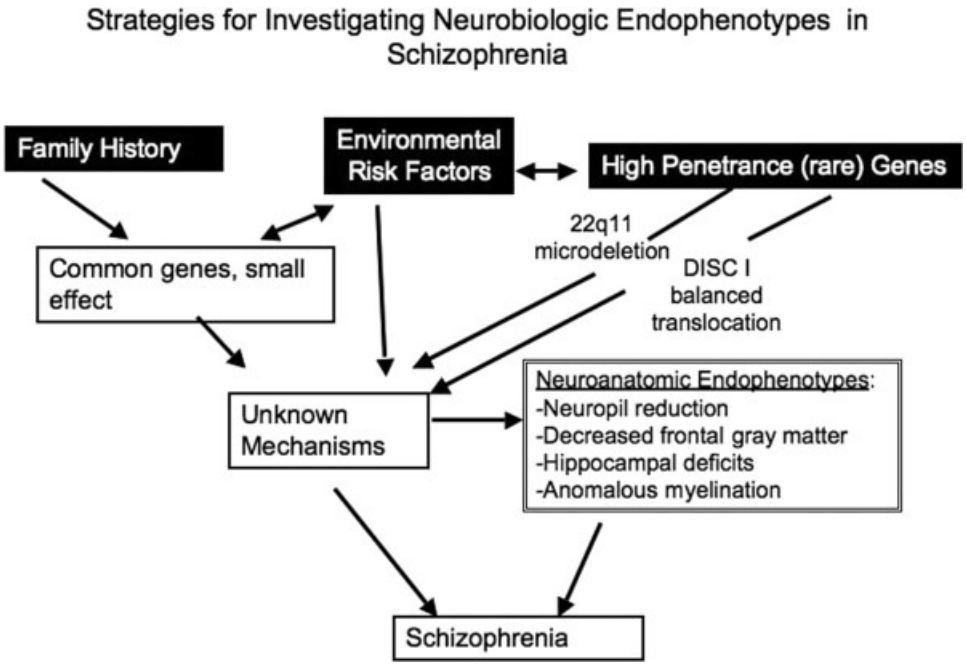

Figure 1.
Schematic of convergent strategies for investigating schizophrenia endophenotypes: Common genes of small effect and rare genetic mutations of high penetrance may result in shared/overlapping neuroanatomic features.

progress. Studies of the inheritance of schizophrenia have revealed that it is—in general—a complex and multifactorial disorder, likely involving multiple genes of small effect that each contribute a modest degree of risk and, possibly in combination with environmental factors, influence numerous central nervous system traits. However, there are, in addition, certain neurogenetic conditions, which confer substantially elevated risk for schizophrenia, and may therefore represent a specific, more homogeneous subtype of the illness, with well-characterized genetic etiology.

Our approach to elucidating the nature of gene-brain-behavior linkages in complex neuropsychiatric disorders such as schizophrenia is based on the premise that these diseases are best conceptualized as sets of quantitative traits that reflect intermediate phenotypes between predisposing genes and syndromal expression ["endophenotypes"; Gottesman and Gould, 2003]. Given that nearly half of all genes are expressed in the brain [Sandberg et al., 2000], and brain structure volumes are highly heritable [Carmelli et al., 1998; Pfefferbaum et al., 2000; Posthuma et al., 2000], neuroanatomic phenotypes offer a compelling alternative to categorically defined disease syndromes. It is our hypothesis that many of these genes contribute to schizophrenia susceptibility through their impact on brain systems involved in motivational, attentional, and memory processes, and that most of these genes have been undetected by previous studies that have examined syndromal status as the phenotypic target.

Here, we describe our use of converging methods to investigate genetic influences on brain structure in the development of psychosis: (1) Concordant and discordant twin studies, which allow us to identify heritable dimensions of CNS pathology in schizophrenia, and (2) Studies of possible "genetic subtypes" of the disease with very high penetrance (i.e., 22q11.2 microdeletions).

Heritability of Brain Structure in Normal Twins

Neurobehavioral phenotypes develop as a result of complex aggregations of, and interactions between, sets of genes impacting particular neural pathways and environmental circumstances that modify the expression of those genes as well as the development and functioning of those pathways. Twin studies can be used to disentangle genetic from shared and unique environmental effects, allowing for the identification of quantitative neurodevelopmental phenotypes that are heritable in the general population.

Prior work using traditional volumetric approaches has shown high heritabilities for major neuroanatomic features [Baare et al., 2001; Bartley et al., 1997; Biondi et al., 1998; Carmelli et al., 1998; Geschwind et al., 2002; Oppenheim et al., 1989; Pennington et al., 2000; Pfefferbaum et al., 2000, 2001; Posthuma et al., 2000; Scamvougeras et al., 2003; Sullivan et al., 2001; Thompson et al., 2001, 2004; Tramo et al., 1998; White et al., 2002; Wright et al., 2002]. Based on variance component analyses, additive genetic influences appear to account for 52–91% of the total variance in intracranial volume [Carmelli et al., 1998; Pfefferbaum et al., 2000; Posthuma et al., 2000], 62–94% for total brain volume [Bartley et al., 1997; Carmelli et al., 1998; Wright et al., 2002], 82–87% for gray and white matter volumes [Baare et al., 2001], 40–69% for hippocampal volume [Sullivan et al., 2001], and 79–94% for corpus callosum areas [Pfefferbaum et al., 2000; Scamvougeras et al., 2003]. However, because many aspects of cortical surface geometry

differ between individuals, and even between pairs of genetically identical cotwins, quantification techniques that do not account for individual differences in these features may be misleading. Thus, a key element of our strategy is the use of computational methods for cortical surface modeling and cortical pattern matching, to aggregate imaging datasets in the same anatomic reference locations across subjects (as in [Thompson et al., 2004]).

These algorithms are exquisitely sensitive to variation in regional tissue densities and other neural features of interest, because homologous sulcal landmarks are in perfect alignment across subjects. Power is greatly increased as the residual anatomic variability is directly modeled, and confounding variations are factored out before between-group comparisons are made. Similar cortical mapping approaches have been applied by other groups developing methods to visualize cortical data [Fischl and Dale, 2000; Hurdal and Stephenson, 2004; Van Essen, 2004].

Using these methods, we created the first cortical maps of genetic influences on human brain structure in twins [Thompson et al., 2001] (Fig. 2). Our sample consisted of 40 healthy normal subjects, including 10 monozygotic (MZ) and 10 dizygotic (DZ) twin pairs, ascertained from a twin cohort composed of all same-sex twins born in Finland between 1940 and 1957 [Kaprio et al., 1990]. These maps revealed a nonuniform genetic continuum, in which brain structure was increasingly similar in subjects with increasing genetic affinity, more so in heteromodal association areas than in other regions. Genetic factors significantly influenced cortical structure in Broca's and Wernicke's language areas, as well as frontal brain regions ($r_{MZ} > 0.8$). Preliminary heritability estimates indicated that localized middle frontal cortical regions, near Brodmann areas 9 and 46, displayed a 90–95% genetic determination of structure. The remarkably high correlations observed between MZ twin pairs indicate that MZ cotwins are virtually identical in terms of gray matter concentration in these regions. Preliminary correlations were performed, suggesting that frontal gray matter differences may be linked to Spearman's *g*, which measures successful test performance across multiple cognitive domains. The findings were subsequently replicated in independent volumetric studies [Baare et al., 2001; Wright et al., 2002], which examined heritabilities of Brodmann area volumes using variance components analysis.

Heritability of Brain Structure in Twins Discordant for Schizophrenia

Structural or functional brain abnormalities that are expressed in individuals with schizophrenia and some of their unaffected relatives are likely to reflect genetic processes that confer vulnerability to the disorder. In contrast, abnormalities that are observed in individuals with schizophrenia but not their relatives could reflect nonshared (genetic or individual-specific environmental) causative factors, and processes secondary to the effects of long-term psychotic illness or its treatment [Cannon et al., 1998].

The potential for neuroimaging methods to detect markers of genetic susceptibility to schizophrenia was first evidenced in sibling studies, in which our group and others documented differences in regional cortical brain volumes and ventricular volume in the unaffected first-degree relatives of patients with schizophrenia [Cannon et al., 1998; Staal et al., 2000]. While these studies may demonstrate genetic influences on various neuroanatomic features, the discordant twin design provides a unique opportunity to evaluate various cortical features for a dose-dependent relationship with genetic liability to schizophrenia. This is done by comparing the unaffected MZ cotwins of patients with schizophrenia, who are genetically identical to the affected proband, the unaffected DZ cotwins of probands, who share on average half their genes with the affected individual, and normal control subjects, who represent the base rate of schizophrenia-associated genes in the general population.

The symptoms of schizophrenia (e.g., profound social and motivational deficits, formal thought disorder, and information-processing deficits) imply disruption to the most recently evolved brain systems that support higher-order cognitive activity. To investigate the topography of genetically encoded deficits in cortical gray matter in schizophrenia, we created the first three-dimensional cortical surface maps of intrapair differences in MZ and DZ twins discordant for SZ (10 discordant pairs of each zygosity), along with 10 pairs of demographically matched control twins of each zygosity [Cannon et al., 2002] (Fig. 3).

Within each pair of discordant MZ twins, a three-dimensional map of gray matter volume in the schizophrenic patient was subtracted from that of his or her MZ cotwin, after both images were elastically realigned to standard stereotaxic space using the cortical pattern matching procedures described above. This procedure matches locations with the same relation to the primary folding pattern across subjects. The within-pair difference images were then averaged across pairs, isolating the nongenetic, disease-specific variation in gray matter volume by eliminating genetic sources of variability between cases and controls. This map detected gray matter reductions of 5–8% in dorsolateral prefrontal cortex (BA 9/46), Broca's area (BA 44/45), premotor cortex and frontal eye fields (BA 6/8), superior parietal lobule (BA 7/40), Heschl's gyrus (BA 41/42), and middle temporal gyrus (BA 21) (Fig. 3a). The observed disease-related deficits in gray matter do not appear to reflect secondary phenomena, as they were associated with increased severity of negative and positive symptoms and with cognitive dysfunction, but not with duration of illness or antipsychotic drug treatment. Additionally, a map encoding gray matter variation associated with genetic proximity to a patient (MZ cotwins > DZ cotwins > control twins) isolated deficits primarily in polar and dorsolateral prefrontal cortex, indicating substantial genetic influence on these cortical regions (Fig. 3b). In each

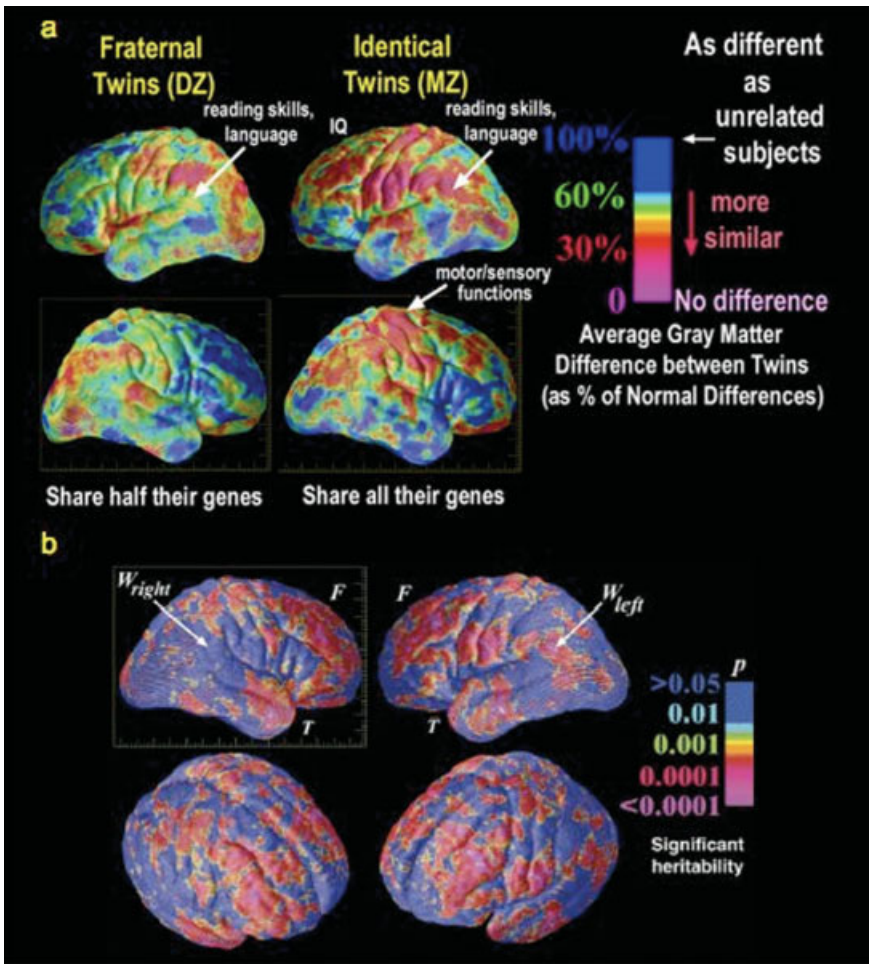

Figure 2.

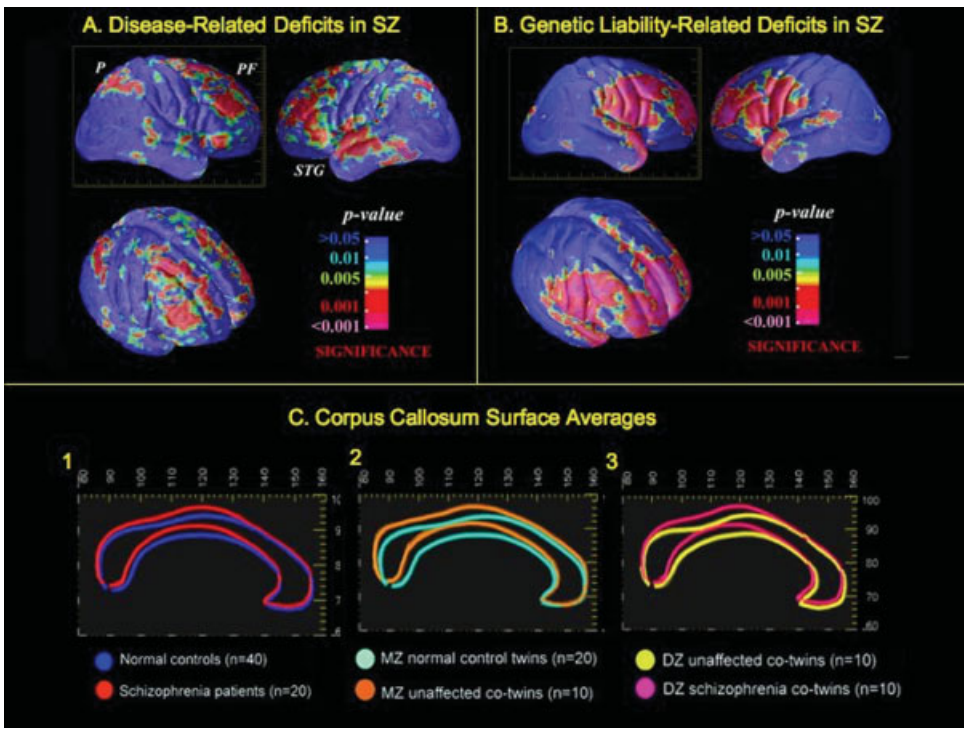

Figure 3.

case, statistical significance was confirmed through analysis of 10,000 Monte Carlo permutations, and the remaining cortex was shown to be significantly less affected by contrast analysis. Genetic and disease-specific influences thus appear to affect gray matter in partially nonoverlapping areas of predominantly heteromodal association cortex, changes that may act synergistically in producing overt behavioral features of the disorder. Our structural findings are further bolstered by functional neuroimaging work assessing working memory-related cortical physiology during performance on a working memory task in the nonpsychotic siblings of patients with schizophrenia [Callicott et al., 2003]. These investigators found that—despite intact performance on the task—siblings of schizophrenia patients had an exaggerated physiological response in the right dorsolateral prefrontal cortex, qualitatively similar to that observed in prior fMRI studies of patients with schizophrenia. This exaggerated response implies inefficient prefrontal information-processing in individuals with a high genetic load for schizophrenia. Collectively, these data suggest that risk for schizophrenia is increased by the inheritance of alleles that contribute to gray matter deficits and disruption of prefrontal cortical circuitry.

We have extended this computational brain-mapping approach to some medial and midline brain structures implicated in schizophrenia, to examine genetic versus shared or disease-specific environmental contributions to callosal anatomy and hippocampal volume [Narr et al., 2002b; van Erp et al., 2004]. Specifically, in a partially overlapping sample of twin pairs discordant for schizophrenia and healthy control twins ($N = 40$ pairs; 10 MZ and 10 DZ twin pairs discordant for schizophrenia, and 10 control pairs of each zygosity), we used anatomical mesh modeling methods to derive group average and surface variability maps of the callosum. As the major interhemispheric commissure of the brain, the corpus callosum is important for interhemispheric transfer of information. Although several other studies have documented abnormalities of the corpus callosum in patients with schizophrenia (e.g. DeQuardo et al., 1996; Keshavan et al., 2002], the only other study to examine callosal integrity in the non-ill MZ cotwins of patients with schizophrenia [Casanova et al., 1990a,b] found an upward bowing of the callosum in the affected, relative to the unaffected, cotwin. Consistent with these findings, we observed vertical displacements of the callosum in patients with schizophrenia, which were most pronounced in males. However, differences in the degree of vertical displacement were observed between dizygotic, but not monozygotic cotwins discordant for schizophrenia. Like their affected cotwins, the unaffected monozygotic cotwins of the schizophrenia probands exhibited significant callosal displacements, suggesting that genetic rather than disease-related or shared environmental influences contribute to altered callosal morphology in schizophrenia [Narr et al., 2002a] (Fig. 3c). Lateral and third ventricle enlargements were associated with callosal displacements. An upward bowing of the callosum may thus provide an easily identifiable neuroanatomic marker that may identify individuals possessing a biological vulnerability for schizophrenia.

In a separate investigation on a sample of 16 MZ and 32 DZ twin pairs discordant for schizophrenia, 7 MZ pairs concordant for schizophrenia, and matched groups of healthy twins (28 MZ and 26 DZ pairs), we used mixed-model regression, correlational, and variance components

Figure 2.

(**a**) Depicts the degree of similarity (expressed in terms of % difference) of the distribution of gray matter density (GMD) in monozygotic (MZ) and dizygotic (DZ) twins. MZ twins are almost perfectly correlated in GMD measures, particularly in frontal (F), sensorimotor (S/M), and perisylvian language cortices, suggesting strong genetic control of brain structure in these regions, but not others (shown in blue). Fraternal twins are significantly less alike in frontal cortices, but are 90–100% correlated in perisylvian language-related cortex and spatial association cortices, including supramarginal and angular gyri. Color-coded maps show the percentage reduction in intrapair variance for each cortical region. (**b**) The significance of genetic control of gray matter distribution. Brain regions for which cortical gray matter distribution is under significant genetic control are shown in red. Frontal (F) and lateral temporal (T) regions show significant heritability, consistent with their near-identity in identical twins (a) and the weaker correlations observed in fraternal twins, who are less similar genetically. Wernicke's area shows significantly higher heritability in the left hemisphere (W_{left}), which is generally dominant for language function [Thompson et al. 2001].

Figure 3.

(**a**) In discordant twins, disease-specific cortical gray matter deficits were found in dorsolateral prefrontal cortex (PF), superior temporal gyrus (STG), and superior parietal lobule (P). Disease-specific deficits correlated with symptom severity and working and episodic memory impairment, but not with illness duration or treatment. (**b**) Significance map of genetic liability-related deficits: Gray matter deficits correlated with genetic proximity to a patient in polar and superior prefrontal cortex [Cannon et al. 2002]. (**c**) Callosal surface averages mapped in groups defined by biological risk for schizophrenia. Average anatomical mesh models of the corpus callosum are shown in different colors to illustrate group differences. Midsagittal callosal averages are mapped in the following: (1) schizophrenia patients and normal controls; (2) unaffected MZ cotwins of the schizophrenia probands and MZ control twin pairs, indicating genetic factors contribute to callosal displacement in schizophrenia, and (3) unaffected DZ cotwins of the schizophrenia probands versus their cotwin with SZ.

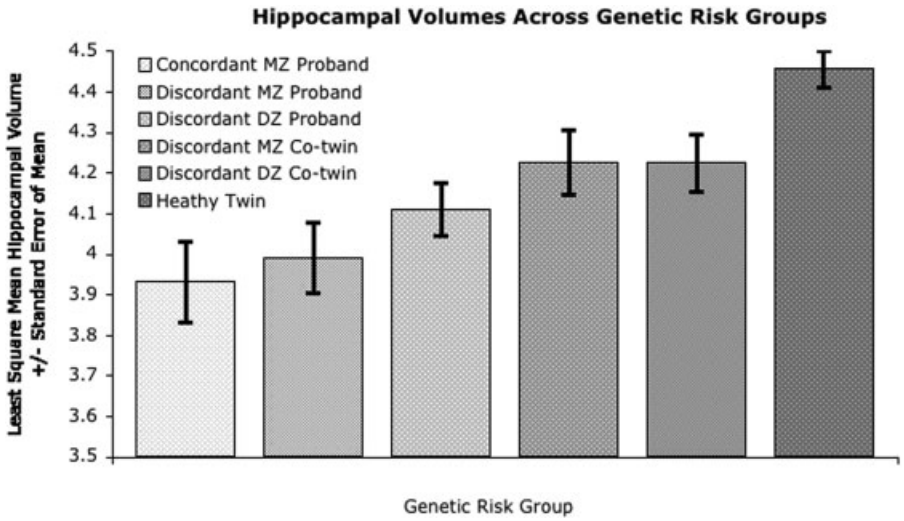

Figure 4.
Least squares mean hippocampal volumes across risk groups. CC indicates concordant; MZ, monozygotic; DC, discordant; DZ, dizygotic. Error bars represent SEM.

analyses to examine the relative contributions of genetic and environmental factors to hippocampal volume reduction in schizophrenia. Probands' hippocampal volumes were smaller than those of their non-SZ MZ and DZ cotwins and healthy subjects, and probands' nonill cotwins' hippocampal volumes were smaller than those of healthy subjects, but nonill MZ and DZ cotwins of SZ patients did not differ from each other (Fig. 4). The intraclass correlations (ICCs) for hippocampal volumes among healthy MZ pairs were larger than those found in healthy DZ pairs, but the ICCs for hippocampal volumes among discordant MZ and DZ pairs were equivalent. Results from variance components analysis further indicated that the effect of additive genes on hippocampal volume (corrected for cortical gray matter volume) is 71% in the healthy twins, but only 42% in the discordant twins. Together, these findings indicate that while hippocampal volume in healthy subjects is under substantial genetic control, hippocampal volume in SZ patients and their relatives appears to be influenced to a greater extent by unique and shared environmental factors [van Erp et al., 2004]. A similar pattern of results was observed in a Dutch twin sample [van Haren et al., 2004]. These results extend those of prior studies demonstrating medial temporal abnormalities in the unaffected relatives of schizophrenia patients [Seidman et al., 2003; Tepest et al., 2003]. Furthermore, these findings converge well with the pattern of neurocognitive deficits associated with genetic risk for schizophrenia, where unaffected relatives (who presumably carry susceptibility genes for the illness) show a profile of memory impairment intermediate between normal controls and their ill relatives (for whom disease-specific factors may contribute to greater severity of deficit; see Trandafir et al. [2006] for a meta-analysis). Although here we did not examine specific candidate genes that may contribute to the observed hippocampal alterations, brain-derived neurotrophic factor (BDNF) is widely expressed in the hippocampus and has been implicated in the neurobiology of schizophrenia. Szeszko et al. [2005] found differences in hippocampal volume as a function of BDNF (val66met) genotype in a combined sample of schizophrenia patients and controls and, secondly, that genotype explained more variance in hippocampal volume for schizophrenia patients relative to healthy volunteers. This suggests that the BDNF gene may contribute to variation in human hippocampal volume, and that this effect may be amplified in patients with schizophrenia.

Linkage and Association Analyses of the DISC1 Locus, Working Memory, and Prefrontal Cortical Volume

Given that abnormalities of working memory and prefrontal cortical structure and function are associated with genetic liability to schizophrenia, it should be possible to identify specific genes that underlie these disturbances. For example, Weinberger and colleagues have reported evidence of one such genetic influence—the met/val polymorphism of the COMT (catechol-*O*-methyltransferase) gene on chromosome 22q, with val alleles promoting more rapid breakdown of synaptic dopamine leading to prefrontal hypofunction during performance on a working memory task in patients with schizophrenia [Egan et al., 2001]. These findings have now been extended to show a significant effect of COMT genotype on working memory performance (assayed by the n-back task) for patients with schizophrenia, their healthy siblings, and controls [Goldberg et al., 2003], as well as differential response to amphetamine as a function of COMT genotype, supporting the notion of a characteristic inverted-"U" functional-response curve to increasing prefrontal dopamine signaling [Mattay et al., 2003]. In addition, the G-protein signaling subtype 4 (RGS4) gene, which is located on chromosome 1q21, a region that has been linked with schizophrenia in a number of studies [Harrison and Owen, 2003], was recently shown to be associated with reduced prefrontal cortical gray matter volume in neuroleptic-naïve first-episode schizophrenia patients,

but not in controls [Prasad et al., 2005]. Furthermore, in a sample of child-onset schizophrenia patients, Addington et al. [2006] recently found that a risk allele at the neuregulin locus was associated with poorer premorbid social functioning, as well as a different trajectory of gray and white matter volume change over time, suggesting the intriguing possibility of a disease-specific pattern of gene action in schizophrenia.

Another potential susceptibility locus that has shown replicated evidence of linkage with schizophrenia and may affect prefrontal cortical function is the disrupted-in-schizophrenia 1 (DISC1) gene on chromosome 1q42.1. In a large Scottish pedigree, a balanced translocation in this region (1q42.1;11q14.3) was strongly linked to psychopathology, including schizophrenia, mania, and depression [Millar et al., 2000; St Clair et al., 1990]. In addition, the peak linkage signal observed in the 1q42 region within the Finnish population was intragenic to DISC1 [Ekelund et al., 2001, in press; Hennah et al., 2003], and several other linkage findings have also pointed to this region [Curtis et al., 2003; Ekelund et al., 2000; Hwu et al., 2003].

DISC1 is translated to a protein that impacts on neurodevelopmental and neurochemical processes that are likely to be involved in the pathophysiology of SZ, including neurite outgrowth, synaptogenesis, and glutamatergic transmission [Millar et al., 2003; Miyoshi et al., 2003; Morris et al., 2003]. The regional expression of DISC1 in brain tissue appears to be greatest in the hippocampus [Ma et al., 2002]. Recently, three haplotypes incorporating different blocks of single nucleotide polymorphic (SNP) markers in the DISC1 and immediately adjacent TRAX genes were found to be associated with SZ (two under- and the other over-transmitted to affected cases) in a study of multiplex families from Finland [Hennah et al., 2003]. Moreover, DISC1 is near the peak linkage signal observed in a genome scan in several large Scottish families multiply affected with bipolar disorder [Macgregor et al., 2004], suggesting that DISC1 may confer generalized susceptibility to a broader psychopathological phenotype [Porteous et al., 2006].

Several recent findings suggest that the DISC1 locus contributes to alterations in prefrontal cortical and hippocampal structure and function, and altered working and declarative memory performance in schizophrenia patients and their relatives. First, using a combined linkage and association analysis strategy in dizygotic Finnish twins discordant for schizophrenia [Gasperoni et al., 2003] found that allelic variation in a marker located near DISC1 was associated with variation in spatial working memory performance. Other linkage studies in the Finnish population have reported associations of haplotypes within the DISC1 gene with visual working memory [Hennah et al., 2005], and verbal learning and memory (semantic clustering) [Paunio et al., 2004]. Moreover, Callicott et al. [2005] found that a common SNP within the DISC1 gene (Ser704Cys) was associated with schizophrenia in a family-based sample, and that allelic variation at this locus was associated with altered hippocampal structure and function in healthy subjects.

Recently, we applied the brain mapping algorithms described above to genetic linkage and association tests of DISC1 and another putative schizophrenia susceptibility gene on chromosome 1q42, translin-associated factor X (TRAX). We examined a series of haplotype blocks of single-nucleotide polymorphic markers (SNPs) from a segment of 1q42 spanning the DISC1 and TRAX genes for association with schizophrenia, and several endophenotypic traits thought to be associated with disease pathogenesis. In the samples of Finnish twin pairs concordant and discordant for SZ and healthy control twins described above, we found that a common haplotype incorporating three SNP markers near the translocation break point of DISC1 (odds ratio, 2.6 [$P = 0.02$]) and a rare haplotype incorporating four markers from the DISC1 and TRAX genes (odds ratio, 13.0 [$P = 0.001$]) were significantly overrepresented among individuals with schizophrenia [Cannon et al., 2005]. These haplotypes were also associated with several quantitative endophenotypic traits previously observed to covary with schizophrenia and genetic liability to schizophrenia; specifically, impairments in short- and long-term memory functioning and reduced gray matter density in the prefrontal cortex (Fig. 5). In addition, while the rare HEP2/HEP3 haplotype was not associated with hippocampal volume, there was a trend toward association of the homozygous HEP1 haplotype with reduced hippocampal volume. Thus, allelic variation within the DISC1 and TRAX genes on chromosome 1q42 may contribute to genetic risk for schizophrenia through disruptive effects on the structure and function of the prefrontal cortex, medial temporal lobe, and other brain regions. These effects are consistent with the known function of these genes in terms of their production of proteins that play roles in neuritic outgrowth, neuronal migration, synaptogenesis, and glutamatergic neurotransmission. However, it is important to note that the haplotypes examined here did not contain the Ser704Cys SNP identified by Callicott et al. The lack of convergence of these findings suggests that other risk alleles may be in linkage disequilibrium (LD) with the Ser704Cys polymorphism, and that the increased risk may be due to the overtransmission of a DISC1 haplotype that does not include this particular allele. Differences in results may also be a function of SNP marker density used across studies. Bolstering this conclusion, a prior case–control association study of patients with schizophrenia and bipolar disorder using four common SNPs and a microsatellite in the DISC1 region [Devon et al., 2001] found neither cosegregation with disease status nor significant association; however, they did not detect LD between all the markers in the control population, suggesting that an even greater density of informative markers is required to test rigorously for association in this genomic region.

In summary, these twin studies confirm prior evidence of genetic influences on gray matter density in frontal brain regions. They also provide converging evidence for a role of chromosome 1q42 in the pathogenesis of schizophrenia, by

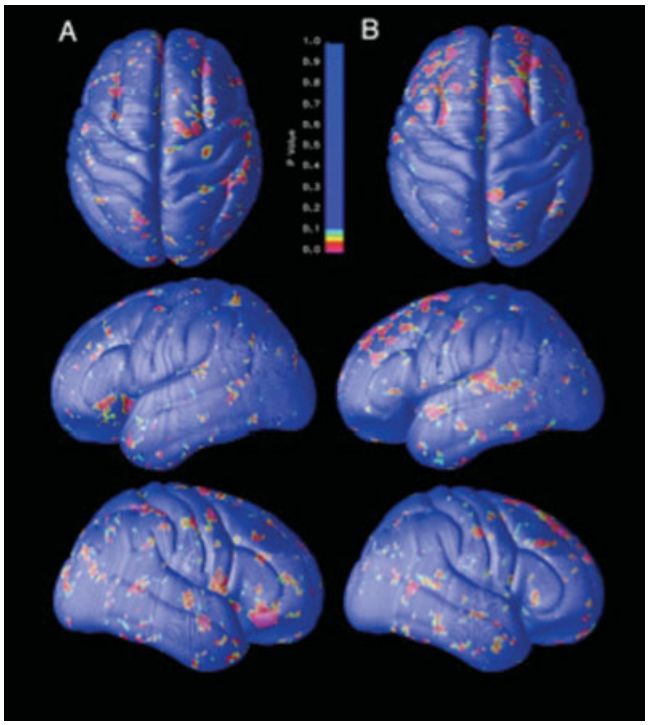

Figure 5.
Statistical anatomical maps of DISC1/TRAX Associations with cortical gray matter density (GMD): (**a**) Areas of the cortical surface in which significant reductions in GMD are associated with a common haplotype (HEP1; TCG) of a 3-SNP block of markers located near the translocation breakpoint on the *DISC1* gene; (**b**) GMD reductions associated with a rare haplotype (AATG) of a 4-SNP block of markers spanning the DISC1 and TRAX genes. Top, left, and right views of each map are displayed [Cannon et al. 2005].

demonstrating linkage and association of markers of the TRAX and DISC1 genes with prefrontal cortical gray matter deficits in twins discordant for schizophrenia.

Taken together, these findings provide compelling evidence that specific genetic loci suspected to predispose to schizophrenia may affect quantitative variation in neural indicators underlying disease pathogenesis. Here, we have illustrated these approaches using samples of healthy monozygotic (MZ) and dizygotic (DZ) twin pairs, as well as MZ and DZ twin pairs discordant for schizophrenia, but the methods can be generalized to other classes of relatives and to other diseases as well.

Brain Mapping in Rare Neurogenetic Disorders Associated with Schizophrenia

A complementary approach in the search for susceptibility genes for schizophrenia involves the study of chromosomal abnormalities such as translocations, duplications, and deletions, which might segregate with the disorder. Research efforts on other complex diseases—for example, the strong association between early-onset dementia and Down's syndrome—suggest that this strategy may be particularly valuable for understanding the genetics and underlying pathophysiology of diseases with complex inheritance patterns [Murphy, 2002].

The 22q11.2 Deletion Syndrome (Velocardiofacial/DiGeorge Syndrome) involves cardiac and craniofacial anomalies, marked deficits in visuospatial cognition, and elevated rates of psychopathology. In most diagnosed cases, the syndrome results from a 3 megabase (Mb) *de novo* deletion at chromosome 22q11.2. This region of the genome is thought to be particularly susceptible to chromosomal rearrangement due to the groups of low copy

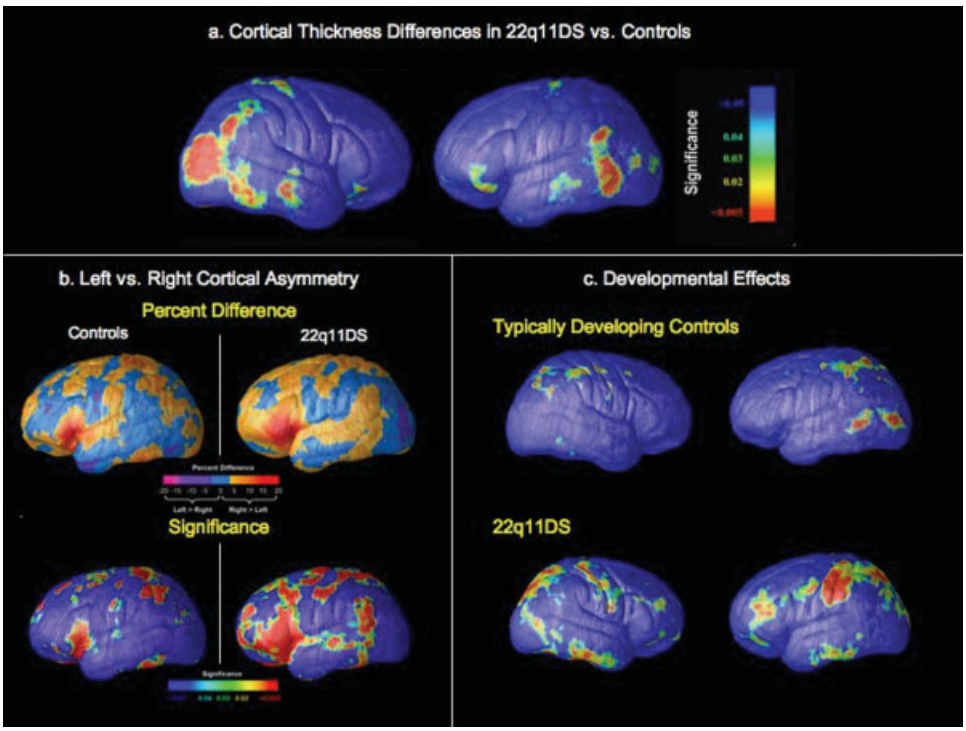

Figure 6.

repeat sequences flanking the deletion breakpoints, which may cause misalignment due to high sequence homology [Shaffer and Lupski, 2000].

Twenty-five to 30% of adults with this syndrome develop schizophrenia, making 22q11.2DS one of the greatest known risk factors for schizophrenia identified to date [Murphy et al., 1999]. The greatly increased risk for psychosis in this syndrome suggests that a gene or genes within the 22q11.2 deletion region may contribute to schizophrenia susceptibility in the broader population. Support for this notion is provided by genetic linkage and association studies implicating genes within the 22q region in schizophrenia (i.e., proline dehydrogenase (PRODH), COMT, *ZDHHC8,* and G-protein-coupled receptor kinase (GRK3; Gogos et al., 1999; Mukai et al., 2004; Paterlini et al., 2005], documentation of 22q11 as a region of interest in the meta-analysis of Lewis et al. [2003], and the finding that mice heterozygously deleted for some of the genes in this region have sensorimotor gating and memory impairments similar to those observed in schizophrenia [Gogos et al., 1998, 1999; Paylor et al., 2001]. As such, individuals with this syndrome may have genetically determined differences in brain anatomy that predispose to schizophrenia [van Amelsvoort et al., 2004], although currently the mechanism for the development of schizophrenia in individuals with this syndrome is not known.

Using the cortical pattern matching methods described above, we mapped cortical thickness in millimeters based on structural MRI images of 21 children with confirmed 22q11.2 deletions and 13 demographically matched healthy comparison subjects [Bearden et al., 2006]. All participants with 22q11.2DS had the same 3 Mb typical deletion. Thickness was mapped at 65,536 homologous points, based on the 3D distance from the cortical gray–white matter interface to the external gray-CSF boundary [Thompson et al., 2005]. A pattern of regionally specific cortical thinning was observed in superior parietal cortices and the right parieto-occipital cortex, regions critical for visuospatial processing, and bilaterally in the most inferior portion of the inferior frontal gyrus (*pars orbitalis*), a key area for language development (Fig. 6]. Even in this modest sample size, the observed gray matter deficits appear to have functional implications, as gray matter volume was significantly correlated with IQ in the children with 22q11.2DS, although this relationship was not significant in the control sample (Fig. 7).

Several of the 30 genes encoded in the deleted segment are highly expressed in the developing brain, and known to affect early neuronal migration. These quantitative maps of cortical integrity thus reveal how haploinsufficiency for genes in the 22q11.2 region can affect cortical development, and suggest a possible underlying pathophysiology of the neurobehavioral phenotype.

Notably, the characteristic 22q11.2DS cognitive profile—involving relative strengths in verbal memory, in contrast to marked deficits in visuospatial memory—bears striking similarity to that seen in another genetic deletion syndrome, Williams Syndrome [Bearden et al., 2002]. However, unlike Williams Syndrome (WS), patients with 22q11.2DS are not generally reported to be hypersociable, or to show particular strengths in musical ability [Karmiloff-Smith et al., 2004]. Using identical cortical thickness mapping methods to those described here, Thompson et al. [2005] observed a failure of cortical maturation in patients with WS, involving a zone of right hemisphere perisylvian cortex that was 5–10% thicker in WS than in matched controls, despite pervasive gray and white matter deficits, but with corresponding deficits in the adjacent dorsal stream, including superior parietal brain regions. Recently developed image analysis methods have revealed increased gyrification bilaterally in occipital regions and over the cuneus in WS subjects [Gaser et al., 2006; Tosun et al., 2006], as well as numerous cortical folding abnormalities in brain regions associated with multiple sensory modalities, as well as cognitive and emotional behavior [Van Essen et al., 2006]. Using functional brain imaging during visual processing tasks, Meyer-Lindenberg et al. [2004] identified a pattern of hypoactivation in subjects with WS in the parietal portion of the dorsal stream, concomitant with gray matter volume

Figure 6.

(**a**) Statistical significance maps of cortical thickness reductions in 22q11.2DS, as compared to typically developing control children, plotted as a map of *P*-values. A previous finding by Eliez et al. [2000] indicating reduced parietal lobule volume in 22q11.2DS, even after adjusting for differences in brain volume, is consistent with the thinning of parietal cortex seen here. (**b**) Asymmetry effects in 22q11.2 versus Controls: Maps of cortical thickness asymmetry expressed as a percentage, for control subjects (top left panel) and 22q11.2DS (top right panel). Negative values on the color bar (purple and magenta) encode a greater thickness in the LH (i.e., leftward asymmetry), while positive values (orange and red) represent greater thickness in the RH (i.e., rightward asymmetry). Bottom panel depicts maps of significant cortical thickness asymmetry, in controls (bottom left) and 22q11.2DS (bottom right). Blue-shaded regions are not significantly different between LH and RH. Measures of asymmetry are shown on one hemisphere only as they are, by definition, the same for both hemispheres. Rightward (R > L) asymmetries of cortical thickness were of greatest magnitude in the inferior frontal gyrus in both 22q11.2DS and control children but were more extensive in the brains of 22q11.2DS participants. (**c**) Developmental Effects: Brain regions in which age is significantly negatively correlated with cortical thickness, shown separately for typically developing controls (top) and age-matched subjects with 22q11.2DS (bottom). Consistent with independent studies of cortical development and aging [Gogtay et al., 2004; Sowell et al., 2003], controls showed localized regions of cortical thinning in superior parietal and middle temporal regions associated with increasing age, but children with 22q11.2DS showed more widespread areas of age-related cortical thinning, particularly in the inferior temporal gyrus and parietal regions.

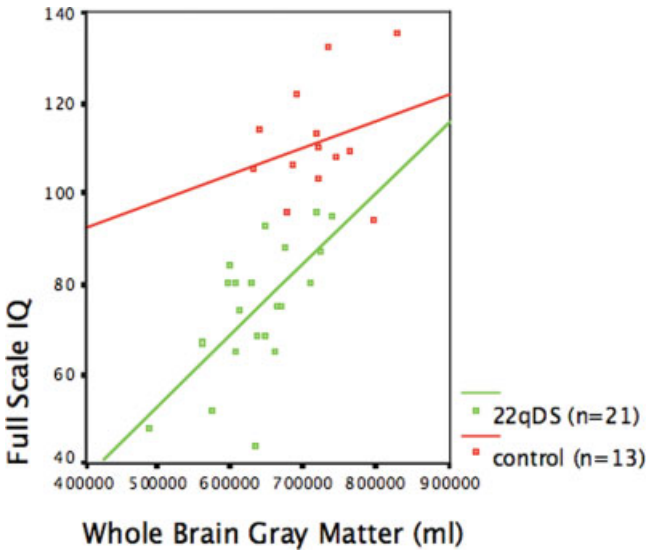

Figure 7.
Scatterplot of cognitive outcome variables with gray matter volume: For children with 22q11.2DS, but not typically developing controls, gray matter volume was a significant predictor of Full Scale IQ (FSIQ).

reduction in the immediately adjacent parieto-occipital/intraparietal sulcus. Using path analysis, they found support for their hypothesis that the structural abnormalities in the parietal region may serve as a "roadblock" to dorsal stream information flow in WS. Similarly, the localized thickness deficits in 22q11.2DS may underlie the visuospatial cognitive impairments characteristic of the syndrome, by affecting the flow of information through distributed neural systems; this hypothesis awaits further testing using multimodal imaging approaches, as illustrated by the pioneering work of Meyer-Lindenberg et al. [2006].

Interestingly, the cortical anomalies observed in this group of children and adolescents with 22q11.2 deletions do not closely resemble those seen in schizophrenia, where prefrontal and temporal regions show the greatest gray matter deficits [Wright et al., 2000]. Developmental factors are likely to play an important role in these differences. As seen in Figure 6c, we observed a moderate inverse relationship between age and cortical thickness in our cross-sectional study, in both patients with 22q11.2DS and healthy controls, although qualitative inspection of the maps suggests that there may be a more pronounced effect of age on cortical thickness in 22q11.2DS as compared to typically developing controls. Controls showed localized regions of cortical thinning in superior parietal and middle temporal regions associated with increasing age, consistent with independent studies of cortical development and aging [Gogtay et al., 2004; Sowell et al., 2003], but children with 22q11.2DS showed more widespread areas of cortical thinning that were significantly correlated with age, particularly in the inferior temporal gyrus bilaterally, and in parietal regions.

In addition, using identical cortical pattern matching methods to those described here, Thompson et al. [2001] and Vidal et al. [2006] mapped cortical changes over time in adolescents with childhood onset of schizophrenia. This study revealed that early deficits in parietal brain regions progressed anteriorly into temporal lobes, engulfing sensorimotor and dorsolateral prefrontal cortices over a 5-year period. This trajectory appears to be an exaggeration of the normal sequence of dendritic pruning and myelination [Gogtay et al., 2004]. Only the latest changes included dorsolateral prefrontal cortex and superior temporal gyri, deficit regions found consistently in adult studies, suggesting that these structural changes occur later in the course of illness. More recent work has shown that the dynamic trajectory of deficits is different in children with early-onset bipolar illness [Gogtay et al., 2007], and may be opposed by certain types of psychotropic agents (e.g., atypical antipsychotics or mood stabilizers; [Bearden et al., in press; Time-lapse mapping reveals different disease trajectories in schizophrenia depending on antipsychotic treatment, submitted]).

In this study, involving children and adolescents with the 22q11.2 microdeletion, we did not find evidence for differences in patterns of cortical thickness between patients with and without psychiatric disorders. However, using quantitative measures, we previously found a relationship between reduced temporal gray matter and elevated Thought Problems, as assessed by the Child Behavior Checklist [Bearden et al., 2004]. Consistent with this, Campbell et al. (2006) recently observed a significant positive correlation between severity of schizotypy score and gray matter volume in temporo-occipital regions and basal ganglia. Emotional and social problems were associated with gray matter volume in frontostriatal regions, suggesting that quantitative indices of psychopathology may be related to differences in brain development in this syndrome, even in the absence of categorical syndrome-based group differences.

In the only longitudinal neuroimaging study of 22q11.2DS to date, Gothelf et al. [2005] found that the COMT low-activity (Met) allele was associated with decline in prefrontal cortical volume and cognition, and with development of psychotic symptoms during adolescence. These intriguing findings highlight the importance of investigating the evolution of psychotic symptoms in relation to genes and neuroanatomy over time in this syndrome.

CONCLUSIONS AND FUTURE DIRECTIONS

The "endophenotype" approach is a sensitive method for measuring phenotypic variation that may make it easier to identify susceptibility genes and their mechanisms of action for traits with complex inheritance patterns. Such investigations may be further empowered by complementary strategies involving chromosomal abnormalities associated with schizophrenia, which offer an alternative approach to help localize causative genes and better understand the genetic complexity of the illness [Bassett

et al., 2000]. With regard to this strategy, it should be noted that it is not assumed that cytogenetic rearrangements such as the 22q11.2 microdeletion account for a substantial proportion of the trait variance or disease liability in schizophrenia overall [Porteous et al., 2006]. Rather, the study of such cytogenetic anomalies may provide another window into discovering a potential genetic route of causation. As such, the examination of quantitative endophenotypes in these rare disorders—and their potential overlap with CNS indicators in schizophrenia—may offer a complementary strategy to examine genotype–phenotype relationships, in which genotype is clearly identified.

To decipher the complex nature of genotype–phenotype relationships within the multiple neural systems compromised in neuropsychiatric syndromes such as schizophrenia, sophisticated computational brain mapping methodologies are needed. As illustrated here, these methods allow us to represent population variability in neural traits, and to probe their heritable and molecular genetic bases. Moreover, the high heritability estimates obtained for a variety of neuroanatomic traits suggest that neuroimaging paradigms may provide more reliable measures than behavioral and clinical assays, resulting in improved sensitivity to genetic variation. These findings illustrate the way in which imaging-genetics paradigms can advance our understanding of the contribution of specific genetic variants to the neurobehavioral phenotype of schizophrenia.

The methods reviewed here for hypothesis driven, voxel-based association analyses for candidate genes that may predispose to schizophrenia can also be applied in genome-wide linkage and association studies. Clearly, procedures to control for multiple-testing must be further refined in such applications, as the permutation methods developed to handle these issues thus far would not be computationally efficient under those circumstances. However, as it is not feasible to conduct neuroimaging studies on thousands of subjects in the near future, as would be required for this type of investigation, it is more likely that this methodology will first be applied to focal linkage and association analyses of specific genomic regions that have been previously implicated in the pathogenesis of a particular disorder.

Future studies are warranted to elucidate how multiple genes interact in determining dysfunction in various neurobehavioral domains in schizophrenia, and to clarify how much these gene–endophenotype relationships overlap with other serious psychiatric disorders with complex inheritance patterns, particularly bipolar disorder. Our current investigations to address these questions include a population-based study of twins discordant for schizophrenia and bipolar disorder, and studies of extended pedigrees multiply affected with severe bipolar disorder in genetically isolated populations, applying the above-mentioned methodologies.

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