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# Heritability of Subcortical and Limbic Brain Volume and Shape in Multiplex-Multigenerational Families with Schizophrenia

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## ABSTRACT

**BACKGROUND:** Brain abnormalities of subcortical and limbic nuclei are common in patients with schizophrenia, and variation in these structures is considered a putative endophenotype for the disorder. Multiplex-multigenerational families with schizophrenia provide an opportunity to investigate the impact of shared genetic ancestry, but these families have not been previously examined to study structural brain abnormalities. We estimate the heritability of subcortical and hippocampal brain volumes in multiplex-multigenerational families and the heritability of subregions using advanced shape analysis.

**METHODS:** The study comprised 439 participants from two sites who underwent 3T structural magnetic resonance imaging. The participants included 190 European-Americans from 32 multiplex-multigenerational families with schizophrenia and 249 healthy comparison subjects. Subcortical and hippocampal volume and shape were measured in 14 brain structures. Heritability was estimated for volume and shape.

**RESULTS:** Volume and shape were heritable in families. Estimates of heritability in subcortical and limbic volumes ranged from .45 in the right hippocampus to .84 in the left putamen. The shape of these structures was heritable (range, .40–.49), and specific subregional shape estimates of heritability tended to exceed heritability estimates of volume alone.

**CONCLUSIONS:** These results demonstrate that volume and shape of subcortical and limbic brain structures are potential endophenotypic markers in schizophrenia. The specificity obtained using shape analysis may improve selection of imaging phenotypes that better reflect the underlying neurobiology. Our findings can aid in the identification of specific genetic targets that affect brain structure and function in schizophrenia.

*Keywords:* Endophenotypes, Heritability, Hippocampus, Neuroimaging-genetics, Schizophrenia, Structural MRI

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The identification of genetic variants that influence brain structure (1–3) is an important step in elucidating the biological mechanisms underlying neuropsychiatric disorders. Structural brain abnormalities are common in patients with schizophrenia (4–6), and variation in regional brain volume is considered a putative endophenotype for the disorder (7–9). Reduced gray matter volume associated with schizophrenia is present before illness onset and is heritable (8,10). Consistent with the endophenotype concept (11), unaffected first-degree relatives of patients with schizophrenia also exhibit reduced regional brain volume compared with healthy control subjects, but of a lesser extent than that observed in patients (12–16). There is evidence that quantitative brain measurements, such as volume and cortical thickness, are heritable, as shown in healthy (17–22) and neuropsychiatric samples (8,10,23–25). However, little is known about specific genetic targets underlying structural brain variation in schizophrenia. The gap may relate to the heterogeneity of the disorder (26) or the morphometric abnormalities (4,7,27). Because heritability differs across brain structures (22), it is possible that particular regions or subregions would show greater heritability (28). Neuroimaging studies in healthy individuals (17,29–31) and in large extended pedigrees (22) show a substantial range of heritability estimates across brain structures (22); this pattern also extends to subcortical brain regions and hippocampus (17,32). These findings suggest that some brain structures and measures are more heritable than others and may serve as better endophenotypes. The few studies supporting heritability of brain volume in patients with schizophrenia employed twin pairs (33) or mostly nuclear families (24). No previous study has examined heritability of brain structures in large extended families affected with schizophrenia. In the present study, we evaluate the influence of shared genetic ancestry on brain structure within large, multiplex-multigenerational families with schizophrenia.

In this study, we focus on subcortical and limbic brain structures, which are heritable in healthy (17,29,31,34) and clinical populations (35,36). These regions show consistent

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**Table 1. Sample Characteristics for Sample as a Whole and at Each Study Site**

| Group | Site | Sample Size | Sex (M/F) | Age (Years) | GAF[a] | SANS[b] | SAPS[c] |
|---|---|---|---|---|---|---|---|
| SZ | All | 33 | 23/10 | 52 (11)[d] | 50 (16)[d,e] | 34 (21)[d,e] | 31 (25)[d,e] |
| | Penn | 20 | 14/6 | 54 (9) | 46 (17) | 41 (18) | 36 (27) |
| | Pitt | 13 | 9/4 | 49 (12) | 56 (11) | 18 (17) | 18 (15) |
| FAM | All | 153 | 74/79 | 43 (18) | 82 (14)[d] | 9 (13)[d] | 1 (4)[d] |
| | Penn | 75 | 41/34 | 41 (19) | 78 (14) | 12 (14) | 2 (5) |
| | Pitt | 78 | 33/45 | 45 (17) | 88 (12) | 3 (9) | 1 (3) |
| HC | All | 246 | 115/131 | 39 (16) | 90 (11) | 3 (7) | 0 (1) |
| | Penn | 125 | 57/68 | 40 (16) | 87 (8) | 6 (9) | 0 (1) |
| | Pitt | 121 | 58/63 | 39 (16) | 93 (13) | 1 (1) | 0 (1) |

Values are mean (SD).

F, females; FAM, multiplex family members; GAF, Global Assessment of Functioning; HC, healthy comparison subjects; M, males; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SZ, patients with schizophrenia.

[a]Tests based on sample of 222, HC; 30, SZ; 129, FAM.

[b]Tests based on sample of 222, HC; 29, SZ; 127, FAM.

[c]Tests based on sample of 222, HC; 29, SZ; 127, FAM.

[d]Significantly different from HC; permutation tests, 100,000 permutations, $p < .01$.

[e]Different from SZ; permutation tests, 100,000 permutations, $p < .01$.

volumetric reductions in patients with schizophrenia (4,37–43) and to some extent in family members (13,44–47). More recently, morphometric changes in schizophrenia have been scrutinized further using shape analysis (13,39,43,44,48,49), which allows for the estimation of disease-related regional deformation. This complex approach is a reliable (48,50–53) and sensitive measure (54) of subtle, localized morphologic changes in brain structure in patients with schizophrenia (27,39,43,49) and, to a lesser extent, in family members (13,44). Such localized alterations may be related to distinctive wdimensions of psychopathology and may be determined by specific genetic risk factors that are unique to subsets of patients with schizophrenia or particular families (13,28,55). The specificity obtained using shape analysis may improve the selection of imaging phenotypes that are closer to schizophrenia pathophysiology and that may be affected by risk gene variants.

In this study, we estimate heritability of subcortical and limbic brain regions in multiplex-multigenerational families and healthy comparison subjects. We focus on estimating heritability of 1) volume of subcortical and limbic brain regions, including the amygdala, caudate, hippocampus, accumbens, pallidum, putamen, and thalamus, and 2) the local deformation patterns of these brain structures.

## METHODS AND MATERIALS

### Participants

The sample consisted of 439 participants from two sites (223 from University of Pennsylvania, 216 from University of Pittsburgh), including 190 European-Americans from 32 multiplex-multigenerational families with schizophrenia and 249 healthy volunteers (Table 1). This cohort is a subsample of a previously characterized cohort (56,57) with the addition of new family members. Patients had an extended multigenerational family and a consensus best-estimate DSM-IV diagnosis of schizophrenia or schizoaffective disorder. An example pedigree is shown in Figure 1. Participants were >15 years old at initial contact and provided signed informed consent. The institutional review boards of the University of Pennsylvania and University of Pittsburgh approved the study. For minors <18 years old, assent was obtained from the child, and consent was obtained from a parent. These data were collected as part of a larger project examining genetic mechanisms of schizophrenia. To reduce genetic heterogeneity, the sample was restricted to Caucasian individuals.

Patients with schizophrenia were competent to provide informed consent, capable to participate, and not exhibiting acute positive symptoms that required medication adjustment or hospitalization. Medications included second-generation antipsychotics in 23 patients, first-generation antipsychotics in 2 patients, and a combination of first-generation and second-generation antipsychotics in 4 patients. One individual was not medicated, and medication information was unavailable for one other patient. Family members were excluded if they had mental retardation (IQ < 70), had a central nervous system disorder that could potentially affect brain function, or were not proficient in English. Global functioning was measured using the Global Assessment of Functioning (58) with higher scores indicating better functioning. The Scale for the Assessment of Negative Symptoms (59) was used to rate the presence and severity of negative symptoms, and the Scale for the Assessment of Positive Symptoms (60) was used to rate the presence and severity of positive symptoms. At least one patient with schizophrenia and at least one family member (135 individuals) were provided to the sample by 21 families, only patients (3 individuals) were provided by 2 families, and only family members (52 individuals) were provided by 9 families. Overall, the multiplex sample included 33 patients with schizophrenia and 156 family members. There is a higher prevalence of mood (~26% vs. ~10%) (61) and substance-related disorders (~15% vs. ~6%) compared with the general population (62) (Table 2).

The healthy comparison group included 249 psychiatrically, medically, and neurologically healthy European-Americans with no Axis I or Axis II cluster A disorders and no history of psychosis or mood disorder in first-degree relatives. Healthy comparison subjects were recruited from the same