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Brain Structure Biomarkers in the Psychosis Biotypes: Findings From the Bipolar-Schizophrenia Network for Intermediate Phenotypes

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ABSTRACT

BACKGROUND: The current definitions of psychotic illness lack biological validity, motivating alternative biomarker-driven disease entities. Building on experimental constructs—Biotypes—that were previously developed from cognitive and neurophysiologic measures, we contrast brain anatomy characteristics across Biotypes alongside conventional diagnoses, examining gray matter density (GMD) as an independent validator for the Biotypes.

METHODS: Whole brain GMD measures were examined in probands, their relatives, and healthy subjects organized by Biotype and then by DSM-IV-TR diagnosis (n = 1409) using voxel-based morphometry with subsequent subject-level regional characterization and distribution analyses.

RESULTS: Probands grouped by Biotype versus healthy controls showed a stepwise pattern of GMD reductions as follows: Biotype1, extensive and diffusely distributed GMD loss, with the largest effects in frontal, anterior/middle cingulate cortex, and temporal regions; Biotype2, intermediate and more localized reductions, with the largest effects in insula and frontotemporal regions; and Biotype3, small reductions localized to anterior limbic regions. Relatives showed regionally distinct GMD reductions versus healthy controls, with primarily anterior (frontotemporal) effects in Biotype1; posterior (temporo-parieto-cerebellar) in Biotype2; and normal GMD in Biotype3. Schizophrenia and schizoaffective probands versus healthy controls showed overlapping GMD reductions, with the largest effects in frontotemporal and parietal regions; psychotic bipolar probands had small reductions, primarily in frontal regions. GMD changes in relatives followed regional patterns observed in probands, albeit less extensive. Biotypes showed stronger between-group separation based on GMD than the conventional diagnoses and were the strongest predictor of GMD change.

CONCLUSIONS: GMD biomarkers depicted unique brain structure characteristics within Biotypes, consistent with their cognitive and sensorimotor profiles, and provided stronger discrimination for biologically driven biotypes than symptom-based diagnoses.

Keywords: Biological marker, Biotypes, Brain gray matter, Mood disorders-bipolar, Schizophrenia, Voxel-based morphometry

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Current nosological constructs in psychiatry are based on phenomenologic criteria. Despite the routine use of biomarkers spanning genetic-, tissue-, organ-, and system-level measures in other fields of medicine, the application of brain biomarkers in psychiatry is lacking. Conventional symptom-based psychiatric diagnoses map poorly onto emerging biomarker-driven constructs (2,3). The absence of biologically based disease definitions hinders progress in identifying mechanistic targets for effective treatment development. High medical need exists in psychiatry for developing disease entities built on brain biology and supported by objective, quantitative, clinically relevant disease biomarkers—the approach recently emphasized by the Research Domain Criteria (RDoC) (4,5).

The Bipolar-Schizophrenia Network for Intermediate Phenotypes has recently developed biomarker criteria based on a large psychosis sample that capture neurobiologically defined groups of cases, Biotypes (1). This approach provided proof of concept that highly heterogeneous symptom-based categories within the psychosis dimension can be reorganized into biologically meaningful constructs (1). In brief, based on multistep multivariate analyses derived from cognitive,

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electroencephalography-based, and oculomotor paradigms [see Clementz *et al.* (1) for a detailed description of Biotype development], three such constructs emerged: Biotype1 (B1), capturing cases with poor cognitive and sensorimotor function; Biotype2 (B2), characterized by moderately impaired cognitive function and exaggerated sensorimotor reactivity; and Biotype3 (B3), showing near normal cognitive and sensorimotor functions. The distinctive cognitive and sensorimotor profiles were consistent in probands and their first-degree relatives (1). The conventional diagnoses mapped poorly onto Biotypes, with all targeted DSM-IV-TR groups (i.e., schizophrenia, schizoaffective disorder, and psychotic bipolar disorder) represented in all Biotypes. Brain structure measures were not used in the Biotype development and therefore are available to be examined as independent validators for the Biotype constructs.

Reduced gray matter density (GMD) and cortical thickness are established features of psychotic disorders observed in probands and their biological relatives (6–9). In schizophrenia, studies show broadly distributed neocortical and subcortical GMD reductions, with the most significant loss in frontotemporal regions (10–14). Outcomes vary in bipolar disorder, with psychotic phenotype showing GMD alterations similar to those observed in schizophrenia, while nonpsychotic bipolar is associated with rather preserved GMD (15–19). In the absence of in vivo tissue-level biomarkers, GMD along with other brain imaging measures is the most easily accessible proxy for tissue abnormalities underlying psychotic illness. GMD biomarkers show associations with several functional outcomes, including symptom severity and cognitive and neurophysiologic alterations (20–24). Moreover, measures of brain structure are among the best predictors of "conversion" to psychosis, disease progression, and lifetime cumulative psychosis burden (7,25–29). Finally, GMD biomarkers are sensitive to treatment effects, including both pharmacologic (30–36) and cognitive remediation (37) interventions, making them suitable for testing both "primary" and disease-associated (e.g., medication) effects.

We examined whole brain and regional GMD biomarkers as independent validators for Biotype psychosis constructs, tested alongside conventional diagnoses, asking whether GMD measures depict unique brain structure characteristics across Biotypes, and whether these biomarkers better discriminate biologically based Biotype constructs than the symptom-driven diagnoses. We hypothesized that across the Biotypes, B1 probands will show most extensive and diffusely distributed GMD reductions; B2 probands will have intermediate in magnitude and distribution GMD reductions; and B3 probands will show small, localized GMD reductions, compared to healthy controls (HC); and relatives grouped by their respective probands' Biotypes (i.e., B1-Rel, B2-Rel, and B3-Rel), compared to HC, will show GMD reductions regionally similar but less extensive than those detected in their respective probands. We also predicted that across conventional diagnoses, probands with schizophrenia (SZ), schizoaffective disorder (SAD), and psychotic bipolar disorder type I (BD) will show regionally overlapping GMD reductions, the largest in magnitude in SZ and SAD and smallest in BD compared to HC; and their relatives (i.e., SZ-Rel, SAD-Rel, and BD-Rel) will show GMD reductions from HC, regionally similar but less extensive than those observed in probands. Finally, we hypothesized that the Biotypes will show stronger between-group separation based on GMD and be able to better predict GMD changes among probands and relatives than the conventional diagnoses.

METHODS AND MATERIALS

Study Sample

GMD characteristics were assessed in 1409 patients (557 probands, 601 first-degree relatives, and 251 HC) who were initially organized by Biotype and then by DSM-IV-TR diagnosis. Descriptive demographic and clinical characteristics are detailed in Table 1 and Supplemental Table S1. The Bipolar-Schizophrenia Network for Intermediate Phenotypes' logistics and overall sample characteristics are described elsewhere (38); magnetic resonance imaging–pertinent study exclusion criteria are listed in Supplemental Methods. Probands were stable, medicated outpatients. Relatives included both clinically unaffected and those with lifetime psychiatric diagnoses (Supplemental Table S2); the majority of relatives were unmedicated (Table 1). Healthy comparison subjects had no personal history of psychotic or recurrent mood disorders and no family history of SZ/bipolar spectrum disorders in first- or second-degree relatives. Axis I diagnoses were based on the Structured Clinical Interview for DSM-IV-TR (39); Axis II diagnoses in relatives were captured via Structured Interview for DSM-IV Personality Disorders (40). Symptom ratings for psychosis and affective domains and estimates of premorbid intellectual functioning (38) were also gathered.

Magnetic Resonance Imaging Acquisition and Processing

T1-weighted structural images were acquired on 3T magnets across five sites; all subjects at each site were scanned on the same magnet for the duration of the study. T1-weighted magnetization prepared rapid acquisition gradient-echo or inversion recovery-prepared spoiled gradient recoil sequences, as appropriate for scanner brands, were administered following the Alzheimer's Disease Neuroimaging Initiative protocol (available at http://adni.loni.usc.edu/methods/documents/mri-protocols/). The sequence parameters and quality control procedures are detailed in Supplemental Methods.

Whole brain GMD voxelwise analyses with subsequent regional characterization and histogram techniques were used to investigate global and regional GMD biomarkers. The voxelwise analyses were carried out using optimized voxel-based morphometry (41) toolbox (VBM8) for SPM8 (available at http://www.fil.ion.ucl.ac.uk/spm/software/spm8), and incorporated the diffeomorphic anatomical registration through exponentiated lie algebra, a high-dimensional nonlinear inter-subject registration tool (42,43) (Supplemental Methods). To capture subject-level GMD characteristics and distribution patterns across the Biotype and DSM-IV-TR constructs, we implemented the histogram analysis (44,45) (detailed in Supplemental Methods).