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Archival Report

Gray Matter Neuritic Microstructure Deficits in Schizophrenia and Bipolar Disorder

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ABSTRACT

BACKGROUND: Postmortem studies have demonstrated considerable dendritic pathologies among persons with schizophrenia and to some extent among those with bipolar I disorder. Modeling gray matter (GM) microstructural properties is now possible with a recently proposed diffusion-weighted magnetic resonance imaging modeling technique: neurite orientation dispersion and density imaging. This technique may bridge the gap between neuroimaging and histopathological findings.

METHODS: We performed an extended series of multishell diffusion-weighted imaging and other structural imaging series using 3T magnetic resonance imaging. Participants scanned included individuals with schizophrenia (n = 36), bipolar I disorder (n = 29), and healthy controls (n = 35). GM-based spatial statistics was used to compare neurite orientation dispersion and density imaging–driven microstructural measures (orientation dispersion index and neurite density index [NDI]) among groups and to assess their relationship with neurocognitive performance. We also investigated the accuracy of these measures in the prediction of group membership, and whether combining them with cortical thickness and white matter fractional anisotropy further improved accuracy.

RESULTS: The GM-NDI was significantly lower in temporal pole, anterior parahippocampal gyrus, and hippocampus of the schizophrenia patients than the healthy controls. The GM-NDI of patients with bipolar I disorder did not differ significantly from either schizophrenia patients or healthy controls, and it was intermediate between the two groups in the post hoc analysis. Regardless of diagnosis, higher performance in spatial working memory was significantly associated with higher GM-NDI mainly in the frontotemporal areas. The addition of GM-NDI to cortical thickness resulted in higher accuracy to predict group membership.

CONCLUSIONS: GM-NDI captures brain differences in the major psychoses that are not accessible with other structural magnetic resonance imaging methods. Given the strong association of GM-NDI with disease state and neurocognitive performance, its potential utility for biological subtyping should be further explored.

Keywords: Bipolar disorder, GBSS, Gray matter microstructure, Neuritic density, NODDI, Schizophrenia

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Excessive synaptic pruning during adolescence and associated dendritic abnormalities have been implicated as a key pathophysiological process involved in major psychoses (1–4). Consistent with this hypothesis, postmortem studies of gray matter (GM) neuritic microstructure have shown lower dendritic marker (microtubule-associated protein 2 [MAP2]) density (5,6), dendritic tree arborization (7,8), and spine density (7,9,10) in individuals with schizophrenia. Although it has not been investigated as thoroughly, similar deficits in MAP2, dendritic spine density, and dendritic length have been reported in bipolar disorder (11,12). However, conflicting observations, limited number of brain regions examined, small sample sizes, and potential alterations during the postmortem interval before tissue fixation can limit interpretation of postmortem studies (2,13). In vivo neuroimaging of these neural substrates could provide opportunity for new knowledge of the neurobiological underpinnings of severe mental illnesses.

Previous studies of psychiatric disorders have typically focused on analysis of white matter (WM) microstructure using diffusion tensor imaging (14). However, recent advances in diffusion-weighted magnetic resonance imaging (MRI) acquisition and modeling have made it possible to examine GM microstructure in vivo (15–17). Neurite orientation dispersion and density imaging (NODDI) is a recently introduced biophysical diffusion modeling approach that approximates neurites (axons and dendrites) as a set of sticks with zero radii to capture the extremely restricted diffusion perpendicular to the neurites and unhindered diffusion along them (15). Thus, NODDI is well suited for microstructural modeling of GM tissue, which is primarily composed of dendritic trees and crossing axons, because it permits high dispersion of the neuritic orientations (15,18). This technique characterizes 1) the spatial configuration of the neurites with the orientation dispersion index (ODI) and 2) tissue microstructural composition with

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the neuritic density index (NDI), the volume fraction of neurites in brain tissue (15). We have recently shown in healthy individuals that these measures are sensitive to GM changes caused by aging, associated with cognitive performance, and are a better predictor of chronological age than cortical thickness or WM microstructure (19).

Robust differences in GM structural MRI and WM diffusion tensor imaging indices have been documented between individuals with schizophrenia or bipolar disorder and healthy individuals (20,21). However, these methods alone have been unable to fully discriminate between the diagnostic groups (22). Moreover, structural MRI studies have not consistently shown a strong association between GM macrostructure and cognitive deficits in schizophrenia or bipolar I disorder (BDI) (23). Although unique pathophysiological factors are likely involved in schizophrenia and BDI, these two disorders share some genetic risks, underlying pathology, and clinical symptoms (24,25). Using NODDI to characterize GM microstructure, our primary objective was to assess potential differences among individuals with schizophrenia, those with BDI, or those who are healthy (19,26). The majority of the neuropathological findings described in people with schizophrenia and BDI are located in the frontal and temporal lobes (27), and we therefore hypothesized that we would find neuritic abnormalities in the same areas among individuals with schizophrenia and BDI, but with smaller effects in those with BDI. Second, given that these regions are known to be involved in higher cognition, we also assessed the association between GM microstructure and cognitive performance. Finally, we conducted exploratory classification analysis to assess the diagnostic accuracy of NODDI-derived GM microstructural measures in isolation and in combination with other imaging metrics.

METHODS AND MATERIALS

Participants

Individuals with schizophrenia (n = 36) or BDI (n = 29) and healthy individuals of comparable age and sex (n = 35) were recruited at the Centre for Addiction and Mental Health in Toronto, Ontario, Canada (Table 1). All participants were administered the Structured Clinical Interview for DSM-IV-TR for Axis-I disorders and interviewed by a psychiatrist. The schizophrenia group comprised participants with a diagnosis of either schizophrenia or schizoaffective disorder who were assessed using the Positive and Negative Syndrome Scale. Participants with BDI were euthymic based on their scores on the Young Mania Rating Scale (<10) and Hamilton Depression Rating Scale (<10). The BDI group was enriched with patients with a positive history for psychosis (Table 1). To verify absence of a substance use disorder, a urine toxicology screen was obtained. Individuals with a positive urine toxicology screen, current substance abuse, a history of substance dependence within the past 6 months, and a history of severe head trauma (with loss of consciousness or

Table 1. Demographic, Cognitive, and Clinical Characteristics of the Participants[a]

	HC (n = 35)	SZ (n = 36)	BDI (n = 29)
Age, Years, Mean (SD) [Range]	33.6 (12.4) [20–56]	35.5 (8.4) [20–55]	31.5 (11.0) [20–56]
Sex, Female/Male	16/19	17/19	15/14
Education, Years, Mean (SD)	15.3 (2.2)	13.6 (2.1)	14.6 (1.7)
Ethnicity	23 white, 1 AC, 2 H, 7 Asian, 2 other	23 white, 9 AC, 2 H, 2 other	27 white, 2 Asian
HVLT-R, Mean (SD)	26.7 (4.7)	22.5 (5.8)	25.7 (2.6)
LNS, Mean (SD)	16.5 (2.5)	13.3 (2.8)	16.0 (2.0)
SSP, Mean (SD)	18.1 (3.7)	15.4 (3.4)	16.0 (2.7)
CPT-IP, Mean (SD)	3.1 (0.6)	2.3 (0.7)	2.5 (0.6)
BACS-SDC, Mean (SD)	65.1 (15.7)	52.1 (14.2)	53.7 (12.1)
DWI Motion, RMS, Mean (SD)	1.30 (0.27)	1.29 (0.26)	1.25 (0.30)
Age of Onset, Years, Mean (SD)	—	22.2 (5.5)	20.7 (6.1)
Disease Duration, Years, Mean (SD)	—	13.8 (9.3)	11.4 (9.3)
Disease Subtypes	—	27 SZ, 9 SZaff (5 BD type, 2 depressive type, 2 unknown)	23 psychotic, 5 nonpsychotic, 1 unknown
Chlorpromazine Equivalent, mg/day, Mean (SD)	—	314 (341)	212 (312)
Lithium Carbonate, mg/day, Mean (SD)	—	—	705 (618)
PANSS Positive, Mean (SD)	—	12.1 (4.7)	—
PANSS Negative, Mean (SD)	—	11.6 (3.2)	—
PANSS General, Mean (SD)	—	23.8 (6.0)	—
HDRS, Mean (SD)	—	—	4.6 (2.6)
YMRS, Mean (SD)	—	—	2.0 (2.0)

AC, African Canadian; BACS-SDC, Brief Assessment of Cognition in Schizophrenia, symbol-coding subtest; BDI, bipolar I disorder; CPT-IP, Continuous Performance Test, Identical Pairs; DWI, diffusion-weighted imaging; H, Hispanic; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; HVLT-R, Hopkins Verbal Learning Test-Revised; LNS, Letter-Number Sequence; PANSS, Positive and Negative Syndrome Scale; RMS, root mean square deviation (in mm); SSP, spatial span; SZ, schizophrenia; SZaff, schizoaffective disorder; YMRS, Young Mania Rating Scale.

[a]Between-group comparisons for demographic and cognitive characteristics are presented in Supplemental Table S7.