ORIGINAL ARTICLE

# Neuroimaging Evidence for the Deficit Subtype of Schizophrenia

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**Importance:** A major obstacle to the identification of the neurobiological correlates of schizophrenia is the substantial clinical heterogeneity present in this disorder. Dividing schizophrenia into "deficit" and "nondeficit" subtypes may reduce heterogeneity and facilitate identification of neurobiological markers of disease.

**Objective:** To determine whether patients with deficit schizophrenia differ from patients with nondeficit schizophrenia and healthy controls in neuroimaging-based measures of white matter tracts and gray matter morphology.

**Design:** A cross-sectional neuroimaging study of patients with the deficit or nondeficit subtype of schizophrenia and healthy controls.

**Setting:** University hospital.

**Participants:** Seventy-seven patients with schizophrenia and 79 healthy controls.

**Interventions:** All participants were administered the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders and the Positive and Negative Syndrome Scale; IQ was measured using the Wechsler Test for Adult Reading; global cognitive impairment was grossly assessed using the Mini-Mental State Examination; comorbid physical illness burden was measured by administration of the Clinical Information Rating Scale–Geriatrics; high-resolution magnetic resonance imaging was performed as part of a multimodal imaging protocol; and deficit status was determined using the proxy scale for the deficit syndrome.

**Main Outcome Measures:** Diffusion-based measures of white matter tracts, cortical thickness, cortical surface area, and volumes of subcortical structures.

**Results:** In both an individually matched approach (18 patients with deficit schizophrenia, 18 patients with nondeficit schizophrenia, and 18 healthy controls) and an unmatched population-based approach (18 patients with deficit schizophrenia, 59 patients with nondeficit schizophrenia, and 79 health controls), the patients with deficit schizophrenia demonstrated disruption of white matter tracts compared with patients with nondeficit schizophrenia and healthy controls at the right inferior longitudinal fasciculus, the right arcuate fasciculus, and the left uncinate fasciculus. These findings were supported in patients with first-episode schizophrenia (n=20) who had a deficit score that was strongly correlated with disruption at these same tracts. In contrast, patients with schizophrenia of either subtype exhibited cortical thickness reductions compared with healthy controls, in near-identical neuroanatomic patterns. Surface areas and subcortical volumes did not differ significantly among the 3 groups.

**Conclusions and Relevance:** The convergence of findings in our individually matched sample, our unmatched overall sample, and our first-episode schizophrenia sample demonstrate (1) white matter tract disruption as a neurobiological feature of the deficit syndrome and (2) reductions in cortical thickness as a common feature of patients with a diagnosis of schizophrenia. When taken with previous results in gray matter, our findings in white matter tracts point to neural circuitry important for socioemotional function as a core neurobiological feature of the deficit subtype of schizophrenia.

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Schizophrenia is a chronic and severe brain disorder that affects approximately 1% of the world's population. A major obstacle to the identification of the neurobiological correlates of disease in schizophrenia is that its current nosology likely reflects a group of diseases rather than a single disease entity.[1,2] Therefore, the neurobiological underpinnings of what is defined as *schizophrenia* may vary in different patient subgroups.

One well-defined clinical subgroup (approximately 15%-25% of patients with schizophrenia) are considered to have a "deficit" form of schizophrenia,[3] which is



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characterized by primary, enduring negative symptoms and impaired emotion processing, emotion expression, and social function.[2] The deficit syndrome is stable and enduring,[4,5] and it is present from the first episode of schizophrenia.[6] There are no effective treatments for these symptoms, which are major determinants of functional outcome.[7,8] The major impairments and low recovery rates of these patients make this group a high priority for investigation. Furthermore, studying this more clinically homogeneous subgroup may facilitate biomarker discovery,[2,9] which has been a challenge not only for schizophrenia but for psychiatry research as a whole.[2,9,10]

The advent of magnetic resonance imaging (MRI) provided early promise for the discovery of the neuroanatomical correlates of disease for schizophrenia.[11] However, the heterogeneity of the disease and the grouping together of all patients with a diagnosis of "schizophrenia" have likely served as an obstacle to such discovery. Some neuroimaging studies in clinical subtypes of schizophrenia, including the deficit syndrome, have been conducted.[12,13] However, more recent MRI-based analysis approaches, such as cortical thickness mapping, surface area analysis, and diffusion tensor imaging (DTI) of white matter tracts (with the exception of recent findings in the right arcuate[13] and the uncinate fasciculus,[14] both thought to be involved in socioemotional function), have not yet been applied to compare clinical subtypes of schizophrenia. Such a neuroimaging combination in the same study population has the potential to provide sophisticated answers about potentially vulnerable neural circuitry and tissue specificity, which could identify differences between deficit and nondeficit schizophrenia. Therefore, using this combination of neuroimaging approaches, we hypothesized that we would (1) identify unique neurobiological markers in patients with the deficit subtype of schizophrenia (hereafter referred to as deficit patients), compared with patients with nondeficit schizophrenia (hereafter referred to as nondeficit patients) and healthy controls, in regions or circuitry important for socioemotional function, and (2) identify structural brain differences shared by deficit and nondeficit patients compared with healthy controls.

## METHODS

### PARTICIPANTS

Participants were recruited at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, via referrals, study registries, and advertisements. All clinical assessments occurred at CAMH while DT-MRI scans were performed at a nearby general hospital in Toronto. Community-dwelling outpatients (n=77) with schizophrenia and healthy controls (n=79) ranging from 18 to 67 years of age participated in our study and completed all measures. All participants were administered the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders[15] to determine diagnosis and duration of illness, and they were interviewed by a psychiatrist to ensure diagnostic accuracy. The Positive and Negative Syndrome Scale (PANSS)[16] was administered to further characterize illness symptoms. IQ was measured using the Wechsler Test for Adult Reading,[17] and global cognitive impairment was grossly assessed using the Mini-Mental State Examination.[18] Comorbid physical illness burden was measured by administration of the Clinical Information Rating Scale–Geriatrics.[19] Medication histories were initially recorded via self-report and then verified either by the patient's treating psychiatrist or by chart review. All participants received urine toxicology screens, and anyone with current substance abuse or any history of substance dependence was excluded. Individuals with previous head trauma with loss of consciousness or with neurological disorders were also excluded. For controls, a history of a primary psychotic disorder in first-degree relatives was also an exclusion criterion.

Deficit patients were identified among the 77 patients with schizophrenia and were individually matched to nondeficit patients and healthy controls based on the following: age within 5 years, sex, highest level of parental education, and handedness (Edinburgh handedness inventory).[20] After receiving a complete description of our study, participants provided written, informed consent. Our study was approved by the CAMH ethics review board.

### DEFICIT SYNDROME CLASSIFICATION

Characterization of the deficit syndrome was completed according to the proxy case identification method (ie, the proxy for the deficit syndrome [PDS] using the PANSS).[21] The PDS has good specificity, sensitivity, and accuracy for identification of deficit patients.[21] Furthermore, the PDS has been repeatedly shown to be a valid tool for the categorization of patients with schizophrenia into deficit and nondeficit groups, in both early-episode and chronic populations.[22-27] Moreover, studies have examined the stability of the deficit syndrome classification using this proxy case identification method and have shown the PDS characterization to be stable over the short term (24 months)[28] and across serial assessments over a 20-year follow-up period.[5] Overall, these cited studies support that the PDS provides a valid categorization of deficit and nondeficit schizophrenia over the longer term.[22] Specifically, the PDS is defined as the sum of the scores (from the PANSS) of the anxiety, guilt feelings, depressive mood, and hostility items subtracted from the blunted affect item score. A cut point of −2 was used to classify deficit vs nondeficit patients.[21] In our sample, a second PANSS was available on a subset of 20 schizophrenia patients (of the 77 total) who repeated all clinical measures 1 year later as part of our group's ongoing clinical research studies, which enabled us to evaluate the temporal stability of the PDS in these patients.

### NEUROIMAGING

#### Image Acquisition

High-resolution magnetic resonance images were acquired as part of a multimodal imaging protocol using an 8-channel head coil on a 1.5-T GE Echospeed system (General Electric Medical Systems), which permits maximum gradient amplitudes of 40 mT/m. Axial inversion recovery–prepared spoiled gradient recall images were acquired: echo time, 5.3 milliseconds; repetition time, 12.3 milliseconds; time to inversion, 300 milliseconds; flip angle, 20°; and number of excitations, 1 (for a total of 124 contiguous images with 1.5-mm thickness). For DTI, a single-shot spin echo planar sequence was used with diffusion gradients applied in 23 noncollinear directions and $b=1000$ s/mm$^2$. Two $b=0$ images were obtained. Fifty-seven slices were acquired for whole-brain coverage oblique to the axial plane, obtained parallel to the plane passing through the anterior and posterior commissures (ie, anterior commissure–posterior commissure aligned). Slice thickness was 2.6 mm, and voxels were isotropic. The field of view was 330 mm, and the size of the



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acquisition matrix was 128 × 128 mm, with an echo time of 85.5 milliseconds and a repetition time of 15 000 milliseconds. The entire sequence was repeated 3 times to improve the signal to noise ratio.

### Image Processing

All T1-weighted MR images were submitted to the CIVET pipeline (version 1.1.10; Montreal Neurological Institute at McGill University). T1 images were registered to the ICBM152 nonlinear sixth-generation template with a 9-parameter linear transformation, inhomogeneity corrected[29] and tissue classified.[30,31] Deformable models were then used to create white and gray matter surfaces for each hemisphere separately, resulting in 4 surfaces of 40 962 vertices each.[32] From these surfaces, the t-link metric was derived for determining the distance between the white and gray surfaces.[33] The thickness data were subsequently blurred using a 20-mm surface–based diffusion blurring kernel in preparation for statistical analyses. Unnormalized, native-space thickness values were used in all analyses owing to the poor correlation between cortical thickness and brain volume.[34] For the calculation of surface area, the middle cortical surface, which lies at the geometric center between the inner and outer cortical surfaces, was used.[35]

For calculation of subcortical volumes, FSL (FMRIB [Functional MRI of the Brain] Software Library; http://www.fmrib.ox.ac.uk) was used. Each patient's T1-weighted image was processed using the FMRIB Integrated Registration and Segmentation Tool (version 1.2) automated subcortical segmentation pipeline included in the open-access FSL (version 4.1.8) package providing volumes for the hippocampus, amygdala, thalamus, caudate, putamen, globus pallidus, and nucleus accumbens. Brain tissue volume, normalized for head size, was estimated with SEINAX, which is part of FSL.

For DTI analysis, the 3 repetitions were coregistered to the first $b=0$ image in the first repetition using the FMRIB Linear Image Registration Tool within FSL (version 4.0) to produce a new averaged image, with gradients reoriented using a weighted least squares approach. Registration corrects eddy current distortions and subject motion, important artifacts that can affect the data, and averaging improves the signal to noise ratio. A brain mask was then generated. Points were seeded throughout each voxel of the brain. Whole-brain tractography was performed with a deterministic (streamline) approach (Runge-Kutta order 2 tractography with a fixed step size of 0.5 mm). More detailed descriptions of our tractography approach and our clustering segmentation algorithm have been recently published[36,37] and are summarized herein. Threshold parameters for tractography were based on the linear anisotropy measure $C_L$, which provides specific advantages over thresholding using fractional anistrophy.[38] The parameters chosen for our study were $T_{seed}=0.3$ mm, $T_{stop}=0.15$ mm, and $T_{length}=20$ mm. Tractography, creation of white matter fiber tracts, and clustering segmentation were performed using the 3D Slicer (http://www.slicer.org) and Matlab, version 7.0 (The Mathworks Inc; http://www.mathworks.com).

Once the whole-brain cluster model was produced, a trained operator (A.N.V.) combined clusters corresponding to a given fiber tract. Frontotemporal and interhemispheric white matter tracts with evidence for disruption in schizophrenia were selected: the left and right uncinate fasciculi, the inferior occipitofrontal fasciculus, the cingulum bundle, the inferior longitudinal fasciculus, the arcuate fasciculus, and the genu and splenium of the corpus callosum. As reported elsewhere,[37] excellent spatial and quantitative reliability using this clustering method (ie, both voxel overlap and scalar measures of the tensor showed high agreement) has been demonstrated. For each white matter tract, Matlab (version 7.0) was used to calculate mean measures of fractional anisotropy and mean diffusivity[39] along the selected tract. Fractional anisotropy provides measures of directionally dependent diffusion, and thus lower fractional anisotropy reflects a decrease in the directional organization of the white matter fibers (potentially reflecting several factors, such as axonal density, the configuration of axonal packing, or myelin integrity), whereas the mean diffusivity is a measure of the magnitude of diffusion, and thus increases in mean diffusivity reflect a diminished structural integrity of the tissue that could be due to atrophy, inflammation, or other cellular changes.[39,40] Mean diffusivity is a "rotationally invariant" measure whose value is independent of the orientation of anisotropic structures within a voxel.[41]

## STATISTICAL ANALYSIS

Three groups were compared: deficit patients, nondeficit patients, and healthy controls. The first set of neuroimaging comparisons were conducted with the 18 deficit patients who were individually matched on several demographic and clinical variables to 18 nondeficit patients and 18 healthy controls. We then conducted the same neuroimaging comparisons of the 18 deficit patients with the entire sample of 59 nondeficit patients and 79 healthy controls to determine whether any findings in the individually matched groups would be replicated in an unmatched population-based sample. Demographic and clinical characteristics were compared using *t* tests and analysis of variance, as appropriate for the individually matched sample (eTable 1, jamapsych.com) and for the overall unmatched sample (eTable 2). For comparisons of DTI data, a repeated-measures analysis of covariance model was used, with age as a covariate. Separate analyses were conducted for fractional anisotropy and mean diffusivity. Twelve within-group factors were studied: the mean fractional anisotropy (or mean diffusivity) for each of the 12 white matter tracts. Where the main effects of "group" or a group × diffusion measure interaction were found, post hoc *t* tests were conducted. For individual tract analyses, Bonferroni correction for 12 comparisons ($P<.05$) was applied (ie, $P<.004$). When a significant difference was found, tract volume, duration of illness, and chlorpromazine equivalents of medication dosage[42] were regressed against fractional anisotropy (or mean diffusivity) for that fiber tract, to correct for any influence of these variables.

For comparisons of cortical thickness and surface area, the general linear model was used. In this model, "group" was the between-group factor, and age and sex were used as covariates. For cortical thickness and surface area comparisons, a false discovery rate correction threshold of 0.05 was applied, and the analysis was also checked using a threshold of 0.1 to rule out false-negative results[43] (ie, to ensure that differences between groups were not missed). For subcortical volumetric structures, the 3 groups were compared with age and total brain volume as covariates, using a univariate analysis of covariance for each structure, and Bonferroni correction for multiple comparisons was applied.

## RESULTS

Of the 77 patients with schizophrenia, 18 were classified as having the deficit syndrome according to the PDS. No significant differences were present between the individually matched deficit and nondeficit groups on any demographic variables or on medical comorbidity, age at onset, or duration of illness. Healthy controls had more years of education than did deficit and nondeficit patients, and they had higher IQs than did deficit patients (eTables 1 and 2).



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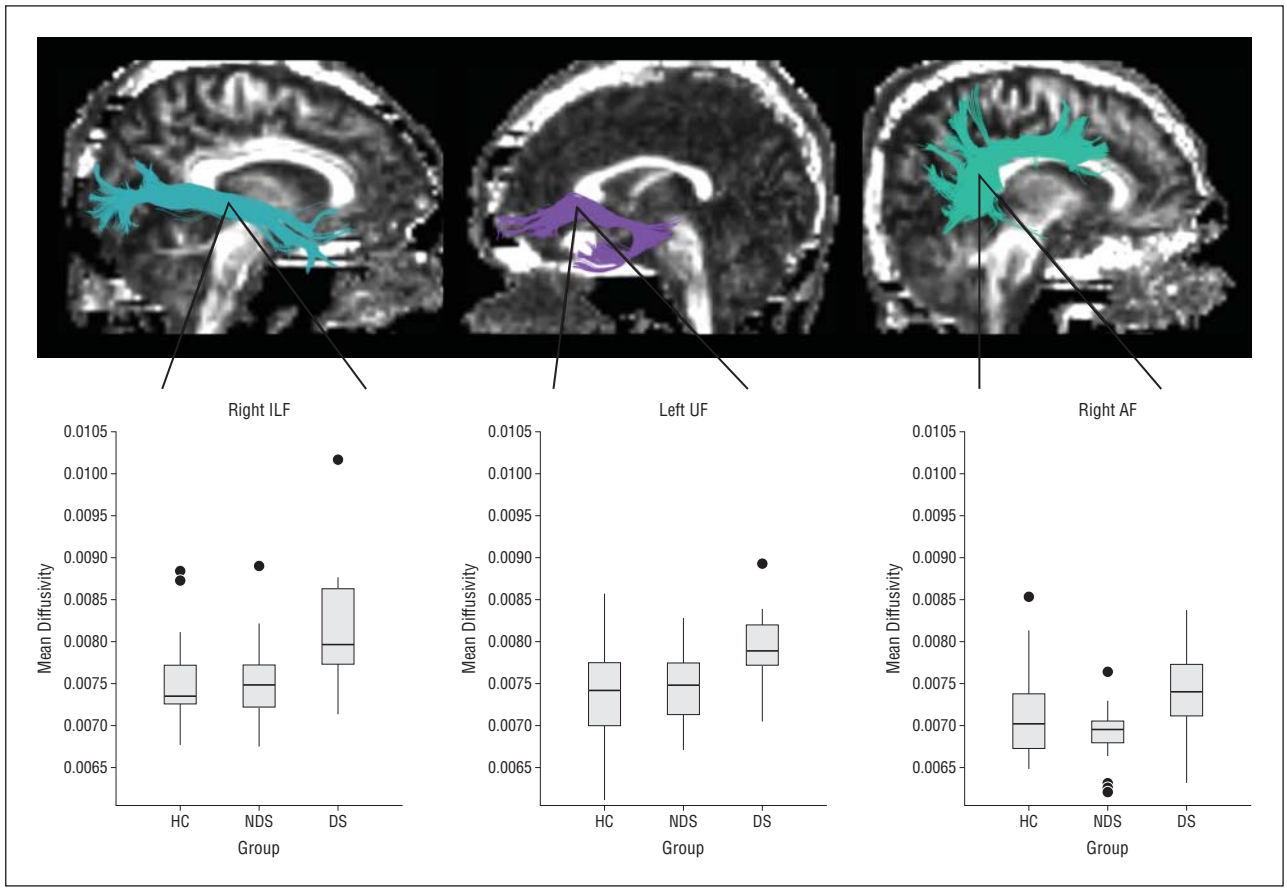


**Figure 1.** Comparison of mean diffusivity for patients with deficit syndrome (DS), patients with nondeficit syndrome (NDS), and healthy controls (HC) in white matter tracts using box and whisker plots. The box boundaries represent first and third quartiles, and the midline is the median. Dots represent values more than 1.5 box lengths from the upper or lower edges, and a reanalysis without these data points did not change the significant results. The patients with DS demonstrated increased mean diffusivity (from left to right) at the right inferior longitudinal fasciculus (ILF), the left uncinate fasciculus (UF), and the right arcuate fasciculus (AF) in both the individually matched sample and the overall sample. Data presented here are from the individually matched sample.

Consistent with the classification of an "ideal deficit group," as previously described,[2] deficit patients had higher negative symptoms scores than did nondeficit patients, and these scores were not due to other factors such as positive symptoms or the burden of adverse effects of medication (assessed with the Abnormal Involuntary Movement Scale, the Simpson-Angus Scale, and the Barnes Akathisia Scale). Positive symptoms scores were no different between groups; dysphoric symptoms were substantially lower in deficit patients than in nondeficit patients; a similar duration of psychotic illness was present; and our deficit sample was of a prevalence comparable to that in published studies. The mean (SD) PDS score of the deficit group was −0.6 (1.2), which was significantly different from that of the nondeficit group with a mean (SD) PDS score of −5.2 (2.2) ($t_{34}$=7.7, $P$<.001, and Cohen $d$=2.6), and was comparable to the original report establishing the validity of the PDS.[21]

From the 20 patients with schizophrenia who were administered a second PANSS 1 year later, we found that the PDS score had very good reliability, with an intraclass correlation of 0.84 ($P$<.001). Importantly, all of these patients retained their respective original deficit or nondeficit classification.

For DTI-based measures, there was a significant main effect of group on fractional anisotropy ($F_{2,50}$=4.0, $P$=.02). No group×tract fractional anisotropy interaction was found (Greenhouse-Geisser correction: $F_{11,550}$=1.0, $P$=.43). Follow-up univariate analyses of covariance revealed that deficit patients had lower fractional anisotropy values than did nondeficit patients at the left uncinate fasciculus ($F_{3,50}$=8.3, $P$=.001). In 2 tracts, differences were detected at a $P$=.05 level, but they did not meet the Bonferroni-corrected threshold: the right arcuate fasciculus ($F_{2,50}$=3.4, $P$=.04) and the splenium of the corpus callosum ($F_{2,50}$=5.4, $P$=.008). Effect sizes for these 3 tracts were large (eg, for the left uncinate fasciculus, partial $\eta^2$=0.25; **Figure 1**). Nondeficit patients did not differ from healthy controls regarding the mean fractional anisotropy for any of the 12 measured tracts.

There was a significant main effect of group on mean diffusivity ($F_{2,50}$=4.6, $P$=.01). No group×tract mean diffusivity interaction was found (Greenhouse-Geisser correction: $F_{2,50}$=1.7, $P$=.06). Follow-up univariate analyses of covariance revealed that deficit patients had a higher mean diffusivity than did nondeficit patients and healthy controls with large effect size (partial $\eta^2$=0.21 for both tracts) at the left uncinate fasciculus ($F_{2,50}$=7.0, $P$=.002) and the right inferior longitudinal fasciculus ($F_{2,50}$=6.6, $P$=.003). Although it did not meet the Bonferroni-corrected threshold, a large effect ($\eta^2$=0.19) was also seen at the right arcuate fasciculus ($F_{2,50}$=5.5, $P$=.007) (eTable



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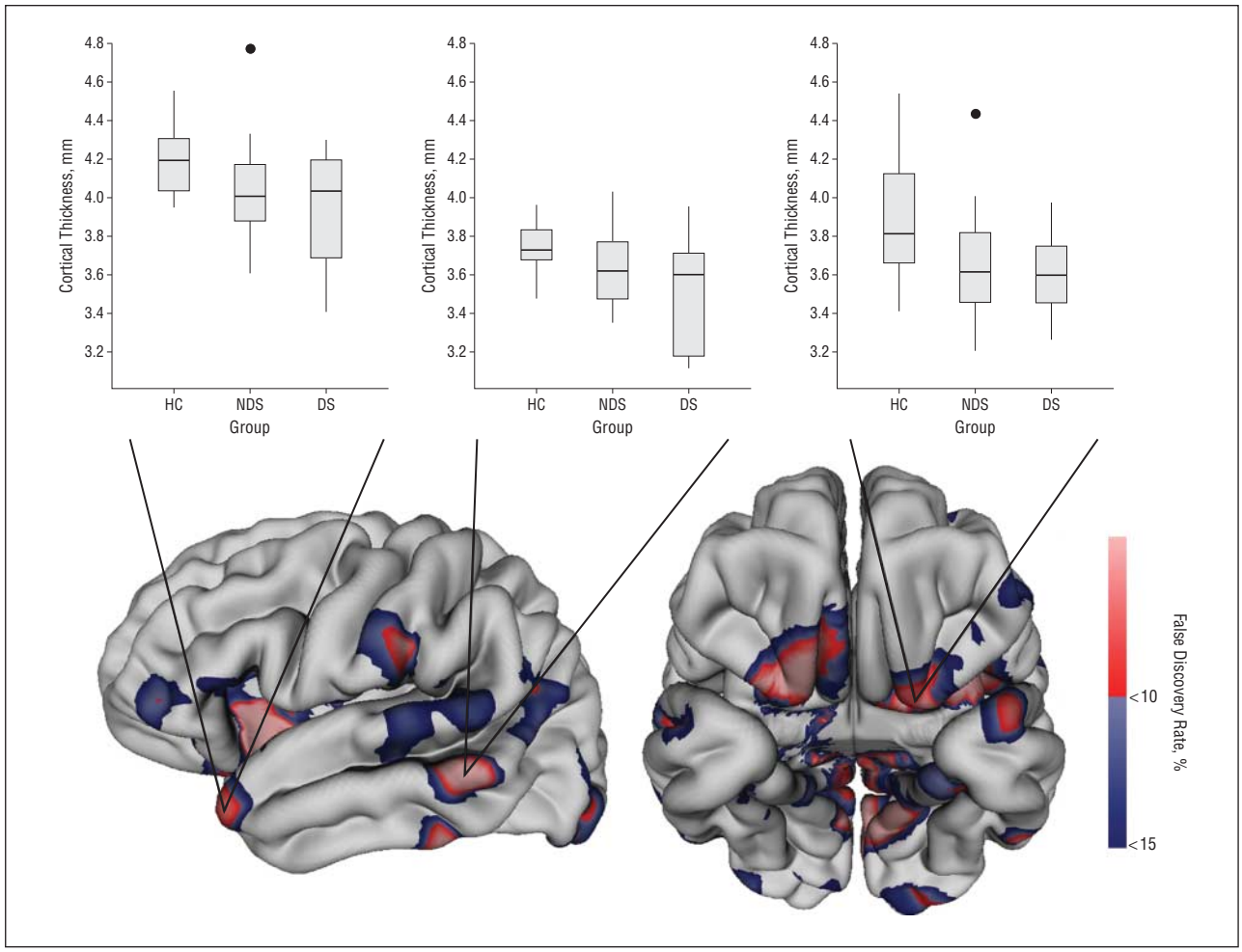


**Figure 2.** Comparison of cortical thickness for patients with deficit syndrome (DS), patients with nondeficit syndrome (NDS), and healthy controls (HC) using box and whisker plots. The box boundaries represent first and third quartiles, and the midline is the median. Dots represent values more than 1.5 box lengths from the upper or lower edges, and a reanalysis without these data points did not change the significant results. The patients with DS or NDS demonstrated reductions in cortical thickness compared with HC at several regions in both the individually matched and overall samples. These reductions are demonstrated in the individually matched sample (from left to right) at the temporal pole, the middle temporal gyrus, and the orbitofrontal cortex.

3). Nondeficit patients did not differ from healthy controls regarding mean diffusivity for any of the 12 tracts measured. No correlation of fractional anisotropy or mean diffusivity was found in relation to tract volume, duration of illness, or chlorpromazine mean equivalent dose.

When the 18 deficit patients were compared with all 59 nondeficit patients and 79 healthy controls, similar results were found. The white matter tracts with the most prominent disruption (as indexed by mean diffusivity) that also met Bonferroni correction occurred at the right inferior longitudinal fasciculus ($F_{2,152}=11.3$, $P<.001$) and the right arcuate fasciculus ($F_{2,152}=6.8$, $P=.001$). The left uncinate fasciculus ($F_{2,152}=4.2$, $P=.02$) also demonstrated increased mean diffusivity (less than an uncorrected $P=.05$ level) but did not meet the Bonferroni correction. All other white matter tract mean diffusivity measures were not different among the 3 groups ($P>.05$).

Analysis of cortical thickness revealed several regions (**Figure 2**) with reduced thickness in both deficit and nondeficit patients compared with healthy controls with large effect size, including the left orbitofrontal cortex, the middle temporal gyrus, the temporal pole, the dorsolateral prefrontal cortex, the parietal operculum, the parahippocampal gyrus, the superior temporal gyrus, and the insula (see eTable 4 for the coordinates in Montreal Neurological Institute space). The findings were bilateral. Similar results were found in the comparison of the 18 deficit patients, the 59 nondeficit patients, and the 79 healthy controls. In several regions, the magnitude of difference was larger for the deficit patients in the right hemisphere, but this was not statistically significant. No differences in cortical surface area were found. Subcortical volumetric analysis showed no statistically significant differences among the 3 groups (total brain volume and age were included as covariates in the model, and there was no difference in total brain volume among the 3 groups [$F_{3,50}=0.18$, $P=.83$]). However, the pattern and magnitude of nonsignificant reduction were similar in both schizophrenia groups compared with controls for hippocampal volume (eFigure) (left: $F_{4,49}=1.8$, $P=.18$; right: $F_{4,49}=2.1$, $P=.13$), and the pattern and magnitude of nonsignificant increases were similar in both schizophrenia groups compared with controls for the volume of the putamen (left: $F_{4,49}=2.4$, $P=.10$; right: $F_{4,49}=1.1$, $P=.30$) and for the volume of the globus pallidus (left: $F_{4,49}=2.0$, $P=.14$; right: $F_{4,49}=3.2$, $P=.06$).



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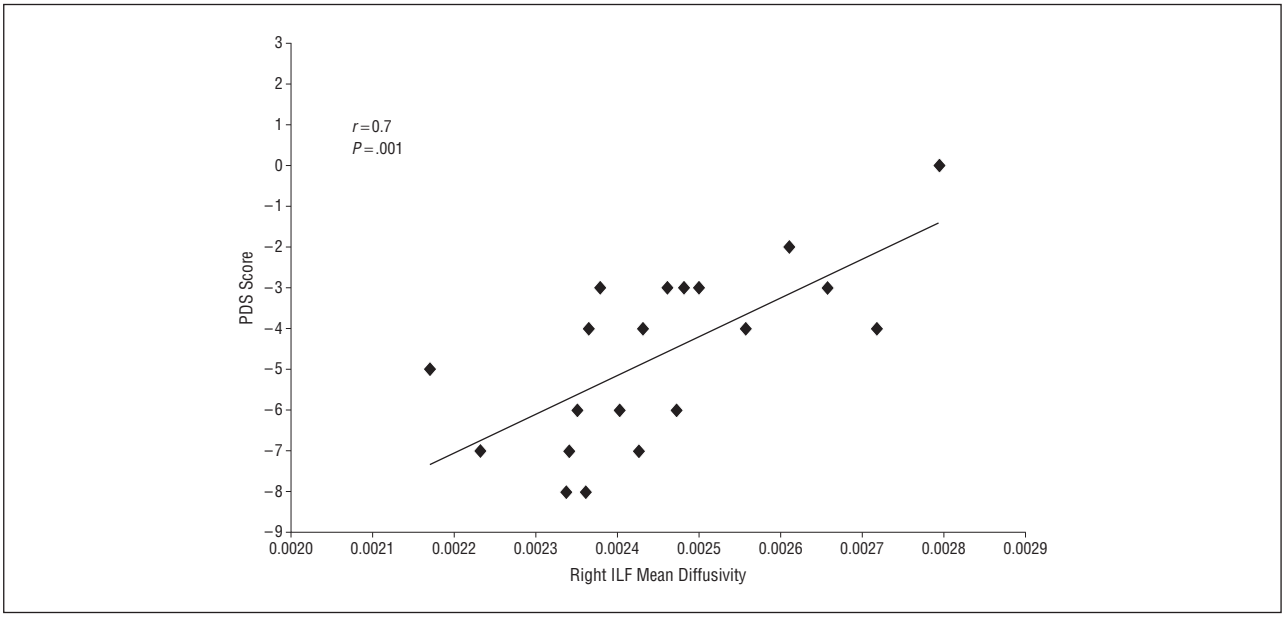


**Figure 3.** Correlation of the proxy for the deficit syndrome (PDS) score with the mean diffusivity of the right inferior longitudinal fasciculus (ILF) in 20 first-episode patients with schizophrenia.

## POST HOC ANALYSIS

We conducted a post hoc analysis with 20 patients with first-episode schizophrenia who were recruited from the first-episode psychosis clinic at CAMH and who underwent all clinical characterization and neuroimaging protocols already described to help rule out the possibility that our findings were due to medication effects, duration of illness, or other confounders that may limit interpretability of the results in a sample of patients with chronic schizophrenia. All of the first-episode participants had illness onset within the past 3 years and had a history of less than 3 years of antipsychotic medication treatment. We used the PDS as a continuous measure, to determine whether patients with a greater burden of deficit syndrome characteristics had a concomitantly greater impairment in brain structure. These patients had a mean (SD) age of 24 (5) years (range, 18-35 years; composed of 16 men and 4 women). Their demographic (years of education, highest level of parental education, and IQ) and clinical characteristics (assessed with the PANSS, the Abnormal Involuntary Movement Scale, the Simpson-Angus Scale, and the Barnes Akathisia Scale) were not different from the remainder of the schizophrenia sample (data not shown). However, the mean (SD) duration of antipsychotic medication exposure was 8 (6) months. Because the right inferior longitudinal fasciculus met Bonferroni correction in both the individually matched sample and the overall sample, we considered it our most rigorous finding. These patients were not different from the matched healthy controls in right inferior longitudinal mean diffusivity. However, when we conducted a Pearson correlation comparing PDS score with right inferior longitudinal fasciculus mean diffusivity, we found a striking relationship ($r = 0.7$, $P = .001$). First-episode patients with higher PDS scores had a higher right inferior longitudinal fasciculus mean diffusivity (**Figure 3**). Significant but less striking correlations were present in the 2 tracts that reached Bonferroni-corrected significance in one sample and Bonferroni-uncorrected significance in the other sample with PDS score: the right arcuate fasciculus mean diffusivity ($r = 0.51$, $P = .02$) and the left uncinate fasciculus mean diffusivity ($r = 0.55$, $P = .01$).

## COMMENT

We examined both the diffusion-based measures of white matter tracts and the analysis of cortical thickness, surface area, and subcortical volumetric measures in deficit patients individually matched to nondeficit patients and healthy controls; we then completed a similar analysis to confirm our results in the larger sample of all individuals in our study. We identified extensive white matter tract disruption in deficit patients compared with nondeficit patients and healthy controls. Our finding within first-episode patients that a more "deficit-like" clinical picture was associated with greater impairment within these same white matter tracts supports the fact that white matter disruption in these patients is a feature of the clinical deficit subtype, rather than other factors such as long-term medication exposure or duration of illness. In contrast, we also found that cortical thickness reductions were present in the same regions in both deficit and nondeficit patients compared with healthy controls, which supports the consistency of cortical thickness findings in different clinical subtypes. The similarity of the results in the individually matched sample and in the overall sample, along with our results from the first-episode sample, provides robust added confidence to our findings.

Overall, the significant main effect of "group" on diffusion-based measures of white matter tracts supports the likelihood of a widespread, subtle alteration of white matter (as reflected by increases in mean diffusivity and reductions in fractional anisotropy) in deficit patients. However, the most profound alterations in these patients occurred at key white matter tracts (ie, the right inferior



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longitudinal, the right arcuate, and the left uncinate fasciculi) that form neural circuitry connecting regions involved in emotion expression, emotion processing, and socioemotional functioning, all characteristically impaired in deficit patients. The right inferior longitudinal fasciculus, disrupted in deficit patients compared with nondeficit patients and healthy controls, met Bonferroni-corrected thresholds in both samples. Such findings provide strong evidence that this tract is impaired in deficit patients, which is further supported by the tight correlation of the right inferior longitudinal fasciculus mean diffusivity with PDS score in the first-episode sample. The right inferior longitudinal fasciculus is critical for facial recognition and visuoemotional processing[44] and connects the visual cortex to the fusiform gyrus, the amygdala, and the parahippocampal region. Damage to the inferior longitudinal fasciculus impairs facial recognition and the ability to process facial expression of emotion.[45] Deficit patients have difficulty in facial affect labeling and have poorer performance than nondeficit patients on basic visuoperceptual face processing tasks.[46,47] Disruption of the right inferior longitudinal fasciculus may provide a mechanistic explanation for the impairments in emotion perception and interpretation characteristic of deficit patients via their inability to effectively process facial affect.

We also found disruption of the right arcuate fasciculus in deficit patients compared with nondeficit patients and healthy controls at an uncorrected significance level in the individually matched sample and at the Bonferroni-corrected threshold in the complete, unmatched sample. Our finding is supported by the only other DTI study to examine deficit patients,[13] which reported data on the right and left arcuate fasciculi, with significant differences in right arcuate integrity. Therefore, we believe that there is a compelling case for disruption of this tract in deficit patients. Alterations of the right frontoparietal network have been shown in patients with schizophrenia with predominant negative symptoms, and reduced functional activation has also been shown in deficit patients participating in tasks that engage this network.[48] This right-lateralized frontoparietal network is associated with self-recognition and social understanding.[49] Both the "self-face" and the "self-body" activate the right frontoparietal network in functional neuroimaging studies.[50] Furthermore, repetitive transcranial magnetic stimulation to the right inferior parietal lobule disrupts self-other discrimination.[51] Of note, the cortical regions connected by the right arcuate fasciculus (right inferior parietal lobule to right frontal operculum) comprise the mirror neuron system.[49] The frontoparietal mirror neuron areas of the brain can effectively function as a bridge between self and other. Whether mirror neuron disruption is a specific mechanism that can explain right frontoparietal disruption in the deficit syndrome is unknown, but the emerging capability to engage mirror neurons in vivo[52,53] represents an important opportunity and novel direction for the field. Finally, it is also notable that the uncinate fasciculus was disrupted in deficit patients compared with other patients and healthy controls, at a Bonferroni-corrected significance in the individually matched sample and at an uncorrected significance in the complete sample. The uncinate fasciculus connects the orbitofrontal cortex to the temporal pole and the amygdala, forming circuitry essential for social cognition and socioemotional processing, which are impaired in deficit patients,[12] and our findings support the results of a recent investigation.[14]

There is a substantial amount of postmortem work supporting alterations of white matter gene expression in schizophrenia.[54,55] Only 2 postmortem studies[56,57] of deficit patients have been published, and they report increased interstitial cells of the white matter in the parietal cortex[56] and the frontal cortex,[57] respectively. The studies from the postmortem schizophrenia literature implicating alterations in the expression of genes that code for white matter proteins or white matter development[58] compared patients with schizophrenia, as a group, with healthy controls. However, as in neuroimaging studies, postmortem work in schizophrenia has been plagued by heterogeneity.[59] Within DTI schizophrenia studies, although there is some consistency of findings to date,[60] we propose that, among other explanations, the heterogeneity of results may be predicated on the number of deficit patients present in a given sample.

Unlike white matter disruption, cortical thickness reductions were found in both deficit and nondeficit patients compared with healthy controls, and thus they may serve as a unifying neurobiological finding in schizophrenia. Until the present study, to our knowledge, there had been no examination of cortical thickness in deficit patients. The pattern of cortical thickness deficits in both deficit and nondeficit patients align closely with the existing literature for schizophrenia[61]; we found a pattern of cortical thickness deficits in the orbitofrontal cortex, the middle and superior temporal gyri, the dorsolateral prefrontal cortex, the parahippocampal gyrus, and the occipitotemporal cortex. Of note, these cortical thickness reductions were shown in primarily the same brain regions across both deficit and nondeficit patients. Therefore, our data support the contention that cortical thickness reduction in these regions is a characteristic feature of the clinical syndrome of schizophrenia. Many studies have examined hippocampal volumes in schizophrenia, with both positive[62] and negative[63] results. In our study, deficit and nondeficit groups had a nearly identical magnitude of reduction of hippocampal volume and a nearly identical increase in striatal volumes compared with healthy controls, but these reductions did not reach statistical significance. When taken together, our results suggest that subcortical volumetric changes are not characteristic of the deficit syndrome.

Our main results feature groups of patients with a long mean duration of illness and a history of antipsychotic medication exposure. Although the deficit and nondeficit groups were carefully matched on these variables, one cannot rule out that such confounders potentially influenced our results. Therefore, we included data from a first-episode sample, which should reduce concerns in relation to age, duration of illness, or medication effects. These data were particularly helpful in light of recent, somewhat conflicting reports regarding the effects of these variables on cortical brain structure.[64,65] With respect to diffusion-based measures in white matter, there is little evidence to date for major effects of antipsychotic medication or duration of illness.[66] In fact, there are data suggesting that certain atypi-



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cal antipsychotics may be protective for tissue substrates in white matter that form the main barriers for water diffusion.[67] Another limitation of our study is our use of the PDS, coupled with the fact that longitudinal clinical data were not available for all participants to confirm their deficit status. Although all 20 of our patients for whom such data were present retained their original PDS classification, and although the vast majority of participants had a deficit status that remained stable over time,[5] it is likely that a small number of individuals might no longer be classified as having deficit schizophrenia over a longer longitudinal course.[68,69] Finally, although our findings provide strong evidence for impairment of white matter tracts in deficit patients only, the exact functional sequelae of these impairments in the patients that we studied are unknown. Future studies examining direct anatomofunctional relationships in these circuits critical for emotion perception and expression, in combination with functional outcome data, will provide essential further insight into the relationship between the neurobiology of this clinical subtype and its real-world impact.

In summary, we found that deficit patients exhibited disruption of white matter tracts that form the core neural circuitry essential for the emotional and social functions characteristically impaired in these patients. At the same time, the nearly identical locations of cortical thickness reduction in both groups of patients compared with healthy controls provides evidence for a pattern of neural deficits common to patients with schizophrenia. When taken together, these results point to white matter tract disruption as a neurobiological marker of the deficit clinical subtype and offer a paradigm for reduced heterogeneity in psychiatric diseases.

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**Conflict of Interest Disclosures:** Within the past 5 years, Dr Pollock has been a member of the advisory board of Lundbeck Canada (his final meeting was May 2009) and Forest Laboratories (his final meeting was March 2008). Dr. Pollock has served one time as a consultant for Wyeth (October 2008) and Takeda (July 2007). He was also a faculty member of the Lundbeck International Neuroscience Foundation (his final meeting was April 2010). Dr Mulsant currently receives medications from Bristol-Myers Squibb and Pfizer/Wyeth to be used in clinical trials funded by the National Institute of Mental Health. During the past 5 years, he has also received research support or honoraria from AstraZeneca, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen, Lundbeck, and Pfizer. Dr Remington has received research support or honoraria during the past 5 years from Novartis, Roche, Medicure, and Neurocrine Biosciences. Dr Foussias has been involved in research sponsored by Medicure and Neurocrine Bioscience and has served as a consultant for Roche.
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