Further Neuroimaging Evidence for the Deficit Subtype of Schizophrenia
A Cortical Connectomics Analysis

Anne L. Wheeler, PhD; Michèle Wessa, PhD; Philip R. Szeszko, PhD; George Foussias, MD, MSc; M. Mallar Chakravarty, PhD; Jason P. Lerch, PhD; Pamela DeRosse, PhD; Gary Remington, MD, PhD; Benoit H. Mulsant, MD; Julia Linke, PhD; Anil K. Malhotra, MD; Aristotle N. Vøineskos, MD, PhD

**IMPORTANCE** The clinical heterogeneity of schizophrenia has hindered neurobiological investigations aimed at identifying neural correlates of the disorder.

**OBJECTIVE** To identify network-based biomarkers across the spectrum of impairment present in schizophrenia by separately evaluating individuals with deficit and nondeficit subtypes of this disorder.

**DESIGN, SETTING, AND PARTICIPANTS** A university hospital network-based neuroimaging study was conducted between February 1, 2007, and February 28, 2012. Participants included patients with schizophrenia (n = 128) and matched healthy controls (n = 130) from two academic centers and patients with bipolar I disorder (n = 39) and matched healthy controls (n = 43) from a third site. Patients with schizophrenia at each site in the top quartile on the proxy scale for the deficit syndrome were classified as having **deficit schizophrenia** and those in the bottom quartile were classified as having **nondeficit schizophrenia**.

**EXPOSURE** All participants underwent magnetic resonance brain imaging.

**MAIN OUTCOMES AND MEASURES** Network-level properties of cortical thickness were assessed in each group. Interregional cortexwide coupling was compared among the groups, and graph theoretical approaches were used to assess network density and node degree, betweenness, closeness, and eigenvector centrality.

**RESULTS** Stronger frontoparietal and frontotemporal coupling was found in patients with deficit schizophrenia compared with those with nondeficit schizophrenia (17 of 1326 pairwise relationships were significantly different, \( P < .05; \) 5% false discovery rate) and in patients with deficit schizophrenia compared with healthy controls (49 of 1326 pairwise relationships were significantly different, \( P < .05; \) 5% false discovery rate). Participants with nondeficit schizophrenia and bipolar I disorder did not show significant differences in coupling relative to those in the control groups (for both comparisons, 0 of 1326 pairwise relationships were significantly different, \( P > .05; \) 5% false discovery rate). The networks formed from patients with deficit schizophrenia demonstrated increased density of connections relative to controls and nondeficit patients (range, 0.07-0.45 in controls, 0.09-0.43 in the nondeficit group, and 0.18-0.67 in the deficit group). High centrality nodes were identified in the supramarginal, middle, and superior temporal and inferior frontal regions in deficit schizophrenia networks based on ranking of 4 centrality metrics. High centrality regions were identified as those that ranked in the top 10 in 50% or more of the thresholded networks in 3 or more of the centrality measures. Network properties were similar in patients with deficit schizophrenia from both study sites.

**CONCLUSIONS AND RELEVANCE** Patients with schizophrenia at one end of a spectrum show characteristic signatures of altered intracortical relationships compared with those at the other end of that spectrum, patients with bipolar I disorder, and healthy individuals. Cortical connectomic approaches can be used to reliably identify neural signatures in clinically heterogeneous groups of patients.
n patients with schizophrenia, heterogeneity of symptoms, of response to treatment, and of functional outcome have hindered neurobiological investigations aimed at identifying neural correlates of this debilitating disorder. Negative symptoms are important predictors of functional outcome, and there is considerable variability in negative symptom burden among patients with schizophrenia. Kirkpatrick et al demonstrated that patients with the deficit form of schizophrenia are characterized by negative symptoms, including restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive, that are both enduring and primary. Patients with deficit schizophrenia follow a course of illness characterized by persistent impairment and poor long-term prognosis with a low likelihood of experiencing recovery, as shown in a 20-year longitudinal follow-up study. Evidence suggests that deficit and nondeficit schizophrenia are not only distinguished by symptoms and course of illness but also have distinct etiologic factors and response to treatment. In addition, early functional and structural imaging studies pointed to alterations in frontoparietal brain circuits specific to deficit schizophrenia, whereas more recent evidence points to structural alterations in the temporal lobe.

Volumetric techniques have produced conflicting results, with some studies reporting more severe volume reductions in patients with deficit schizophrenia and others reporting more severe volume reductions in the nondeficit disease. In contrast, diffusion tensor imaging studies have identified replicable white matter tract impairments in patients with deficit schizophrenia in frontoparietal and frontotemporal circuitry that is important for emotion processing, emotion expression, and socioemotional functioning. These studies provide growing evidence that relationships among the cortical gray matter regions connected by these white matter tracts are altered in patients with deficit schizophrenia. Altered patterns of network connectivity in schizophrenia have been demonstrated, although the results remain inconsistent. The application of graph theoretical analysis to structural network data in schizophrenia has revealed broad network inefficiency, pointing to disturbed integration among brain regions. Topologically central nodes are critical for brain network integration, and network studies have identified node centrality alterations frequently in prefrontal regions and less consistently in temporal and parietal regions. In addition to methodologic differences, some of the inconsistent results of these network studies are likely attributable to the considerable clinical heterogeneity among people with a diagnosis of schizophrenia.

In the present study, we used an approach that leverages the heterogeneity of schizophrenia and includes a comparator disease group with bipolar I disorder. Patients with bipolar I disorder often experience the psychotic symptoms of schizophrenia, but they are typically free of negative symptoms. Through assessment of cortical network properties, using structural correlation and graph theory-based approaches, we first compared patients with deficit schizophrenia and patients with nondeficit schizophrenia with healthy individuals serving as controls. Cutting across the major psychoses, we then compared people with bipolar I disorder with matched controls. We hypothesized that (1) patients with deficit schizophrenia would demonstrate alterations in network properties compared with patients with nondeficit schizophrenia and controls, (2) characteristic network differences identified in patients with deficit schizophrenia would not be present in patients with bipolar I disorder, and (3) networks in patients with deficit schizophrenia would be characterized by node alterations localized primarily to frontal and parietal brain regions.

### Methods

#### Participants and Characterization

A total of 77 patients with schizophrenia and 79 matched healthy controls were recruited at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario, Canada; 51 patients and 51 matched controls were recruited at Zucker Hillside Hospital (ZHH) in Glen Oaks, New York; and 39 patients with euthymic bipolar I disorder and 43 matched controls were recruited from the Central Institute of Mental Health (CIMH) in Mannheim, Germany. Individuals at all sites completed the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (Fourth Revision) for Axis I disorders (SCID-I). Participants recruited at CIMH also completed the SCID-II for Axis II personality disorder diagnoses. The samples were characterized for age at onset, medication history, years of education, IQ, handedness, current clinical symptoms, and current substance use or past dependence (detailed inclusion/exclusion criteria for each sample are provided in the eMethods in the Supplement). After complete description of the study to the participants, written informed consent was obtained as per local institutional review board regulations. Institutional review board approval was obtained from the CAMH, the ZHH, and the CIMH. Participants received financial compensation.

#### Deficit Syndrome Classification

The Positive and Negative Syndrome Scale and the Brief Psychiatric Rating Scale were used to characterize clinical symptoms at CAMH and ZHH, respectively. The deficit and nondeficit schizophrenia groups were selected from the full schizophrenia samples based on characterization of the deficit syndrome according to the proxy for the deficit syndrome. Studies have examined the stability of the deficit syndrome classification using the proxy for the deficit syndrome and have shown the characterization to be stable over the short term (24 months) and across serial assessments over a 20-year follow-up period (eMethods in the Supplement). The proxy for the deficit syndrome is defined as the sum of the scores from either the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale of the anxiety, guilt feelings, depressive mood, and hostility items subtracted from the blunted affect item score. This calculation reflects the lack of negative affect and lack of dysphoria that are characteristic...
of patients with deficit schizophrenia along with their high degree of negative symptoms. The top quartile of proxy case identification scores was used to identify patients with deficit schizophrenia in each sample separately. To enhance the likelihood of correct classification, patients with nondeficit schizophrenia were identified as those who ranked in the bottom quartile of deficit scores in each sample. Healthy control participants from each site were selected based on matching to the deficit and nondeficit groups for age, sex, handedness, and parental education.

**Image Acquisition**
The neuroimaging aspect of the study was conducted between February 1, 2007, and February 28, 2012. Magnetic resonance (MR) images were acquired for all participants.

**Centre for Addiction and Mental Health**
The MR images at CAMH were acquired using an 8-channel head coil on a 1.5-T system (EchoSpeed; General Electric Medical Systems). Axial inversion recovery–prepared spoiled gradient recall images (n = 124) were acquired using a 1.5-mm-thick slice acquisition with the following image parameters: echo time (TE), 5.3 milliseconds; repetition time (TR), 12.3 milliseconds; time to inversion, 300.0 milliseconds; and flip angle, 20°.

**Zucker Hillside Hospital**
The MR imaging examinations at ZHH were conducted on a 3-T whole-body superconducting imager (Signa HDx; General Electric Medical Systems). The spoiled gradient recall images (n = 216) were acquired using a 1-mm-thick slice acquisition with the following image parameters: TE, 3 milliseconds; TR, 7.5 milliseconds; matrix size, 256 × 256; and field of view, 240 mm.

**Central Institute of Mental Health**
The MRI data at CIMH were acquired on a 3-T scanner (Magnetom Trio; Siemens Medical Solutions). The T1-weighted images (n = 160) were acquired using a 1.1-mm-thick slice acquisition with the following image parameters: TE, 2.98 milliseconds; TR, 2300 milliseconds; matrix size, 256 × 240 × 160; and field of view, 256 × 240 × 176 mm.

**Cortical Thickness Processing**
To calculate vertexwise cortical thickness, the T1-weighted images were submitted to the CIVET pipeline, version 1.1.10 (Montreal Neurological Institute, McGill University). Briefly, images were registered to a nonlinear template, with inhomogeneity corrected, skull stripped, and tissue classified. Deformable models were used to create gray and white matter surfaces, and white to gray matter surface distances were determined using the t-link metric. The thickness data were subsequently blurred using a 20-mm-surface-based diffusion blurring kernel and nonlinearly aligned to a template (eMethods in the Supplement).

**Correlation Matrix Construction**
For each participant, vertexwise cortical thickness maps were parcellated using cortical regions defined in the Probabilistic Brain Atlas (http://www.loni.usc.edu/atlases/) with additional manual segmentation of the middle frontal gyri (eMethods in the Supplement). Mean cortical thickness was computed in a total of 52 distinct cortical regions (eTable 1 in the Supplement). For comparison, an alternative parcellation atlas with 74 cortical regions was also used (eTable 2 in the Supplement). Between-subject Pearson correlation coefficients (r) were computed for values in all pairwise combinations of brain regions to assess intracortical coupling. A linear regression was performed at every cortical region to remove the effects of site in the combined diagnostic groups from CAMH and ZHH (32 deficit, 32 nondeficit, and 32 controls), and the correlations among resulting residuals were computed. Correlations in cortical thickness were examined in a sample of 32 patients with bipolar I disorder and 32 matched healthy controls from the CIMH sample. Correlation matrix construction and analyses were performed using MATLAB software (MathWorks Inc, version 8.2.0.701 [R2013b]).

**Network Construction**
Binary networks were created by thresholding cortexwide interregional cortical thickness correlations in each study group. The nodes in the networks represent brain regions, and the correlations that survived thresholding were considered connections. Graph theoretical measures (network density and node centrality) were assessed in networks formed at an array of correlation strength thresholds. The thresholds used ranged from a nominal value of P = .0001 to P = .000000075 (corresponding to a Bonferroni correction that accounts for all pairwise comparisons). This P value range corresponds to an r value range of 0.61 to 0.78. Networks were visualized with Cytoscape, version 3.1.10 (http://www.cytoscape.org).

**Network Density Analysis**
Network density is defined as the proportion of possible connections present in the network and is a measure of the overall level of connectivity. Network density was computed in all 5 groups at each network threshold level.

**Node Centrality Analysis**
Node centrality was characterized in groups with coupling and density distinct from that in the control groups. To characterize centrality, 4 measures (degree, eigenvector centrality, close-
ness, and betweenness) were computed for each node that was part of the largest connected component of each network. Degree corresponds to the number of connections that are incident on a node. Betweenness is the number of all shortest paths in the network that pass through a given node. Closeness is the inverse of the mean shortest path length from one node to all other nodes in the network. Eigenvector centrality assigns relative scores to all nodes in the network based on the concept that connections to high-scoring nodes contribute more to the score than do equal connections to low-scoring nodes. All regions were ranked by degree, eigenvector centrality, closeness, and betweenness in each thresholded network. High-centrality brain regions were classified as those that ranked in the top 10 in more than 50% of the thresholded networks for 3 or more of the centrality measures. All graph theory measures were computed with functions from the Brain Connectivity Toolbox (http://www.brain-connectivity-toolbox.net/).

Replication of Results
All analyses were also performed in the individual samples of deficit schizophrenia, nondeficit schizophrenia, and matched controls from CAMH and ZHH. The additional evaluation was performed to determine whether findings were similar at both sites.

Results
Demographic and Clinical Sample Characteristics
In the CAMH and ZHH samples, no significant differences were present among the healthy control, deficit schizophrenia, and nondeficit schizophrenia groups on any of the demographic variables, and no significant differences were detected between the deficit and nondeficit groups in age at onset or antipsychotic medication load (all P > .05) (eTable 3 and eTable 4 in the Supplement). Consistent with the classification of the deficit syndrome, patients with deficit schizophrenia displayed higher levels of blunted affect and lower levels of anxiety, feelings of guilt, depressive mood, and hostility as well as similar positive symptom scores in the CAMH and ZHH samples (eTable 3 and eTable 4 in the Supplement, respectively). Patients with bipolar I disorder did not differ significantly from the matched healthy controls in any demographic variables (eTable 5 in the Supplement). A summary of participant characteristics is presented in the Table.

Intracortical Coupling Differences
Structural coupling comparisons revealed 49 relationships that were stronger in the patients with deficit schizophrenia than in the healthy controls and 17 relationships that were stronger in the deficit schizophrenia group than in the nondeficit schizophrenia group (all P < .05, corrected). Most of these differences were in frontoparietal and frontotemporal relationships. There were no significant differences between the patients with nondeficit schizophrenia and healthy controls (all P > .05, corrected) (eFigure 1A in the Supplement) or between patients with bipolar I disorder and matched healthy controls (all P > .05, corrected) (eFigure 1B in the Supplement). Similar frontoparietal and frontotemporal differences were also identified in the deficit schizophrenia group after regressing out potential clinical confounders (Figure 2 in the Supplement) and in the separate CAMH and ZHH samples (Figure 3 in the Supplement) as well as when using an alternative cortical parcellation atlas (Table 1, eFigure 4, and eFigure 5 in the Supplement). Comparison of the intracortical coupling relationships between the control group matched to the schizophrenia groups and the control group matched to bipolar I disorder group revealed that only 1 correlation was significantly different between the 2 control groups.

Network Density
Networks were constructed with brain regions as nodes and strong interregional cortical thickness correlations as connections (Figure 2). The density of network connections was greater in the deficit schizophrenia group than in the nondeficit schizophrenia group and healthy control group at the range of correlation thresholds explored (range, 0.07-0.45 in controls, 0.09-0.43 in the nondeficit group, and 0.18-0.67 in the deficit group) (Figure 3A). Networks constructed in the separate CAMH and ZHH samples (eFigure 6 in the Supplement) each demonstrated increased density of connections in the deficit groups compared with the nondeficit and healthy control groups (CAMH: range, 0.10-0.43 in controls, 0.10-0.48 in the nondeficit group, and 0.19-0.63 in the deficit group; ZHH: range, 0.09-0.33 in controls, 0.09-0.33 in the nondeficit group, and 0.31-0.68 in the deficit group) (eFigure 7 in the Supplement). Network density was similar in patients with bipolar I disorder and matched healthy controls (range, 0.08-0.43 in controls and 0.08-0.42 in the bipolar I disorder group) (Figure 3B) and in the schizophrenia- and bipolar I disorder-matched control groups.

Node Centrality
Node centrality was characterized in the group of patients with deficit schizophrenia who had intracortical coupling and network density different from that of healthy controls. Assessing the 4 metrics of node centrality (degree, eigenvector centrality, closeness, and betweenness) in each brain region identified high centrality regions in networks of the deficit schizophrenia group. These regions were the inferior frontal gyrus, supramarginal gyrus, superior temporal gyrus, and middle temporal gyrus bilaterally and the caudal middle frontal gyrus, superior frontal gyrus, superior parietal gyrus, and fusiform gyrus in the right hemisphere (Figure 4). Six of these regions were also identified as having high centrality in each of the separate CAMH and ZHH samples of patients with deficit schizophrenia: the left and right supramarginal gyrus, left and right middle temporal gyrus, left inferior frontal gyrus, and left superior temporal gyrus (eFigure 8 in the Supplement).

Discussion
Using connectomic approaches, we found a highly correlated structural network in patients with the deficit subtype of
schizophrenia defined by high node centrality in inferior frontal, inferior parietal, and middle and superior temporal regions. Intracortical coupling among these regions was significantly stronger in people with deficit schizophrenia than in patients with nondeficit schizophrenia and controls. Network properties were similar in patients with deficit schizophrenia.

Figure 1. Summary of Image Processing and Analysis Methods

A. Cortical thickness processing

Step A: Cortical thickness processing. Each image was aligned to stereotaxic space, corrected for nonuniformity artifacts, tissue classified, and masked, and inner and outer cortical surfaces were extracted. The intersection between surfaces was then determined to define cortical thickness. An atlas was used to parcellate the cortex, and a mean thickness for each region was calculated.

B. Correlation matrix construction

Step B: Correlation matrix construction. Interregional correlations of regional thickness values were assessed in each group as a measure of interregional coupling. The strength of correlation between each pairwise combination of brain regions was color coded and represented in a matrix in which the rows and columns correspond to different brain regions. Statistical comparisons were done on a correlation-by-correlation basis comparing cortexwide coupling between groups.

C. Correlation matrix comparison

Step C: Correlation matrix comparison. Statistical comparisons were done on a correlation-by-correlation basis comparing cortexwide coupling between groups.

D. Network construction

Step D: Network construction. Matrices were thresholded to retain strong positive correlations and were converted to networks in which nodes represent brain regions and connections between regions represent the strong positive correlations that survived thresholding.

E. Graph theory analyses

Step E: Graph theory analyses. The networkwide property of density was assessed as a measure of overall connectivity. The centrality of each node was assessed based on the number of connections (degree) and positioning within the network (betweenness, eigenvector centrality, and closeness). This figure is adapted from Wheeler and Voineskos and Voineskos et al. MRI indicates magnetic resonance image.
Table. Characteristics of the Study Participantsa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CAMH Groupb</th>
<th>ZHH Groupc</th>
<th>CIMH Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Nondeficit SCZ</td>
<td>Deficit SCZ</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>50 (16)</td>
<td>41 (16)</td>
<td>51 (16)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (78)</td>
<td>9 (50)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (22)</td>
<td>9 (50)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Handedness, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right, 1 (6)</td>
<td>R, 16 (89);</td>
<td>R, 17 (94);</td>
<td>R, 14 (100)</td>
</tr>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>NA</td>
<td>24 (8)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Deficit score, mean (SD)</td>
<td>NA</td>
<td>-8 (2)</td>
<td>-1 (1)</td>
</tr>
<tr>
<td>Positive Symptom Score, mean (SD)</td>
<td>NA</td>
<td>17 (5)</td>
<td>15 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: A, ambidextrous; CAMH, Centre for Addiction and Mental Health; CIMH, Central Institute of Mental Health; NA, not applicable; SCZ, schizophrenia; U, unknown; ZHH, Zucker Hillside Hospital.

a Additional demographic and clinical details are presented in eTables 2, 3, and 4 in the Supplement.

Figure 2. Structural Coupling Networks

A Patients with deficit and nondeficit schizophrenia vs control

Deficit schizophrenia

Nondeficit schizophrenia

Healthy control

B Patients with bipolar I disorder vs control

Bipolar I disorder

Healthy control

Networks were constructed by thresholding interregional correlation matrices from eFigure 1 in the Supplement and retaining only the information from the strong positive correlations (in this case, r > 0.78). In the networks, the nodes (circles) represent brain regions and the strong positive correlations that survived thresholding are shown as connections between brain regions (red lines). The size of the nodes in the networks reflects the number of connections that are incident on it (degree). Large nodes have many connections (high degree) and small nodes have few connections (low degree). A, Networks formed from groups of patients with deficit schizophrenia and nondeficit schizophrenia, and from healthy controls. The deficit schizophrenia network has more connections and more highly connected nodes compared with the networks from the other groups. B, Networks formed from patients with bipolar I disorder and matched healthy controls. The bipolar disorder network has a similar number of connections and highly connected nodes as the matched control group.

To our knowledge, this study provides the first graph theory-based results linking clinical heterogeneity with heterogeneity in neuroimaging findings in schizophrenia.
levels that reflect white matter tracts has been reported in other neurodevelopmental disorders. The diminished differentiation of brain regions during development, which constitutes a disruption in healthy synchronized brain maturation, and altered centrality of regions. We found enhanced structural coupling associated with high regional centrality in the inferior frontal, inferior parietal, and middle and superior temporal cortices. Many of these same regions are connected by white matter tracts (ie, inferior longitudinal fasciculus, arcuate fasciculus, and uncinate fasciculus) that have been identified as disrupted in patients with deficit schizophrenia. These findings suggest that conventional regional approaches may not be useful for identifying circuit- or network-based impairment. Previous network-based analyses in patients with chronic schizophrenia have reported deficits in frontotemporal and frontoparietal connectivity and altered centrality of regions. We found enhanced structural coupling associated with high regional centrality in the inferior frontal, inferior parietal, and middle and superior temporal cortices. Many of these same regions are connected by white matter tracts (ie, inferior longitudinal fasciculus, arcuate fasciculus, and uncinate fasciculus) that have been identified as disrupted in patients with deficit schizophrenia. Published data support the hypothesis that regions that show strong structural coupling tend to be connected by white matter tracts. Although the exact relationship between disrupted white matter microstructure and enhanced structural covariance cannot be elucidated here, both increased and decreased coupling between regions connected by white matter tracts has been reported in other neurodevelopmental disorders. When our present findings are considered with previous findings on white matter circuitry, the evidence is compelling that this subgroup of patients with schizophrenia is characterized by distinct impairments in neural circuitry. Furthermore, the possibility that recent network findings in schizophrenia are driven by this subset of patients deserves consideration.

Patients with deficit schizophrenia may represent a subgroup of people with schizophrenia who experience an early-onset, nonprogressive developmental process that interferes with basic cognitive and social skills beginning in early childhood. The increased density in structural coupling networks that we found may reflect altered early neurodevelopment in the deficit group. In support of this interpretation, a longitudinal developmental neuroimaging study in healthy individuals demonstrated that brain regions with synchronized developmental change show strong convergence with regions that demonstrate cross-sectional covariance of cortical thickness. Thus, increased density in the deficit schizophrenia networks found in the present study may reflect decreased differentiation of brain regions during development, which constitutes a disruption in healthy synchronized brain maturation. This diminished differentiation of brain regions may lead to reduced efficiency and increased cost for brain networks that strive for a balance between cost and efficiency. The high levels of centrality that we found in supramarginal, inferior frontal, superior, and middle temporal gyri in patients with deficit schizophrenia offer the interpretation that these regions may have undergone reduced differentiation more so than other brain regions. Reduced specialization of these regions may contribute to impairment in complex emergent properties that require module integration, such as social cognition, global cognition, and language, which are impaired in people with deficit schizophrenia.

The impaired networks identified in patients with deficit schizophrenia are important for processes related to negative symptoms. For example, frontoparietal circuitry in the right hemisphere comprises the mirror neuron system, which is activated during basic emotion understanding and emotion experience sharing. These social cognitive domains are considerably impaired in people with schizophrenia (particularly those with the deficit form), are an important determinant of the deficit form of schizophrenia.
of functioning, and appear to be largely preserved in patients with bipolar I disorder. Future work characterizing cortical brain circuitry and social cognitive performance across patients with schizophrenia or bipolar I disorder can help further clarify whether the impairments observed in this study in patients with deficit schizophrenia are related to social cognitive impairments in the same group of patients.

One limitation of our study is that patient samples were collected at 3 academic centers and image acquisition parameters were different at the 3 sites. Combining schizophrenia groups from the CAMH and ZHH samples provided the power necessary to examine networkwide differences in deficit subtype patients, which are difficult to collect in large numbers. Additionally analyzing the separate samples revealed similar network properties in the deficit schizophrenia patient groups from both sites. A second limitation is that some have argued that regional reductions in brain structure may be an epiphenomenon of antipsychotic medication effects. Although it is possible that medication effects influenced the circuitry findings presented here, antipsychotic medication exposure was not different between the deficit and nondeficit schizophrenia groups at either site. Furthermore, although both approaches have been shown to accurately classify deficit and nondeficit subtypes, the Positive and Negative Syndrome Scale at CAMH and the Brief Psychiatric Rating Scale at ZHH were used to classify people with schizophrenia at each site. Finally, although use of an alternative cortical parcellation atlas produced similar results, some of the specific relation-

---

**Figure 4. High Centrality Regions in Deficit Schizophrenia Networks**

Four measures of centrality (betweenness, closeness, eigenvector centrality, and degree) were assessed. Centrality values were computed and ranked from lowest to highest for each brain region that participated in the largest connected component of each thresholded network. These thresholds correspond to Pearson correlation coefficients ($r$) that range from 0.61 ($P = .0001$ uncorrected) to 0.78 ($P = .0001$ corrected). Centrality measure rankings are color coded, with warm colors representing high centrality rank and cool colors indicating low centrality rank. Black color-coded cells indicate that the node was not part of the largest connected component of the network at that threshold. High-centrality brain regions were those that ranked in the top 10 in more than 50% of the thresholded networks for 3 or more of the centrality measures and are identified in boldface type. Six of these regions were also identified as having high centrality in the analysis of each separate deficit groups from the Centre for Addiction and Mental Health and Zucker Hillside Hospital (eFigure 6 in the Supplement): the left and right supramarginal gyrus and middle temporal gyrus, the left inferior frontal gyrus, and the left superior temporal gyrus. Expansion of the brain region abbreviations is presented in the Figure 2 legend.
ships that were found to be significantly different between groups were dependent on the template atlas used.

**Conclusions**

Our study may resolve some inconsistency in neuroimaging findings by showing that network properties of nodes within frontoparietal circuits are not characteristic of all patients with schizophrenia but rather are a neural signature of those with deficit schizophrenia. In addition, we showed that patients with bipolar I disorder do not demonstrate altered structural coupling among the thickness of cortical brain regions compared with control samples; to our knowledge, this is the first such assessment. Targeting these circuits should assist in novel therapeutic approaches aimed at treating negative symptoms and social impairment in people with schizophrenia.

**ARTICLE INFORMATION**

Submitted for Publication: June 8, 2014; final revision received November 7, 2014; accepted November 9, 2014.


**Author Affiliations:** Kimel Family Translational Imaging Genetics Laboratory, Research Imaging Centre, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Wheeler, Chakravarty, Mulstant, Voineskos); Schizophrenia Division of the Complex Mental Illness Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Wheeler, Foussias, Remington, Voineskos); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Wheeler, Foussias, Chakravarty, Remington, Mulstant, Voineskos); Department of Clinical Psychology and Neuropsychology, Psychological Institute, Johannes-Gutenberg University Mainz, Mainz, Germany (Wessa, Linke); Center for Translational Psychiatry, The Feinstein Institute for Medical Research, Manhasset, New York (Szeszko, DeRosse, Malhotra); Division of Psychiatry Research, The Zucker Hillside Hospital, Division of the North Shore–Long Island Jewish Health System, Glen Oaks, New York (Szeszko, DeRosse, Malhotra); Hofstra North Shore–LIJ School of Medicine, Departments of Psychiatry and Molecular Medicine, Hempstead, New York (Szeszko, DeRosse, Malhotra); Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada (Foussias, Remington, Voineskos); Campbell Family Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Foussias, Remington, Mulstant, Voineskos); Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada (Chakravarty); Program in Neuroscience and Mental Health, Hospital for Sick Children, Toronto, Ontario, Canada (Lerch); Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada (Lerch); Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine, Yeshiva University, Bronx, New York (Malhotra).

**Author Contributions:** Drs Wheeler and Voineskos had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wheeler, Szeszko, Lerch, Voineskos.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Wheeler, Voineskos.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Wheeler, Chakravarty, Lerch, Linke, Voineskos.

Obtained funding: Wheeler, Wessa, Chakravarty, Mulstant, Malhotra, Voineskos.

Administrative, technical, or material support: Szeszko, Foussias, Chakravarty, DeRosse, Remington, Malhotra, Voineskos.

Study supervision: Szeszko, Malhotra, Voineskos.

**Conflict of Interest Disclosures:** Dr Foussias has served on advisory boards for Roche and has received speaker fees from Lundbeck, Novartis, and Roche. Dr Remington has received consultancy fees from Neurocrine, Novartis, and Synchroneuron as well as research and speaker fees from Novartis. Dr Mulstant has received research support in the form of medications for National Institutes of Health–funded clinical trials from Bristol-Myers Squibb, Eli Lilly and Company, and Pfizer. Dr Malhotra has served as a consultant for Genomind Inc. No other disclosures were reported.

**Funding/Support:** Work from Zucker Hillside Hospital was supported by grant P50MH680173 from the National Institute of Mental Health (NIMH). Work from the Centre for Addiction and Mental Health (CAMH) was supported in part by the CAMH Foundation thanks to the Kimel Family, Koerner New Scientist Award, and Paul E. Garfinkel New Investigator Catalyst Award, as well as the Brain and Behavior Research Foundation, Canadian Institutes of Health Research, Ontario Mental Health Foundation, and grant R01MH099167 from the NIMH. Work from Heidelberg was supported by the Deutsche Forschungsgemeinschaft (grant SFB636/ C6, We3638/3-1).

**Role of the Funder/Sponsor:** The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Correction:** This article was corrected on March 25, 2015, to fix a caption.

**REFERENCES**


Network Differences in Deficit Schizophrenia


