Disturbed Structural Connectivity in Schizophrenia—Primary Factor in Pathology or Epiphenomenon?

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Introduction

There is currently general agreement that abnormal brain function in schizophrenia involves an extended network of brain structures including the frontal, temporal, and parietal cortices, the basal ganglia, cerebellum, hippocampus, and thalamus.¹ Evidence for this conclusion has emerged from a generation of functional and structural neuroimaging studies, from studies of neurocognition, and from various electrophysiologic approaches as well as postmortem investigations. Consistent with the prevailing assumption of cognitive neuroscience that even relatively simple information is processed by distributed cortical networks,²,³ impaired neuropsychological performance and related functional imaging and electrophysiological findings in patients with schizophrenia are considered as expressions of disturbed functional connectivity of macro-circuits that are distributed throughout the brain.⁴⁻¹⁴ A major drawback of these studies, however, always has been that functional connectivity measures are limited in being able to differentiate between abnormal function in the anatomical connections between brain regions and abnormal function within these regions per se. To make things even more complicated, even a seemingly uninvolved brain region (e.g., thalamus) can indirectly impact on the functional activity pattern of the brain structures under investigation. The reason for this ambiguity of functional connectivity measures is that functional covariance or correlation (i.e., functional connectivity) depends on the specific activity pattern in all involved cerebral structures, and we have previously argued that the actual complexity of functional measures may be one important reason that the power to predict genetic risk for schizophrenia of functional connectivity measures is apparently lower than that of local activity measures.¹¹

Disconnectivity models derived from functional connectivity investigations nevertheless led to an increased focus on the investigation of subcortical white matter (WM) in schizophrenia. During the past few years, novel magnetic resonance imaging (MRI) techniques like diffusion tensor imaging (DTI) and MTI were used to provide neuropathological information in vivo.¹⁵⁻²² The findings of these studies are still inconsistent, and the specificity of the applied methods for detecting myelin...
Macro-Circuit Connectivity in Schizophrenia

In 1988, Volkow et al.29 suggested that disturbed connectivity of widely distributed brain macro-circuits might be a characteristic feature of schizophrenia. This proposal was based on the observation of an abnormal pattern of correlations of glucose utilization between multiple brain sites measured with 18FDG (fluordeoxyglucose) PET (positron emission tomography). Since then, numerous studies have been published that report findings in agreement with this suggestion including several PET studies,9,30–34 functional MRI investigations,12,13,35–38 and electrophysiological (electroencephalogram) studies.4,10,11,38 Abnormal patterns of correlations between patients and controls have been most frequently reported for the frontotemporal, frontoparietal, corticothalamic, interhemispheric, and corticocerebellar loops. Several functional imaging and electrophysiological studies further suggested that impaired connectivity is also related to the genetic risk for schizophrenia, although the power to predict the genetic risk for schizophrenia appears to be relatively low compared with other endophenotypic measures.10,11,34,39–41

Structural Neuroimaging Findings

Conventional MRI

With conventional MRI, a large number of studies examined global and regional volume differences between schizophrenia patients and normal control subjects, using both traditional region of interest (ROI) and contemporary voxel-based analysis (VBA).42,43 Clinical conventional MRI scans in schizophrenia are mostly negative. Wright et al.44 carried out a meta-analysis of 58 structural MRI studies of 1588 patients with schizophrenia that reported cortical, subcortical, and ventricular volume measurements in relation to comparison groups. They concluded that mean cerebral volume of schizophrenia patients is smaller and mean ventricular volume is greater as compared with control subjects. WM was found to be generally reduced in schizophrenia patients. Shenton et al.45 reviewed 193 MRI studies of schizophrenia, performed between 1988 and 2000: the most important findings included ventricular enlargement (80%) of the studies reviewed, involvement of medial temporal lobe structures (74%), frontal lobe abnormalities (59%), and parietal lobe abnormalities (60%). Most of the reported results were volume differences but only a small number of studies described WM abnormalities. In 27 studies of the corpus callosum, 17 studies reported positive findings but findings have not been further described. Methodological limitations of these previous MRI-based volumetric studies might have contributed to inconsistent results. A number of recent conventional MRI studies, which investigated WM volume differences between schizophrenia patients and healthy probands, not described in the above cited reviews are presented in table 1 (published 2000 or later). A longitudinal MRI study in 73 patients demonstrated the most evident progressive changes in fronto-WM, correlating with functional impairment.57 An interesting recent MRI study demonstrated a significant treatment difference in MRI-volume changes in first-episode schizophrenics emphasizing possible treatment effects on brain morphology.58 Brain volume differences have shown to be already present in first-episode male patients: reduction of gray matter volume in widespread cortical areas, WM reduction in frontal lobes, and increased total cerebrospinal fluid volume.59

Diffusion Tensor Imaging

DTI provides a measure of the orientation (vector) of water diffusion along the axis of gross anatomical compartments.60 Mean diffusivity (MD) is a quantitative measure of directionally averaged diffusion, while fractional anisotropy (FA) is a normalized measure of diffusion anisotropy and ranges from 0 (random diffusion) to 1 (unidirectional diffusion). FA permits the representation of data in 2-dimensional maps (figure 1) and allows data analysis with “traditional” analysis procedures.61 The sensitivity of the method is such that it allows an estimate of the “structural integrity” of coherent brain structures like subcortical WM tracts. Basically, reduced anisotropy can reflect a variety of phenomena and thus impaired structural integrity can mean different things, and therefore, the biologic determinants of diffusion parameters in WM are not yet fully understood. For instance, anisotropy has been shown to increase during myelination62,63 and to decrease during demyelinating processes64 suggesting that the degree of axon myelination substantially contributes to this measure. On the other hand, there is also
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Specific Sample Characteristics</th>
<th>Sample Size (Patients/Controls)</th>
<th>Gender (M/F)</th>
<th>Mean Age (Years)</th>
<th>Illness Duration (Years)</th>
<th>Method (Field Strength [T]/Sequence/Measures)</th>
<th>Investigated Regions</th>
<th>Positive Significant Results in Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigmundsson et al. (2001)&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Chronic schizophrenia</td>
<td>27/27</td>
<td>26/1</td>
<td>34.9</td>
<td>13.9</td>
<td>1.5 T/proton-density–weighted and T2–weighted images/GM, WM, and CSF volume</td>
<td>Whole brain</td>
<td>WM reductions in left temporal and left frontal lobe</td>
</tr>
<tr>
<td>Paillère-Martinot et al. (2001)&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Early onset schizophrenia (EOS)</td>
<td>20/20</td>
<td>All male</td>
<td>29.0</td>
<td>10.0</td>
<td>1.5 T/inversion-recovery prepared fast gradient echo sequence/GM, WM, and CSF volume</td>
<td>Whole brain</td>
<td>Bilateral WM reduction in frontal lobes</td>
</tr>
<tr>
<td>Okugawa et al. (2002)&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Chronic schizophrenia</td>
<td>32/32</td>
<td>All male</td>
<td>39.3</td>
<td>14.6</td>
<td>1.5 T/GRASS/GM, WM, and CSF volume</td>
<td>Whole brain</td>
<td>GM and WM volume reduced in temporal lobe</td>
</tr>
<tr>
<td>Cahn et al. (2002)&lt;sup&gt;49&lt;/sup&gt;</td>
<td>First-episode schizophrenia</td>
<td>20/20</td>
<td>16/4</td>
<td>27.6</td>
<td>1.4</td>
<td>1.5 T/T1-weighted 3D fast field echo/GM and WM volume of several ROIs</td>
<td>Whole brain</td>
<td>No differences in WM volume</td>
</tr>
<tr>
<td>Ho et al. (2003)&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Recent onset schizophrenia</td>
<td>73/23</td>
<td>53/20</td>
<td>24.5</td>
<td>2.0</td>
<td>1.5 T/GRASS/GM, WM, and CSF volume</td>
<td>Whole brain</td>
<td>Reduced frontal lobe WM volume</td>
</tr>
<tr>
<td>Bartzokis et al. (2003)&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Chronic schizophrenia</td>
<td>35/52</td>
<td>All male</td>
<td>27.5</td>
<td>4.5</td>
<td>1.5/dual SE sequence/GM-to-WM ratio</td>
<td>Frontal and temporal lobes</td>
<td>Absence of a WM volume expansion</td>
</tr>
<tr>
<td>Zhou et al. (2003)&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Schizophrenia</td>
<td>53/48</td>
<td>27/26</td>
<td>26.5</td>
<td>5.2</td>
<td>1.5/gradient echo/volume, WM concentration</td>
<td>ALIC, caudate and lentiform nucleus; WM concentration in whole brain</td>
<td>Decreased volume and reduced WM concentration bilaterally in ALIC</td>
</tr>
<tr>
<td>Takase et al. (2004)&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Schizophrenia</td>
<td>25/21</td>
<td>11/14</td>
<td>32.9</td>
<td>6.7</td>
<td>1.5/gradient-recalled pulse sequence/GM and WM volume</td>
<td>Caudate nucleus GM and WM</td>
<td>Smaller absolute and relative volumes of caudate nucleus WM</td>
</tr>
<tr>
<td>Zhou et al. (2005)&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Chronic schizophrenia</td>
<td>59/58</td>
<td>31/28</td>
<td>25.5</td>
<td>3.8</td>
<td>1.5/FLASH gradient echo sequence/volumetric measurement</td>
<td>Frontal lobes and subregions</td>
<td>No differences in total frontal and prefrontal WM</td>
</tr>
<tr>
<td>Davatzikos et al. (2005)&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Schizophrenia, neuroleptic naive</td>
<td>69/79</td>
<td>46/23</td>
<td>29.9</td>
<td>5.6</td>
<td>1.5/GRASS pulse sequence/morphologic analysis</td>
<td>Whole brain</td>
<td>Reduced GM and increased ventricular CSF in several regions</td>
</tr>
<tr>
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<td>First-episode schizophrenia</td>
<td>26/38</td>
<td>12/14</td>
<td>32.0</td>
<td>—</td>
<td>1.5/dual echo fast SE/voxel-based morphometry</td>
<td>Whole brain</td>
<td>Smaller WM global brain volume ratio</td>
</tr>
</tbody>
</table>

Note: ALIC, anterior limb of the internal capsule; CSF, cerebrospinal fluid; FLASH, fast low-angle shot; GM, gray matter; GRASS, gradient-recalled acquisition in the steady state.
evidence that the number or density of axon fibers and the coherence of the fibers influences anisotropy. For instance, several DTI studies have shown significantly reduced FA in amyotrophic lateral sclerosis (ALS) that is thought to be caused by axonal degeneration of pyramidal tracts.

Accordingly, any finding of a FA reduction is expected to have a different neurophysiological impact depending on the cause of the reduction. When the FA reduction is due to a reduced number of axons in a fiber tract, there are simply less nerve impulses transferred, ie, less information is carried. However, when axonal myelination is impaired, a slowdown of conduction velocity of nerve impulses in the affected axons is seen because current is lost through the membrane. Across the fiber bundle, one would expect that impaired myelination should result in variable axonal conduction properties, ie, variable speed of impulse transmission, between neighboring and differentially affected axons, whereas a lower number of axons should only carry less information in the fiber bundle. The downstream effects at the synaptic level of these 2 alternative causes for FA reduction should also be different. Local field potentials (LFPs) are thought to reflect the weighted average of synchronized dendrosomatic components of pyramidal synaptic signals (postsynaptic potentials) and they are the physiological basis of synchronized electromagnetic oscillations and blood-oxygen level–dependent response. Although our current knowledge is still quite sketchy on this issue, one would theoretically predict that a lower number of axons with a decrease of nerve impulses would also decrease the LFP amplitude because less synchronous activity is present (lower “downstream activation”). In contrast, the logical consequence of a higher variability of axonal impulse transmission should be a failure to synchronize postsynaptic activity (more “downstream noise”). In this context, it may be of some interest that previous work from our group provided some evidence on the basis of electrophysiological and functional MRI studies that schizophrenia patients fail to synchronize brain activity.

Most DTI studies applied the single-shot echo-planar imaging method for data collection. A recent study, however, used the line-scan diffusion imaging that offers the advantage of not being as sensitive to susceptibility variations and chemical shift effects. For image analysis, 2 principle methods have been adopted: the ROI and the whole-brain VBA. The ROI method allows a more powerful examination of regions but there is a risk of a systematic placement bias. The VBA has still problems with image analysis, especially normalization algorithms, that were originally not designed for anisotropy images.

In schizophrenia, a number of DTI studies have suggested reduced integrity of subcortical WM tracts (table 2). DTI studies in schizophrenia patients have found reduced anisotropy, compared with healthy control subjects, in prefrontal WM, in the splenium of the corpus callosum, in whole-brain WM, in the anterior cingulum, in the left arcuate fasciculus, bilaterally in the cingulum, bilaterally in the middle cerebellar peduncles. In addition, some investigations demonstrated reduced asymmetry in WM tracts in the uncinate fasciculus and the anterior cingulum. On the other side, several other studies did not find reduced FA in schizophrenia patients. In general, there is considerable inconsistency between findings—perhaps because of different sensitivity and resolution of the applied measurement technology and their vulnerability to various artifacts.

As DTI findings in schizophrenia are of particular relevance with regard to the concept of structural disconnectivity, some of the most important DTI studies in schizophrenia will be briefly summarized at this point. Kubicki et al. investigated the uncinate fasciculus, the largest of the 3 WM tracts connecting temporal and frontal lobes. Schizophrenia patients showed a lack of normal left-greater-than-right asymmetry that was interpreted as an indication for frontotemporal disconnectivity in schizophrenia. The same study group performed an ROI investigation of the cingulum, most important cerebral fiber bundle, and showed smaller volume and reduced anisotropy in schizophrenics using line scan DTI. Burns et al. performed the study with the largest sample size to date (30 patients, 30 control subjects): FA was determined in the 3 most important subcortical fiber tracts: the anterior cingulum, the uncinate fasciculus, and the arcuate fasciculus, and analysis was based on an optimized voxel-based morphometry technique. Reduced FA was found in the left arcuate and the left uncinate fasciculus, suggesting frontotemporal and frontoparietal structural disconnectivity in schizophrenia. Two studies of WM integrity in schizophrenia used a VBA of FA of the whole brain, but both with limited sample size: Agartz et al. demonstrated bilaterally reduced FA in the splenium of the corpus callosum and the adjacent WM (forceps major) in schizophrenics while...
<table>
<thead>
<tr>
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<th>Gender (M/F)</th>
<th>Mean Age (Years)</th>
<th>Illness Duration (Years)</th>
<th>Method (Field Strength [T]/Sequence)</th>
<th>Study Type (ROI-VBA/DTI Parameters)</th>
<th>Investigated Regions</th>
<th>Positive Significant Results in Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchsbaum et al. (1998)</td>
<td>Chronic schizophrenia</td>
<td>5/6</td>
<td>3/2</td>
<td>34</td>
<td>8.4</td>
<td>1.5/LSDI</td>
<td>VBA/RA (relative anisotropy)</td>
<td>Whole brain</td>
<td>Reduced in PFC, temporal lobe, internal capsule</td>
</tr>
<tr>
<td>Lim et al. (1999)</td>
<td>Chronic schizophrenia</td>
<td>10/10</td>
<td>All male</td>
<td>47.7</td>
<td>—</td>
<td>1.5/EPI</td>
<td>ROI/FA</td>
<td>Prefrontal, temporal-parietal, and parietal-occipital region</td>
<td>Widespread decreased FA</td>
</tr>
<tr>
<td>Foong et al. (2000)</td>
<td>Chronic schizophrenia</td>
<td>20/25</td>
<td>15/5</td>
<td>37.6</td>
<td>13.7</td>
<td>1.5/EPI</td>
<td>ROI/D,FA</td>
<td>Genu and splenium of the corpus callosum</td>
<td>Reduced FA in splenium</td>
</tr>
<tr>
<td>Agartz et al. (2001)</td>
<td>Chronic schizophrenia</td>
<td>20/24</td>
<td>11/9</td>
<td>38.4</td>
<td>14</td>
<td>1.5/EPI</td>
<td>VBA/FA</td>
<td>Whole brain</td>
<td>Reduced FA in splenium</td>
</tr>
<tr>
<td>Steel et al. (2001)</td>
<td>Chronic schizophrenia</td>
<td>10/10</td>
<td>5/5</td>
<td>34</td>
<td>15</td>
<td>2/EPI</td>
<td>ROI/FA</td>
<td>Prefrontal WM</td>
<td>No differences</td>
</tr>
<tr>
<td>Foong et al. (2002)</td>
<td>Chronic schizophrenia</td>
<td>14/19</td>
<td>11/3</td>
<td>38.6</td>
<td>13.4</td>
<td>1.5/EPI</td>
<td>VBA/D,FA</td>
<td>Whole brain</td>
<td>No differences</td>
</tr>
<tr>
<td>Agertz et al. (2001)</td>
<td>Chronic schizophrenia</td>
<td>14/-</td>
<td>All male</td>
<td>40.5</td>
<td>—</td>
<td>1.5/EPI</td>
<td>ROI/D,FA</td>
<td>Frontal WM</td>
<td>No control group</td>
</tr>
<tr>
<td>Kubicki et al. (2002)</td>
<td>Chronic schizophrenia</td>
<td>15/18</td>
<td>All male</td>
<td>43</td>
<td>21.3</td>
<td>1.5/LSDI</td>
<td>ROI/FA</td>
<td>Uncinate fasciculus</td>
<td>Lack of normal left-greater-than-right asymmetry</td>
</tr>
<tr>
<td>Kubicki et al. (2003)</td>
<td>Chronic schizophrenia</td>
<td>17/18</td>
<td>All male</td>
<td>43</td>
<td>22</td>
<td>1.5/LSDI</td>
<td>ROI/FA</td>
<td>Cingulum</td>
<td>Reduced FA in cingulum</td>
</tr>
<tr>
<td>Minami et al. (2003)</td>
<td>Chronic schizophrenia</td>
<td>12/11</td>
<td>5/7</td>
<td>30.8</td>
<td>—</td>
<td>1.5/EPI</td>
<td>ROI/FA</td>
<td>Several regions</td>
<td>Reduced FA in all regions</td>
</tr>
<tr>
<td>Sun et al. (2003)</td>
<td>Chronic schizophrenia</td>
<td>30/19</td>
<td>18/12</td>
<td>27.4</td>
<td>4.1</td>
<td>1.5/EPI</td>
<td>ROI/FA</td>
<td>WM, several regions</td>
<td>Reduced FA in anterior cingulum</td>
</tr>
<tr>
<td>Ardekani et al. (2003)</td>
<td>Chronic schizophrenia/schizoffective</td>
<td>14/14</td>
<td>11/3</td>
<td>30.8</td>
<td>—</td>
<td>1.5/EPI</td>
<td>VBA/FA</td>
<td>Whole brain</td>
<td>Reduced FA in several regions</td>
</tr>
<tr>
<td>Burns et al. (2003)</td>
<td>Chronic schizophrenia</td>
<td>30/30</td>
<td>15/15</td>
<td>36.4</td>
<td>—</td>
<td>1.5/EPI</td>
<td>ROI/FA</td>
<td>Cingulum, uncinate/arcuate fasciculus</td>
<td>Reduced FA in left uncinate/arcuate fasciculus</td>
</tr>
<tr>
<td>Wolkin et al. (2003)</td>
<td>Chronic schizophrenia</td>
<td>10/-</td>
<td>All male</td>
<td>&lt;50</td>
<td>—</td>
<td>1.5/EPI</td>
<td>ROI/FA,D</td>
<td>Frontal WM</td>
<td>No control group</td>
</tr>
<tr>
<td>Wang et al. (2003)</td>
<td>Chronic schizophrenia</td>
<td>29/20</td>
<td>All male</td>
<td>28.5</td>
<td>4.2</td>
<td>1.5/EPI</td>
<td>ROI/FA,D</td>
<td>Superior and middle cerebellar peduncles</td>
<td>No changes</td>
</tr>
<tr>
<td>Begre et al. (2003)</td>
<td>First-episode schizophrenia</td>
<td>7/7</td>
<td>6/1</td>
<td>22.6</td>
<td>0.5</td>
<td>1.5/EPI</td>
<td>ROI/FA</td>
<td>Hippocampi</td>
<td>No changes</td>
</tr>
<tr>
<td>Okugawa et al. (2004)</td>
<td>Schizophrenia</td>
<td>25/21</td>
<td>12/13</td>
<td>29.8</td>
<td>6.3</td>
<td>1.5/EPI</td>
<td>ROI/FA,D</td>
<td>Middle cerebellar peduncles</td>
<td>Reduced FA in middle cerebellar peduncles</td>
</tr>
<tr>
<td>Wang et al. (2004)</td>
<td>Chronic schizophrenia</td>
<td>21/20</td>
<td>All male</td>
<td>29.4</td>
<td>—</td>
<td>1.5/EPI</td>
<td>ROI/FA</td>
<td>Anterior and posterior cingulum</td>
<td>Reduced FA in anterior cingulum, reduced asymmetry</td>
</tr>
<tr>
<td>Kumra et al. (2004)</td>
<td>Adolescent EOS</td>
<td>12/9</td>
<td>9/3</td>
<td>16.5</td>
<td>3.4</td>
<td>1.5/EPI</td>
<td>ROI/FA</td>
<td>Frontal, occipital WM, corpus callosum</td>
<td>Reduced FA in frontal and occipital WM</td>
</tr>
<tr>
<td>Author and Year</td>
<td>Specific Sample Characteristics</td>
<td>Sample Size (Patients/Controls)</td>
<td>Gender (M/F)</td>
<td>Mean Age (Years)</td>
<td>Illness Duration (Years)</td>
<td>Method (Field Strength [T]/Sequence)</td>
<td>Study Type (ROI-VBA/DTI Parameters)</td>
<td>Investigated Regions</td>
<td>Positive Significant Results in Patients</td>
</tr>
<tr>
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</tr>
<tr>
<td>Kalus et al. (2004)</td>
<td>Chronic schizophrenia</td>
<td>15/15</td>
<td>9/6</td>
<td>32.3</td>
<td>3.2</td>
<td>1.5/EPI</td>
<td>ROI/FA, COH</td>
<td>Anterior and posterior hippocampus</td>
<td>Reduced FA bilaterally in the posterior hippocampus and the left total hippocampus</td>
</tr>
<tr>
<td>Hubl et al. (2004)</td>
<td>Schizophrenia with/without hallucinations</td>
<td>26/13</td>
<td>16/10</td>
<td>32.2</td>
<td>8.2</td>
<td>1.5/LSDI</td>
<td>VBA/FA</td>
<td>Whole brain</td>
<td>Reduced FA in parts of the arcuate fasciculus and the anterior corpus callosum (patients with hallucinations)</td>
</tr>
<tr>
<td>Kubicki et al. (2005)</td>
<td>Chronic schizophrenia</td>
<td>21/26</td>
<td>—</td>
<td>(18–55)</td>
<td>—</td>
<td>1.5/LSDI</td>
<td>VBA/FA (MTR)</td>
<td>Whole brain</td>
<td>Reduced FA in fornix, corpus callosum, bilaterally in cingulum, SOF, internal capsule, inferior occipitofrontal fasciculus (right), arcuate fasciculus (left)</td>
</tr>
<tr>
<td>Kalus et al. (2005)</td>
<td>Chronic schizophrenia</td>
<td>14/14</td>
<td>9/6</td>
<td>32.3</td>
<td>3.2</td>
<td>1.5/EPI</td>
<td>ROI/COH (MTR)</td>
<td>Amygdala</td>
<td>Reduced COH bilaterally in amygdala</td>
</tr>
<tr>
<td>Price et al. (2005)</td>
<td>First-episode schizophrenia</td>
<td>20/29</td>
<td>14/6</td>
<td>24.9</td>
<td>—</td>
<td>1.5/EPI</td>
<td>ROI/FA, D</td>
<td>Splenium and genu of the corpus callosum</td>
<td>No significant differences</td>
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<td>First-episode schizophrenia</td>
<td>10/13</td>
<td>6/4</td>
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<td>—</td>
<td>1.5/EPI</td>
<td>VBA/FA</td>
<td>Whole brain</td>
<td>Reduced FA in left internal capsule, WM left middle frontal gyrus/left posterior superior temporal gyrus</td>
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<td>ROI/FA,D</td>
<td>Fornix</td>
<td>Reduced FA in fornix</td>
</tr>
</tbody>
</table>

*Note: COH, intervoxel coherence; D, diffusivity; EOS, early onset schizophrenia; EPI, echo-planar imaging; LSDI, line-scan diffusion–weighted imaging.*
examination of volumes did not show any differences between the 2 groups (20 patients, 24 controls). Ardekani et al.82 examined 14 patients and 14 control subjects and showed lower FA in the corpus callosum, left superior temporal gyrus, parahippocampal gyri, middle temporal gyri, inferior parietal gyri, medial occipital lobe, and the deep frontal perigenual region. The authors emphasize that their findings in these regions are consistent with other reported structural abnormalities in schizophrenia. Wang et al.84 examined superior and middle cerebellar peduncles as main pathways of neural fibers in the cerebellum in 29 patients and 20 healthy controls with ROI analysis and did not find any difference in FA and MD in these regions.

Foong et al.76 performed a ROI-DTI study of the corpus callosum in 20 schizophrenia patients and 25 healthy controls and found a significant reduction of FA while MD was significantly increased in schizophrenics in the splenium but not in the genu of the corpus callosum. The authors suggested that these DTI findings might demonstrate a disturbance of the commissural connectivity in schizophrenia. The same study group investigated FA and MD in 6 slices of WM using a VBA.16 They did not find any differences, but it must be mentioned that sample size (14 patients/19 controls) and number of slices (6) was limited. An interesting DTI study was just recently published by Jones et al.96 They found that age affected DTI-based measures in schizophrenia patients in a different way from comparison subjects, most notably in the left superior longitudinal fasciculus. The youngest schizophrenia patients had lower diffusion anisotropy than age-matched comparison subjects, but this difference diminished with increasing age. The main conclusion of this study was that direct comparisons of absolute DTI-based measures between individuals with schizophrenia and comparison subjects may be problematic and misleading because of underlying age-related differences in brain maturation between groups. Salat et al.97 performed a DTI study investigating age-related WM changes in 38 subjects across the adult age span, showing age-related decline of FA mainly in frontal WM regions, while temporal and parietal WM was relatively preserved.

Pfefferbaum et al.98 compared 10 younger and 10 older individuals, and DTI analysis confirmed that the age-related FA decline was most pronounced in frontal WM. These findings support the hypothesis that WM abnormalities in chronic schizophrenia patients might be in part caused by pronounced age-related changes, neurodevelopmental pathology like dysregulation of WM maturation and myelination might be less important in pathogenesis of schizophrenia. Long-term medication effects may also play an important role as antipsychotic medication effects on brain morphology have been shown: for instance, Lieberman et al.58 demonstrated significant decreases in gray matter volume in haloperidol-treated patients but not in olanzapine-treated patients.

To date, only a small number of DTI studies in first-episode schizophrenia have been performed:92,99–101 2 ROI studies investigated WM changes in hippocampi and the corpus callosum100 and did not find group differences in FA, which would suggest that neuropathological abnormalities may appear later and be progressive. Szeszko et al.92 performed a VBA study demonstrating lower FA in patients in WM of the left middle frontal gyrus and left posterior superior temporal gyrus, suggesting that WM abnormalities are already present in the very early course of the illness. Another voxel-based investigation showed decreased FA in several WM areas bilaterally.101 Kumra et al.88 investigated several ROIs in early onset schizophrenia patients and found reduced FA in the frontal WM bilaterally and in the right occipital WM. In total, these 4 cited studies present contradictory results; additional studies with higher sample sizes are needed to demonstrate whether there is already WM pathology present in the initial state of the illness. There is evidence for gray matter abnormalities in early states of the illness from several functional and structural imaging studies.102–105 This supports the hypothesis of structural WM pathology as a secondary degeneration caused by neural dysfunction in the course of the illness.

A systematic review of 19 DTI studies in schizophrenia investigated WM differences between schizophrenia patients and control subjects.74 They concluded that DTI studies of schizophrenia patients to date have not yet provided consistent findings of WM abnormalities. Group differences might be too slight to be demonstrated reliably and sample sizes of all studies were relatively small (median 15 patients) with relatively high variance of the obtained findings. Additionally, it was pointed out that there was no common area examined in most of the studies. The most frequently investigated area, the corpus callosum, showed reduced FA in 4 studies and normal FA in 4 other studies. In the cingulum, 4 studies demonstrated reduced FA and 5 did not. Kanaan et al. emphasize that effect size was shown in only 8 studies that does not allow a meta-analysis of the mentioned studies.

Kubicki et al.21 reviewed 18 DTI studies, and pointed out that decreased FA and increased MD within prefrontal and temporal areas and within the fiber tracts between these regions (cingulum, arcuate, and uncinate fasciculus) are the most frequent findings. The authors emphasize the role of DTI-neuropsychological correlations. Accordingly, correlations between anisotropy in prefrontal WM and negative symptoms, impulsiveness and aggressiveness have been shown. Anisotropy in frontotemporal connections have been demonstrated to correlate with measures of errors in executive functions. In another recent review about the evidence for WM abnormalities in schizophrenia including imaging, histological, and genetic findings, Kubicki et al.106 pointed out that
discrepancies reported in DTI studies may be caused by the relatively low resolution and high noise of today’s diffusion scans—compared with structural MRI.

As the contribution of possible confounding factors like treatment, age, individual variation is largely unknown, most of the DTI studies in schizophrenia appear to be underpowered; in addition, effect sizes were not provided in most cases. In this context, another critical issue is the choice of the applied analysis procedure. Most of the above mentioned studies used ROI methodology that is particularly difficult in regions of fiber tracts even if ROI methodology may be more sensitive in large fiber tracts that can be easily identified. However, it might be less suitable for WM regions due to variability and directionality of fibers. On the other hand, VBA is limited due to normalization and smoothing processes but does not have the problem of bias due to the choice of location of ROIs. Four of the mentioned DTI studies in schizophrenia adopted a voxel-based registration of the whole brain but then analyzed specific regions.

These issues may in part explain why DTI studies in schizophrenia to date are inconsistent (table 2). A promising new approach to the analysis of diffusion data is the tract-based spatial analysis that attempts to bring together the advantages of VBA and ROI analysis by a carefully tuned nonlinear registration, followed by projection onto an alignment-invariant tract representation, the “mean FA skeleton” (figure 2). Another methodological issue in analysis of DTI data is the size of the smoothing filter, which is highly variable across the studies. The effect of varying filter sizes has been investigated using DTI data from schizophrenia patients and controls, and within the range of smoothing from 0 to 16 mm, 4 different results have been demonstrated.

Further investigations with standardized methodology of data acquisition and analysis and larger sample sizes are needed to better understand which fiber tracts are particularly affected in schizophrenia.

**Magnetization Transfer Imaging**

MTI is a promising new MR technique to improve contrast and tissue characterization. It visualizes the weakly bound protons in macromolecular structures that are normally invisible because of their short relaxation times. The mechanisms for magnetization transfer (MT) include the chemical shift of tightly bound protons with water, dipolar cross relaxation, and diffusion of water from the surface of macromolecules into the bulk environment. When saturation from the bound protons is transferred, signal from the pool of free protons decreases, leading to lower signal intensity in MR images. Magnetization transfer ratio (MTR) is an index for signal loss derived from the exchange of magnetization between bound protons and free water and is postulated to be a marker of macromolecular structure integrity.

In brain parenchyma, myelin protons may account for a substantial portion of the observed measurement effects. Studies of neurological diseases have shown large reductions of MTR in neurological diseases with myelin loss like multiple sclerosis, progressive multifocal leukoencephalopathy, and central pontine myelinolysis. Therefore, MTI is proposed as a promising approach to the diagnostics of neurological diseases.

Current MTI technique is highly dependent on pulse sequence parameters that makes any comparison of findings between study sites difficult. Therefore, several research groups currently try to develop a standardized method for measuring MTR on MR images from different manufacturers. Davies et al. reported on a new quantitative MT technique that is less dependent of MT acquisition protocol and may provide more information about myelin affection in WM.

So far, several investigations using MTI have been conducted with schizophrenia patients, however, again providing inconsistent findings (table 3). Foong et al. performed the first MTI study in schizophrenia patients, using ROI methodology and general linear mixed modeling in WM regions in 25 patients and 30 controls. They showed several WM MTR reductions bilaterally in the temporal lobe, predominantly in the middle temporal gyri. In the same subject groups, Foong et al. also used VBA for MTR maps and found widespread MTR reductions in the frontal and temporal cortex in schizophrenics compared with controls.

Kubicki et al. intended to further specify DTI findings in schizophrenia by combing DTI with MTI. Line-scan diffusion imaging and T1-weighted sequences with and without saturation pulse were used to examine 21 chronic schizophrenia patients and 26 control subjects using VBA. Diffusion anisotropy and MTR maps demonstrated changes in different regions; decreased MTR was seen in several fiber tracts, including the right posterior cingulum bundle, corpus callosum, internal capsule, fornix, and superior occipitofrontal fasciculus. FA and MTR showed highest correlations in the left cingulum, corpus callosum, and fornix. The authors postulated that WM abnormalities observed in both DTI and MTI may indicate the presence of myelin abnormalities.

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<th>Gender (M/F)</th>
<th>Mean Age (Years)</th>
<th>Illness Duration (Years)</th>
<th>Method (Field Strength [T]/Sequence)</th>
<th>Study Type (ROI-VBA/Parameters)</th>
<th>Investigated Regions</th>
<th>Positive Significant Results in Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foong et al. (2000)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Chronic schizophrenia</td>
<td>25/30</td>
<td>19/6</td>
<td>37.3</td>
<td>14.3</td>
<td>1.5/SE MT</td>
<td>ROI/MTR</td>
<td>Several regions in WM</td>
<td>Reduced MTR in several temporal regions bilaterally</td>
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<td>Foong et al. (2001)&lt;sup&gt;109&lt;/sup&gt;</td>
<td>Chronic schizophrenia</td>
<td>25/30</td>
<td>19/6</td>
<td>37.3</td>
<td>14.3</td>
<td>1.5/SE MT</td>
<td>VBA/MTR</td>
<td>Whole brain</td>
<td>Reduced MTR widespread in cortices, genu of corpus callosum</td>
</tr>
<tr>
<td>Bagary et al. (2002)&lt;sup&gt;113&lt;/sup&gt; Bagary et al. (2003)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Chronic schizophrenia First-episode schizophrenia</td>
<td>25/25</td>
<td>19/6</td>
<td>37.2</td>
<td>14.3</td>
<td>1.5/dual echo sequence</td>
<td>ROI/MTR</td>
<td>Thalamus</td>
<td>No differences</td>
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<tr>
<td>Bagary et al. (2002)&lt;sup&gt;113&lt;/sup&gt; Bagary et al. (2003)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Chronic schizophrenia First-episode schizophrenia</td>
<td>30/30</td>
<td>19/11</td>
<td>27.3</td>
<td>5.3</td>
<td>1.5/SE MT</td>
<td>VBA/MTR</td>
<td>Whole brain</td>
<td>Reduced MTR bilaterally in medial PFC, insula, fasciculus uncinatus</td>
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<td>Chronic paranoid schizophrenia</td>
<td>14/14</td>
<td>9/5</td>
<td>31.4</td>
<td>—</td>
<td>1.5/GE FLASH</td>
<td>ROI/MTR, T2b,T2f,T1</td>
<td>Hippocampus</td>
<td>No group differences</td>
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<td>Chronic schizophrenia</td>
<td>21/26</td>
<td>—</td>
<td>(18–55)</td>
<td>—</td>
<td>1.5/LSDI</td>
<td>VBA/MTR</td>
<td>Whole brain</td>
<td>MTR differences in corpus callosum, fornix, right internal capsule, SOF bilaterally, right posterior cingulum</td>
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<tr>
<td>Kalus et al. (2005)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Chronic schizophrenia</td>
<td>14/14</td>
<td>9/5</td>
<td>27.9</td>
<td>2.2</td>
<td>1.5/FLASH</td>
<td>ROI/MTR, T2b,T2f,T1</td>
<td>Amygdala</td>
<td>Difference in T2b and T2, no difference in MTR in amygdala</td>
</tr>
</tbody>
</table>

Note: FLASH, fast low-angle shot; LSDI, line-scan diffusion-weighted imaging; SE, spin echo; SOF, superior occipitofrontal fasciculus; T2f, T2 relaxation time of free protons.
while DTI findings in regions without MTI abnormalities may be caused by differences in the organization and coherence of fibers and not by myelin pathology.20

Bagary et al.18 acquired high-resolution volumetric T1-weighted images and MT images from 30 schizophrenia patients and 30 controls, using a voxel-based whole-brain analysis. MTR was found to be reduced bilaterally in the medial prefrontal cortex (PFC) (right greater than left), insula (left greater than right), and WM incorporating the uncinate fasciculus (left greater than right) while—at the same time—significant volume differences have not been found.

Kalus et al.22 performed a multimodal MRI study including high-resolution volumetry, DTI, and quantitative qMTI in 14 patients and 14 controls using an ROI tracing of the amygdala. DTI and quantitative MTI parameters T1 and T2b (T2 relaxation time of restricted protons) of the amygdala showed significant changes in schizophrenia while the normalized amygdala volumes and the semiquantitative MTR, which was used in most of previous studies, did not show differences between groups.

Another ROI investigation of hippocampal subregions using semiquantitative MTR and quantitative MT parameters was conducted by Kiefer et al.114 Significant differences of quantitative MT parameters were demonstrated between the subregions of the hippocampal formation, possibly due to their structural and functional diversity while no significant group differences between 14 schizophrenia patients and 14 control subjects have been observed.

When MTR and DTI are conducted together, both methods may differentiate between WM fiber tract abnormalities that are due to abnormalities deriving from alterations in axonal coherence, density or thickness (when only FA is abnormal), and myelin sheath thickness or composition, when both FA and MTR are affected.20 This is a promising new approach to investigate neuropathological correlates of connectivity and needs further multimodal MRI examinations, including animal studies and human postmortem studies.

Magnetic Resonance Spectroscopy

Postmortem studies indicate reductions in phospholipids and essential fatty acids in the brain of schizophrenia patients.115 Phosphorous magnetic resonance spectroscopy (31P-MRS) quantifies the resonances of phosphomonoesters (PME), phosphodiesters (PDE), inorganic orthophosphate, phosphocreatine (PCr), and nucleoside adenosine triphosphate (ATP). It can provide important information about high-energy metabolism and neuronal membranes, such as levels of PME that reflect the building blocks of neuronal membranes and PDE that reflect breakdown products.

A large number of 31P-MRS studies in patients with schizophrenia have been performed, demonstrating a variety of alterations in neuronal membrane biochemistry. Several review articles provide an overview of 31P-MRS study results in schizophrenia.116–120 Results of recent 31P-MRS investigations in schizophrenia, not taken into account in the cited review articles, are represented in table 4. However, the results of 31P-MRS studies in schizophrenia are not consistent, perhaps related to the variations in medication, phase of illness and differences in MRS methodology.118 A decrease in the level of PME and an increase in the level of PDE have been demonstrated in the prefrontal lobe of neuroleptic-naive schizophrenia patients. Study results in medicated schizophrenia patients were less consistent and have shown mostly decreased PME and/or increased PDE.120 PDE were found to be elevated in the temporal lobes of neuroleptic-naive schizophrenia patients, but data about the temporal lobes of medicated schizophrenia patients have not been consistent. Except for the reduction in the ATP in the basal ganglia and the increase in the frontal lobe PCr, data related to changes in high-energy phosphates in 31P-MRS are contradictory.130

Taken together, results of 31P-MRS have been interpreted as reflecting a relative increase in cell membrane degradation in prefrontal cortical regions at certain phases of schizophrenia.119 This supports the hypothesis that decreased myelination and alteration of structural connectivity in schizophrenia might be related to decreased lipid membrane components.131 Issues of sensitivity, specificity, measurement reliability, and functional significance of the MRS findings need to be further clarified.118

Myelination Deficit in Schizophrenia

The electrophysiological, functional, and structural neuroimaging findings suggestive of disturbed connectivity have encouraged speculations that such abnormal relationships across brain regions might reflect myelination pathology in the pathways that transfer information between these regions. The idea that a myelination deficit may contribute to schizophrenia illness, however, is not entirely new. As early as 1910, Alzheimer132 described a rare, slowly progressive demyelination disorder, ie, metachromatic leukodystrophy (MLD), that—among other symptoms—is quite frequently characterized by psychosis early in the course of the illness when it first presents during adolescence and young adulthood. The condition is often misdiagnosed as schizophrenia, sometimes for years, before neurological symptoms appear. MLD is now known to be a familial, autosomal recessive disorder with demyelination of corticocortical and corticosubcortical axons as well as of peripheral nerve fibers resulting from a partial or complete absence of arylsulfatase A or its spherolipid activator protein B.133,134 In 1992, Hyde et al.135 first suggested on the basis of an extensive literature review that MLD may—in fact—serve
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Specific Sample Characteristics</th>
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<th>Illness Duration (Years)</th>
<th>Field Strength (T)</th>
<th>Method</th>
<th>Investigated Regions</th>
<th>Positive Significant Results in Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen et al. (2002)</td>
<td>Chronic schizophrenia</td>
<td>11/11 11/0</td>
<td>42.9 21.6</td>
<td>4 T</td>
<td>15 cc volumes in 12 brain regions</td>
<td>3D-CSI</td>
<td>PME and PDE alterations in several brain regions</td>
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<td>Yacubian et al. (2002)</td>
<td>Schizophrenia</td>
<td>53/35 30/23</td>
<td>31.2 8.4</td>
<td>1.5 T</td>
<td>ISIS</td>
<td>Left prefrontal lobe</td>
<td>Reduced PDE, no correlation between PME and PDE</td>
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<td>Wood et al. (2003)</td>
<td>First-episode schizophrenia</td>
<td>56/21 36/20</td>
<td>21.7 —</td>
<td>1.5 T</td>
<td>PRESS</td>
<td>Left medial temporal lobe, left dorsolateral PFC</td>
<td>No differences</td>
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<tr>
<td>Jayakumar et al. (2003)</td>
<td>Schizophrenia, never treated</td>
<td>20/30 15/5</td>
<td>27.0 3.7</td>
<td>1.5 T</td>
<td>ISIS</td>
<td>Basal ganglia</td>
<td>Elevated PME/PDE ratio bilaterally</td>
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<tr>
<td>Gangadhar et al. (2004)</td>
<td>Schizophrenia</td>
<td>19/31 15/4</td>
<td>27.0 3.7</td>
<td>1.5 T</td>
<td>ISIS</td>
<td>Basal ganglia</td>
<td>Lower PCr/total phosphorus and PCr/total ATP ratios</td>
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<td>Jensen et al. (2004)</td>
<td>First-episode schizophrenia</td>
<td>15/15 13/2</td>
<td>22.5 0.7</td>
<td>4.0 T</td>
<td>CSI</td>
<td>Thalamus, hippocampus, cingulum, cerebellum, prefrontal and parieto-occipital cortex</td>
<td>Increased glycophosphocholin, inorganic phosphate, PCr, ATP creatine in ACC</td>
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</tr>
<tr>
<td>Jensen et al. (2006)</td>
<td>First-episode schizophrenia</td>
<td>12/11 11/1</td>
<td>23.2 0.6</td>
<td>4.0 T</td>
<td>CSI</td>
<td>Frontotemporal-striatal region, frontal lobes</td>
<td>Increased ATP levels in WM and decreased ATP levels in GM in frontotemporal-striatal region</td>
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<td>Smesny et al. (2006)</td>
<td>Schizophrenia</td>
<td>31/31 15/16</td>
<td>37.1 —</td>
<td>1.5 T</td>
<td>CSI</td>
<td>Several brain regions</td>
<td>PME, PDE, PCr and Pi reduced bilaterally prefrontal, medial temporal, caudate nucleus, thalamus and anterior cerebellum</td>
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<td>Jayakumar et al. (2006)</td>
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<td>12/11 10/2</td>
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<td>2D-CSI</td>
<td>Basal ganglia</td>
<td>Lower PCr/total phosphorus and lower PCr/ADP ratio bilaterally</td>
<td></td>
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</tbody>
</table>

Note: ADP, adenosine diphosphate; CSI, chemical shift imaging; GM, gray matter; ISIS, image-selected in vitro spectroscopy; Pi, inorganic orthophosphate; PRESS, point-resolved spectroscopy.
as a model for schizophrenia illness because hallmarks of the illness, ie, complex auditory hallucinations and bizarre delusions, are seen with a much higher prevalence in MLD of early adult onset than in any other neurological disorder. Hyde et al. concluded that schizophrenia illness could possibly involve a neurodevelopmental deficit resulting in a disruption of corticocortical and corticostriatal connections, particularly those engaging the PFC. In this context, it is worth mentioning a recent postmortem study using a stereological method allowing the quantification of myelinated nerve fibers: the total length of myelinated WM fibers was estimated to be about 129 000 km in schizophrenics and 137 000 km in controls.\textsuperscript{136}

**Myelin Pathology in Postmortem Brain Tissue**

With growing evidence of disturbed connectivity in schizophrenia, myelin pathology has been a target of recent postmortem studies. As oligodendrocytes are essential for the production of myelin, disturbed myelination might be caused by dysfunctional oligodendrocytes or a reduced number of oligodendrocyte cells. Many postmortem studies are focussing on the investigation of numerical density of oligodendroglial cells and structural alterations of myelin sheaths (table 5).

As numerous neuroimaging studies demonstrated the PFC as a site of functional and structural abnormalities in schizophrenia, several study groups decided to investigate this area in postmortem tissue.\textsuperscript{23,24,137–142} The first direct evidence of a myelination deficit in schizophrenia was obtained from a series of studies conducted by the Russian group around Uranova and Vostrikov. Based on several electron microscopy investigations, ultrastructural abnormalities of the myelin sheaths in the PFC, including a reduction of myelin compactness and inclusions between the lamellas of the myelin sheath were demonstrated.\textsuperscript{23,24,137} Originally, this research group compared the central part of the caudate nucleus in 25 cases of schizophrenics and 25 controls and demonstrated several histological abnormalities like swelling of axon terminals, swollen mitochondria, few synaptic vesicles, shrinkage of some axon boutons, concentric laminar bodies inside or close to axon terminals, and degeneration of axon boutons in schizophrenics.\textsuperscript{23} The authors suggested that dystrophic processes of astrocytes might be due to a disturbance in synaptic transmission. Subsequently, Uranova et al.\textsuperscript{24} investigated oligodendroglial cells and myelinated fibers both in schizophrenia and bipolar patients. Ultrastructural alterations of myelin sheaths (increased density of concentric lamellar bodies) were found in the PFC and in the caudate nucleus of schizophrenia patients. In addition, ultrastructural signs of apoptosis and necrosis of oligodendrocytes were shown in prefrontal areas and caudate nucleus in schizophrenics and bipolar patients. The following investigation of the same study group used optical dissector methodology to perform a morphometric study of numerical density of oligodendroglial cells in Brodmann area 9 in the PFC. A significant reduction of oligodendroglial cells in layer VI (–25%), but not in adjacent WM in schizophrenia patients was shown.\textsuperscript{137} However, in another morphometric study using again optical disector methodology, Vostrikov et al.\textsuperscript{142} described a loss of oligodendroglial cells in schizophrenia patients in layer VI (by 31%) and adjacent WM (by 12%). Similarly, conducting a stereologic analysis of numbers, densities, and spatial distribution of oligodendrocytes, Hof et al.\textsuperscript{138} also found a decrease in total number in cortical layer III and WM in the superior frontal gyrus in schizophrenics compared with control cases. However, Selemont et al.,\textsuperscript{139} who investigated neuronal and glial density and soma size in Broca’s area 44 in the ventral frontal lobe of 9 schizophrenics and 14 controls via stereologic cell counting, did not detect any significant abnormality of glial density. On the other hand, Flynn et al. demonstrated reduced immunoreactivity of 2 oligodendrocyte-associated proteins (2’,3’-cyclic nucleotide 3’-phosphodiesterase by 33%, myelin-associated glycoprotein by 27%) in the anterior frontal cortex of schizophrenia patients.\textsuperscript{142} Also, Schmitt et al.\textsuperscript{143} found decreased major myelin components (spingomyelin and galactocerebrosides 1 and 2) in left thalamus of schizophrenia patients.

**Gene Expression Profiling Studies**

Gene expression profiling investigations have further contributed to our understanding of myelination-related changes in schizophrenia. Hakak et al.\textsuperscript{25} reported abnormal expression of a cluster of several oligodendrocyte-related genes using DNA microarray analysis in homogenized tissue of dorsolateral PFC. In this study, over 6500 genes were compared between 12 schizophrenic patients and 12 control subjects. Only 7 genes were downregulated in patients and 6 were oligodendrocyte-related genes. The mean fold expression change of these 6 genes was in the range between 1.4 and 1.6. Davis and Haroutunian\textsuperscript{144} emphasize that these findings imply impaired oligodendrocyte function and not cell loss because most oligodendrocyte-related genes were not downregulated. Tkachev et al.\textsuperscript{26} investigated a sample of 15 schizophrenia and 15 bipolar patients compared with 15 control subjects from the Stanley brain collection with indexing-based differential display polymerase chain reaction (PCR) cross-validated with quantitative PCR. In this study, they found evidence for downregulated oligodendrocyte-related gene expression and confirmed abnormally reduced expression of erbB3, transferrin (TF), and myelin-associated glycoprotein (MAG) as described by Hakak et al. In this context, it is of some interest that in another study,\textsuperscript{26} downregulation of expression of these myelin-related genes was even greater in brains of patients with bipolar illness that, if valid, might...
<table>
<thead>
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<th>Method</th>
<th>Investigated Regions</th>
<th>Positive Significant Results in Patients</th>
</tr>
</thead>
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<tr>
<td>Uranova et al. (1996)</td>
<td>Paranoid schizophrenia</td>
<td>9/9</td>
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<td>Blind quantitative electron microscopic study of astrocyte organelles</td>
<td>Left caudate nucleus</td>
<td>Decreased number of mitochondria and volume of preserved mitochondria</td>
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<td>Arnold et al. (1997)</td>
<td>Schizophrenia</td>
<td>8/8</td>
<td>4/4</td>
<td>80.4</td>
<td>56.4</td>
<td>Microscope, spatial point pattern analysis</td>
<td>Layer II, III, V of entorhinal cortex</td>
<td>Layer III: abnormally clustered dispersion of neurons; layer II: increased effective radius; no differences in layer V</td>
</tr>
<tr>
<td>Highley et al. (1999)</td>
<td>Schizophrenia</td>
<td>26/29</td>
<td>15/11</td>
<td>67.1</td>
<td>—</td>
<td>Microscope (&lt;100 objective)</td>
<td>Corpus callosum</td>
<td>Density of axons: in females greater than males among controls, in patients reversed difference</td>
</tr>
<tr>
<td>Uranova et al. (2001)</td>
<td>Schizophrenia</td>
<td>16/16</td>
<td>3/13</td>
<td>59.9</td>
<td>28.4</td>
<td>Qualitative electron microscopy</td>
<td>Pole of PFC (BA10), head of caudate nucleus (left)</td>
<td>Damage of myelin sheath lamellae and formation of concentric lamellar bodies in both regions; decrease of volume density of mitochondria in oligodendrocytes</td>
</tr>
<tr>
<td>Hof et al. (2003)</td>
<td>Schizophrenia</td>
<td>7/7</td>
<td>3/4</td>
<td>77</td>
<td>—</td>
<td>Stereologic analysis of number, density, and spatial distribution of oligodendrocytes</td>
<td>Layer III and gyral WM in superior frontal gyrus (BA9)</td>
<td>Decrease in number and density in layer III and gyral WM, less clustered spatial distribution</td>
</tr>
<tr>
<td>Flynn et al. (2003)</td>
<td>Schizophrenia</td>
<td>13/11</td>
<td>6/7</td>
<td>46</td>
<td>—</td>
<td>Immunoreactivity of oligodendrocyte-associated proteins</td>
<td>Anterior frontal cortex</td>
<td>Less immunoreactivity of 2',3'-cyclic nucleotide 3'-phosphodiesterase, myelin-associated glycoprotein</td>
</tr>
<tr>
<td>Author and Year</td>
<td>Specific Sample Characteristics</td>
<td>Sample Size</td>
<td>Gender (M/F)</td>
<td>Mean Age (Years)</td>
<td>Illness Duration (Years)</td>
<td>Method</td>
<td>Investigated Regions</td>
<td>Positive Significant Results in Patients</td>
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<td>Eastwood and Harrison (2003)</td>
<td>Schizophrenia</td>
<td>12/14</td>
<td>7/5</td>
<td>60</td>
<td>—</td>
<td>Distribution and density of IWMNs, immunostained with neuronal marker NeuN; in situ hybridization</td>
<td>WM of superior temporal gyrus</td>
<td>Increased distribution and density of IWMNs in superficial WM but not in deep WM; reelin expression decreased</td>
</tr>
<tr>
<td>Rioux et al. (2003)</td>
<td>Schizophrenia</td>
<td>41/15</td>
<td>12/29</td>
<td>77.9</td>
<td>54.2</td>
<td>Distribution of MAP2-labeled neurons by computer-assisted microscopy</td>
<td>Anterior region of parahippocampal gyrus</td>
<td>IWMNs located deeper in WM in schizophrenia patients</td>
</tr>
<tr>
<td>Marner and Pakkenberg (2003)</td>
<td>Schizophrenia</td>
<td>8/9</td>
<td>All male</td>
<td>60</td>
<td>—</td>
<td>Stereotactic calculation of number and length of nerve fibers</td>
<td>Whole brain WM</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Selemion et al. (2003)</td>
<td>Schizophrenia</td>
<td>9/14</td>
<td>6/3</td>
<td>56.2</td>
<td>—</td>
<td>Stereologic cell counting, neuronal and glial density and somal size</td>
<td>BA44, (cell density in BA9 as control)</td>
<td>No differences in neuronal and glial density or somal size (decrease of neuronal density in BA9)</td>
</tr>
<tr>
<td>Aston et al. (2004)</td>
<td>Schizophrenia</td>
<td>12/14</td>
<td>7/5</td>
<td>45</td>
<td>—</td>
<td>Microarray analysis, expression of myelin-related genes</td>
<td>Middle temporal gyrus</td>
<td>Decreases in the expression of myelin-related genes MAG, PLLP, PLP1, and erbB3</td>
</tr>
<tr>
<td>Schmitt et al. (2004)</td>
<td>Chronic schizophrenia</td>
<td>18/23</td>
<td>10/8</td>
<td>79</td>
<td>53</td>
<td>Lipid extraction and thin-layer chromatography</td>
<td>left thalamus</td>
<td>Decreased membrane phophatidylycholine, shingomyelin and galactocerebrosides 1 and 2</td>
</tr>
<tr>
<td>Black et al. (2004)</td>
<td>Chronic schizophrenia</td>
<td>15/18</td>
<td>7/8</td>
<td>59.9</td>
<td>—</td>
<td>Ring intersection analysis</td>
<td>Layer V pyramidal neurons in PFC</td>
<td>40% fewer total ring intersections per neuron; smaller basilar dendritic field size in proximal and distal branches</td>
</tr>
<tr>
<td>Vostrikov et al. (2004)</td>
<td>Schizophrenia</td>
<td>23/20</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Optical dissector methodology</td>
<td>Layer VI and adjacent WM of PFC (BA10)</td>
<td>Reduced density of oligodendroglial cells in layer VI (−31%) and adjacent WM (−12%)</td>
</tr>
<tr>
<td>Uranova et al. (2004)</td>
<td>Schizophrenia</td>
<td>15/15</td>
<td>9/6</td>
<td>44.5</td>
<td>20.6</td>
<td>Optical dissector methodology (×100 light microscope)</td>
<td>Layer VI and adjacent WM of PFC (BA9)</td>
<td>Reduced density of oligodendroglial cells in layer VI, but not in adjacent WM</td>
</tr>
</tbody>
</table>

Note: MAP2, microtubule-associated protein; PLLP, plasmolipin; PLP1, proteolipid protein 1.
strengthen the view that both disorders may share some of their biologic and genetic determinants. Alternatively, it might suggest that findings in both sets of cases are epiphenomena of chronic psychiatric illness, of comorbid illnesses, or of potential cohort artifacts (e.g., substance abuse, age, agonal effects, or antemortem changes). This is because findings in postmortem tissue of chronically ill psychiatric patients are difficult to interpret, as primary from secondary phenomena are not easily distinguished, and oligodendrocytes are an especially vulnerable cell population for diverse antemortem and agonal pathologies. In a review of the literature, Davis et al. pointed out that the evidence for abnormal expression of myelin-related genes in schizophrenia is currently strongest for the genes MAG, ERB3, TF, 2′, 3′-cyclonucleotide, 3′-phosphodiesterase, and myelin and lymphocyte protein. However, only MAG is specific to oligodendrocytes and NRG1 is also important for neuronal development and function on the synaptic level (see below).

While one might consider these neuropathological findings as an indication for impaired myelination contributing to disconnectivity as observed with electrophysiology and neuroimaging, it needs to be taken into account that alternative neuropathological changes other than myelination-related alterations may also contribute to dysconnectivity. For instance, Highley et al. investigated the cross-sectional area and fiber composition in 26 schizophrenia patients and 29 controls and showed a gender × diagnosis interaction in the density of axons in most regions of the corpus callosum. In healthy controls, females were reported to have a greater density than males while in patients this difference was reversed. In addition, they also showed a significant reduction of the fiber number in female patients compared with controls. A similar finding was also obtained when they studied fiber density and fiber number of the cross-sectional area of the anterior commissure in a subset of cases demonstrating a reduction of fiber density in female patients but not in male patients. Both findings were interpreted by the authors as correlates of disturbed interhemispheric connectivity in schizophrenia.

Another example that disconnectivity may not necessarily be linked to myelination is provided by a study of Arnold et al. They investigated cytoarchitectural abnormalities in the entorhinal cortex in schizophrenia; Nissl-stained neurons were mapped in layers II, III, and V in 8 patients with schizophrenia and 8 controls. A dispersion of neurons and a reduced neuron effective radius were found in schizophrenics in layer III, an increased effective radius in layer II, whereas no differences were found in layer IV. Others have reported abnormal distribution of interstitial white matter neurons (IWMNs) in schizophrenia. The authors suggest that altered density and distribution of IWMNs may be residual markers of an abnormal cortical subplate as a result of defective neuronal migration or abnormal pruning, which gives support to the neurodevelopmental hypothesis of schizophrenia.

**Oligodendrocyte Biology and Myelination**

Even if abnormal oligodendrocyte biology or myelination turns out to be a valid finding, it will not be discernible from phenomenological studies such as MRI measures or gene expression profiles whether it is involved as a primary or secondary factor in brain circuitry dysfunction in schizophrenia. This is because neuronal activity influences oligodendrocyte function and myelination. By extension, pathological neuronal function may impact on myelination.

**ALS** is an example for secondary degeneration of fibers. Animal studies of ALS have demonstrated that motor neuron pathology begins at the distal axon and proceeds in a “dying back” pattern and human postmortem studies are in agreement with this model. Karlsborg et al. studied DTI changes at 3 different levels in the corticospinal tract (corona radiata, internal capsule, and pons) of ALS patients and healthy controls and supported the hypothesis of a retrograde axonal degeneration (“dying back mechanism”) in ALS. In schizophrenia, the pathological process might proceed in reverse order: neuronal pathological function in several cortical regions (predominantly frontotemporal) may lead to a secondary axonal degeneration and myelination deficit in WM fiber tracts connecting these areas. Underlying mechanisms are not yet clarified, but this secondary pathological process may appear with a latency of several years after the primary cortical lesions. Neuronal dysfunction as a neurodevelopmental impairment may occur before the first clinical symptoms, while secondary WM pathology may develop after illness onset. This is in accordance with above described DTI findings, an age-related reduction of FA has shown to be more pronounced in schizophrenia patients.

**Neuregulin 1**

Uncertainties notwithstanding, a provocative new chapter in thinking about abnormal connectivity in schizophrenia has been opened, based on a potential pathology of the cabling itself, perhaps because of abnormal oligodendrocyte development or function. At least one of the genes recently strongly implicated in susceptibility to schizophrenia, NRG1 is important in oligodendrocyte development and function. Defects of the expression of erbB3, one of the NRG1 receptors, have been demonstrated in the PFC of schizophrenia patients. Hakak et al. compared gene expression profiles of schizophrenia patients and controls and found a significant reduction in the level of erbB3 expression. These findings were accompanied by a reduced expression of oligodendrocyte-specific genes. Corfas et al. propose 2 interpretations for these findings: Alterations in erbB
signaling cause deficiencies in oligodendrocytes or alterations in erbB3 are secondary to oligodendrocyte defects in schizophrenia. In addition, there is evidence that NRG1-erbB signaling in radial glia participates in neuronal migration. 158 Defects in NRG1-erbB signaling during brain development could cause alterations in neuronal migration that leads to disturbance in cortical connectivity. 157 However, it needs to be acknowledged that the question on the biological effects of a pathologically changed molecular NRG1-Erb3 cascade in schizophrenia is yet entirely unanswered due to the complex function of the involved genes. Animal studies have only been instructive to some extent. Homozygous mutations of the NRG1 gene turned out to be lethal already during the embryonic stage. Using heterozygous and conditional knockout strategies, it could be demonstrated that NRG1 signal strength—mediated through ErbB2—determines the number of lamellas during myelination of peripheral nerve axons by Schwann cells. 159,161 However, whether these findings in peripheral nerve models can be transferred to CNS, has not yet been investigated. Likewise, it is unclear whether genetic variations in the NRG1 gene contribute to myelination in humans. In a pilot study (Winterer G, Konrad A, Vucurevic G, Musso F, Stoeter P, Dahmen N, unpublished data) of n = 50 healthy subjects, we failed to detect any association of DTI measures with a NRG1 coding genetic variation (rs3924999), which has been previously reported to be associated with schizophrenia. 162 While certainly more work needs to be done along this line, it will also be important to conduct comparable association investigations with phenotypic markers of synaptic function. This is because NRG1 is found in virtually every brain area and cell type in the adult brain 163 and the NRG1-ErbB3/B4 cascade is involved—as briefly mentioned above—in a variety of functions during neuronal development and subsequent neurodegeneration, ie, neuronal migration, myelination, gliogeneis, synaptogenesis, synaptic plasticity, and apoptosis. 164,165

Conclusions

There is now some but still controversial evidence from neuroimaging and postmortem studies for subtle changes of structural (subcortical) macro-circuit connectivity in schizophrenia. However, even if present, 2 important questions are essentially unanswered. First, does it affect “wiring” itself, ie, is the number of subcortical fibers reduced and/or is myelination of these fibers impaired. If the latter is true as currently suggested by most studies, is it a primary factor in schizophrenia pathology or is it simply a downstream effect or an epiphenomena of little relevance for schizophrenia pathophysiology arising secondarily from dysfunctional synaptic connectivity within cortical microcircuits as previously suggested by us. 11 It is anticipated that it will be difficult to answer these questions beyond all reasonable doubt but perhaps more converging evidence can be obtained that speaks for one of the 2 possibilities. Thus, it would be helpful to better understand the consequences of cortical synaptic microcircuit lesions on myelination of subcortical fibers, which could be investigated in animal models. Also, it would be interesting to know how certain gene variations in association with schizophrenia—such as in NRG1—differentially affect cortical synaptic function and axonal subcortical fiber myelination. More studies are needed combining structural and functional imaging to further investigate WM abnormalities in schizophrenia and their relationship to clinical symptomatology and other variables like age and medication effects.

References


149. Eastwood SL, Harrison PJ. Interstitial white matter neurons express less reelin and are abnormally distributed in schizophrenia: towards an integration of molecular and morphologic aspects of the neurodevelopmental hypothesis. Mol Psychiatry. 2003;8:821–831.


