White matter and cognitive function in schizophrenia

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Abstract

Abnormalities of cerebral white matter, oligodendrocytes, and myelin have been observed in schizophrenia with in-vivo imaging and post-mortem biochemistry. White-matter abnormalities are also frequently associated with cognitive impairment in both healthy and diseased individuals, and cognitive dysfunction is an important component of schizophrenia. While many studies have documented these associations, only a handful have examined the role of white matter in cognitive function in schizophrenia. In this paper, we explore what is known about white-matter deficits in relation to schizophrenia, cognitive deficits, or both together, in order to generate a theoretical model for the role that compromise of white matter might play in producing cognitive impairment in schizophrenia.

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Introduction

Abnormalities of cerebral white matter, myelin, and oligodendrocytes have been reported in schizophrenia (reviewed in Davis et al., 2003; Sullivan and Pfefferbaum, 2003; Walterfang et al., 2006). White-matter abnormalities are also a common feature of dementia, particularly, but not exclusively, when of vascular origin (Bronge, 2002; Chin and Goldman, 1996; Hachinski, 1990). Cognitive impairment is now recognized as a core feature of schizophrenia. In young individuals with schizophrenia, cognitive deficits are often detectable on psychological testing (Goldberg and Weinberger, 1988; Green et al., 2004). In the majority of elderly individuals with schizophrenia, cognitive impairments are of a severity that would be characterized as dementia in individuals without schizophrenia (Arnold et al., 1995; Davidson et al., 1995; Dwork et al., 1998).

The neuropathological substrates of cognitive impairment in schizophrenia are unknown. In elderly individuals with schizophrenia, cognitive deficits are often detectable on psychological testing (Goldberg and Weinberger, 1988; Green et al., 2004). In the majority of elderly individuals with schizophrenia, cognitive impairments are of a severity that would be characterized as dementia in individuals without schizophrenia (Arnold et al., 1995; Davidson et al., 1995; Dwork et al., 1998).

The neuropathological substrates of cognitive impairment in schizophrenia are unknown. In elderly individuals with schizophrenia, there is no increase in Alzheimer-type changes (Arnold et al., 1998; Dwork et al., 1998; Purohit et al., 1998), and the cholinergic deficits found in Alzheimer’s disease are not present (Haroutunian et al., 1994). Although diminished cognitive reserve in schizophrenia may increase susceptibility to the cognitive effects of mild Alzheimer-type changes that commonly occur with age, many elderly individuals with schizophrenia and severe cognitive impairment lack such changes (Dwork et al., 1998; Ortakov et al., 1999). Two neuropathological processes, however, are common to dementia and schizophrenia. The first is a loss of presynaptic and post-synaptic elements in cerebral cortex (Bigio et al., 2001; Browning et al., 1993; Davidsson et al., 1999; Dawson and Hallenbeck, 1996; DeKosky and Scheff, 1990; Eastwood et al., 1995; Eastwood and Harrison, 1995, 1999; Gabriel et al., 1997; Garey et al., 1998; Glantz and Lewis, 1997, 2000; Goto and Hirano, 1990; Hamos et al., 1989; Harrison, 1999; Honer et al., 1992, 1997; Honer and Young, 2004; Karson et al., 1999; Law et al., 2004; Masliah et al., 1989, 1991; Ferdahl et al., 1984; Perrone-Bizzozero et al., 1996; Regeur et al., 1994; Rosoklija et al., 2000; Tcherepanov and Sokolov, 1997; Terry et al., 1991; Vawter et al., 1999). The second, which is the focus of this study, is an alteration of cerebral white matter.

Although white-matter changes appear to be less severe in schizophrenia than in many forms of dementia, they could nonetheless be an intrinsic component of schizophrenia that contributes eventually
to dementia. In addition, normal or pathological variation in white matter that is not related to schizophrenia could have cognitive consequences that are exaggerated in individuals with schizophrenia. One such consequence might be a lessening of cognitive reserve, or the capacity to resist the cognitive manifestations of normal ageing processes or age-associated degenerative changes (Stern, 2006). The concept of cognitive reserve comprises both anatomical capacity (e.g. size of brain or neurons) and the ability to recruit neuronal activity. Both types of reserve are probably impaired in schizophrenia. Pre-existing impairment may predispose to the development of schizophrenia and may worsen its prognosis, and schizophrenia may progressively impair cognitive reserve (Barnett et al., 2006). Myelin integrity correlates with cognitive processing speed (Liston et al., 2006), and might thus contribute to cognitive reserve. On the other hand, factors conventionally associated with cognitive reserve, such as education or physical activity, appear to protect against loss of processing speed in conditions associated with myelin loss, e.g. ageing (Dik et al., 2003), infection with human immunodeficiency virus (Stern et al., 1996), or white-matter hyperintensities on magnetic resonance imaging (MRI) (Nebes et al., 2006). It thus seems likely that early-life myelination is relatively resistant to ageing and contributes to cognitive reserve, while the various components of cognitive reserve impart resistance to the cognitive effects of pathological or age-related loss of myelin.

White-matter abnormalities in schizophrenia

The majority of studies implicating white-matter alterations in schizophrenia employ in-vivo imaging. T2-weighted signal intensity is largely determined by water content, and therefore serves as a sensitive indicator of demyelination, oedema, or inflammation. Early studies, looking for regions of T2 hyperintensity, gave mixed results, but white-matter hyperintensities were certainly not consistently present (Brown et al., 1992, 1995; Hulshoff Pol et al., 2000; Keshavan et al., 1996; Lane et al., 1996; Rivkin et al., 2000; Symonds et al., 1997). Brown et al. (1995) concluded that T2 hyperintensities in schizophrenia were associated with stroke or hypertension and were no more common than in non-psychiatric subjects. Thus, the abnormalities uncovered by more sensitive MRI techniques must be considered relatively subtle, which is consistent with the failure of conventional neuropathological studies of schizophrenia to note any excess of white-matter lesions.

Volumetric studies of white matter (reviewed in Walterfang et al., 2006) give conflicting results, particularly with regard to the size and shape of the corpus callosum. The more consistent findings include reduction in volume of the left uncinate fasciculus and the anterior limb of the internal capsule. These structures contain fibres connecting the thalamus with frontal and cingulate cortices, and frontal cortex with rostral temporal cortex, respectively. In general, similar decrements in schizophrenia are reported for grey-matter volumes and white-matter volumes, suggesting that the latter may simply reflect the former. However, this interpretation should be viewed with caution; with the possible exception of the medial dorsal nucleus of the thalamus (Byne et al., 2002; Dorph-Petersen et al., 2004; Pakkenberg, 1992; Young et al., 2000) there is little replicated evidence for neuronal loss in schizophrenia (reviewed in Dwork, 1997; Harrison, 1999; Heckers, 1997). Therefore, white-matter deficits probably cannot be simply explained by deficits in neurons giving rise to axons.

Magnetic resonance spectroscopy (MRS) exploits the magnetic resonance spectra of specific organic compounds to localize and quantify these compounds in vivo. Commonly analysed compounds include N-acetylaspartate (NAA), which is believed to be unique to neurons and is generally accepted as a measure of density or viability of neurons and axons. NAA is quantified either in absolute terms or relative to creatine, a relatively stable component of neurons and glia (Hammen et al., 2003). MRS has demonstrated decreased NAA, increased creatine or a decreased NAA/creatine ratio in right prefrontal white matter (Choe et al., 1994), white matter in general (Lim et al., 1998), and parietal white matter (Auer et al., 2001) in schizophrenia. Bartha et al. (1999), finding no change in NAA signal in a medial temporal region of interest designed to include predominantly grey matter, concluded that previously reported decreases in NAA probably reflected a loss in white matter. Reductions of NAA in prefrontal white matter reported by Steel et al. (2001) were not statistically significant.

The studies pointing most frequently to abnormalities of white matter in schizophrenia employed diffusion tensor imaging (DTI). DTI applies several magnetic gradients in various orientations in order to obtain a set of diffusion-weighted images, from which is derived a tensor corresponding to the apparent rate of diffusion of water in three orthogonal dimensions within each voxel (typically several mm in each dimension). For each voxel, several indices are obtained from this procedure, including (a) trace or mean diffusivity ($D = \text{trace}/3$), measures of average diffusivity,
independent of direction, (b) fractional anisotropy (FA) or relative anisotropy (RA), measures of the degree of directionality of apparent diffusion (these employ different formulas, but both range theoretically from 0 with equal diffusion in all directions to 1 with diffusion confined to one direction), (c) $\lambda_{ij}$, or axial diffusivity, the apparent diffusion constant in the direction of maximal apparent diffusivity, and (d) $\lambda_{\perp}$, or radial diffusivity, the mean rate of diffusion in the perpendicular dimensions (Basser and Jones, 2002; Basser and Pierpaoli, 1996; Kingsley and Monahan, 2005). Comparison of diffusion tensors in adjacent voxels is employed for fibre tract tracing (diffusion tractography, e.g. Pierpaoli et al., 2001) who point out the danger of artefactual construction of non-existent tracts or measures of intervoxel coherence, the average angle between the vector of maximum diffusivity in a given voxel and those of its neighbours (Pierpaoli and Basser, 1996).

In complex systems, such as cerebral white matter, the arrangement of fibres must obviously contribute to anisotropy (see, e.g. Pierpaoli et al., 2001). In tissues such as peripheral or optic nerve, where most of the fibres are oriented in parallel, $\lambda_{ij}$ is the apparent diffusion constant in the direction of fibre orientation; however, even in isolated preparations of such tissue, the anatomical factors contributing to the tensor are complex (reviewed in Beaulieu, 2002). In healthy nerve, $\lambda_{ij}$ is nearly equal to the diffusion of free water, while $\lambda_{\perp}$ is several times smaller. Myelin probably contributes to anisotropy by reducing $\lambda_{\perp}$, but it is not required for anisotrophic construction of non-existent tracts or measures of intervoxel coherence, which is readily observed in normally unmyelinated nerves or in genetically myelin-deficient rat spinal cords. The latter show increased $\lambda_{ij}$ and somewhat greater increases in $\lambda_{\perp}$. With Wallerian degeneration, in which axons and myelin disintegrate distal to an injury of peripheral nerve, $\lambda_{ij}$ decreases and $\lambda_{\perp}$ increases; anisotropy eventually returns to normal with regeneration, although regenerated peripheral nerves typically have thinner myelin sheaths than previously. While attention is frequently focused on diffusion of water within axons, diffusion in the extracellular space should also have important effects on anisotropy.

In pathological conditions of the nervous system, axonal damage, myelin loss, and reactive processes tend to occur in unison. Thus, it is very difficult to determine, even with histological examination and DTI of the same piece of tissue, how an individual component of tissue damage affects various indices of diffusion. One exception is the shiverer mouse, in which a mutation of the gene for myelin basic protein (MBP) results in myelin sheaths that are thin, loosely wrapped, or absent, without evidence of axonal injury or tissue reaction. In major cerebral white-matter tracts of live shiverer mice, Song et al. (2002) found decreases in RA (~20%), with $\lambda_{ij}$ unchanged, but $\lambda_{\perp}$ increased by ~20%. Thus, a relatively pure deficit in myelin resulted in a modest increase in radial diffusivity, with no effect on axial diffusivity and preservation of a considerable degree of anisotropy. This is essentially consistent with the conclusion of Beaulieu (2002) that the axolemma forms the principal boundary to radial diffusion, with the myelin sheath playing a modulatory role. It is also notable that, while axonal packing density was unchanged in the shiverer mice of Song et al. (2002), the illustrations show an increase in water-accessible space between adjacent myelin sheaths and between layers of individual myelin sheaths. One difficulty in interpreting such studies is that tissue can change during fixation and histological preparation. In white matter of fixed shiverer brains, soaked in the contrast-enhancing agent gadoteridol, $\lambda_{ij}$ and $\lambda_{\perp}$ were both increased, with a 10–20% decrease in FA and a slightly larger increase trace, compared with wild-type mice (Tyszka et al., 2006).

In more complex pathological models [retinal ischaemia (Song et al., 2003; Sun et al., 2006a), $\beta$-amyloid overexpression (Song et al., 2004; Sun et al., 2005), experimental allergic encephalomyelitis (Kim et al., 2006) cuprizone toxicity (Song et al., 2005; Sun et al., 2006)], increases in $\lambda_{\perp}$ and decreases in $\lambda_{ij}$ were interpreted as damage to myelin and axons, respectively, but as noted by the authors, other interpretations are plausible.

Another refinement of MRI is the measurement of magnetization transfer (MT), simplistically, the suppression of the T2 signal of water by the transfer of proton spin from adjacent, immobilized macromolecules. Presumably, loss of macromolecules, such as myelin lipids, results in decreased MT, which is distinguishable from a simple increase in water content (Grossman et al., 1994).

Of at least 39 DTI or MT studies of schizophrenia (Table 1), only four were entirely negative (Begre et al., 2003; Foong et al., 2002; Price et al., 2005; Wang et al., 2003); only one of these four (Foong et al., 2002) surveyed all regions of cerebral white matter, and that study imposed stringent criteria for statistical significance. The remaining studies, while all showing decreased FA somewhere in the white matter, are not entirely consistent about where such loss is located. In prefrontal white matter, the results suggest a predominance of ventral abnormalities (Ardekani et al., 2003; Buchsbaum et al., 1998, 2006a,b; Hao et al., 2003; Kumra et al., 2004). Some studies found generalized
Table 1. Studies of schizophrenia by diffusion tensor or magnetization transfer imaging (diffusion measures other than FA, when available, appear in italics)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Regions of white matter with decreased fractional anisotropy or decreased magnetization transfer</th>
<th>Regions without decreased fractional anisotropy or magnetization transfer</th>
<th>Schizophrenia sample</th>
<th>Non-psychiatric sample</th>
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<td>Age (av, s.d.) (range)</td>
<td>M/F</td>
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<tr>
<td>Buchsbaum et al. (1998)</td>
<td>Prefrontal WM (ventral more than dorsal)</td>
<td></td>
<td>All other regions</td>
<td>34, 7</td>
<td>3/2</td>
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<tr>
<td>Lim et al. (1999)</td>
<td>Widespread in both hemispheres, from frontal to occipital</td>
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<td>48, 8</td>
<td>10/0</td>
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<tr>
<td>Foong et al. (2000a)</td>
<td>Right and left temporal regions (by magnetization transfer imaging)</td>
<td>Frontal, parietal, occipital, corpus callosum.</td>
<td>No correlation of temporal lobe anisotropy with age, duration of illness, or symptoms</td>
<td>37</td>
<td>19/6</td>
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<tr>
<td>Foong et al. (2000b)</td>
<td>Splenium of corpus callosum.</td>
<td>Genu of corpus callosum.</td>
<td></td>
<td>38</td>
<td>15/5</td>
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<tr>
<td>Agartz et al. (2001)</td>
<td>Splenium of corpus callosum and adjacent occipital WM</td>
<td>All other regions</td>
<td></td>
<td>38, 8</td>
<td>11/9</td>
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<tr>
<td>Hoptman et al. (2002)</td>
<td>In schizophrenia, impulsivity correlated with decreased FA in right ventromedial prefrontal WM, aggression and assaultiveness with increased trace</td>
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<td>37, 7</td>
<td>19/6</td>
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<td>Kubicki et al. (2002)</td>
<td>Uncinate fasciculus: Schizophrenia associated with loss of L &gt; R asymmetry and with correlations to cognitive test scores</td>
<td>Uncinate fasciculus: no difference between groups in magnitude</td>
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<td>43, 7</td>
<td>15/0</td>
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<tr>
<td>Foong et al. (2002)</td>
<td>Bilateral deep frontal perigenual region, left superior temporal gyrus, bilateral middle temporal gyri, bilateral parahipocampal gyri, bilateral inferior parietal lobules, bilateral medial occipital lobes, corpus callosum</td>
<td>All WM. D unchanged</td>
<td></td>
<td>39</td>
<td>11/3</td>
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<tr>
<td>Ardekani et al. (2003)</td>
<td>Bilateral deep frontal perigenual region, left superior temporal gyrus, bilateral middle temporal gyri, bilateral parahipocampal gyri, bilateral inferior parietal lobules, bilateral medial occipital lobes, corpus callosum</td>
<td>All other regions</td>
<td></td>
<td>31, 9</td>
<td>11/3</td>
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<tr>
<td>Bagary et al. (2003)</td>
<td>Uncinate fasciculus (by magnetization transfer)</td>
<td>Most other abnormalities were in grey matter</td>
<td></td>
<td>27, 7</td>
<td>19/11</td>
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<tr>
<td>Begre et al. (2003)</td>
<td>Bilateral hippocampi in first-episode schizophrenia</td>
<td>Bilateral anterior cingulate gyri, right uncinate fasciculus, right arcuate fasciculus</td>
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<td>25</td>
<td>6/1</td>
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<tr>
<td>Burns et al. (2003)</td>
<td>Left uncinate fasciculus, left arcuate fasciculus</td>
<td>Bilateral anterior cingulate gyri, right uncinate fasciculus, right arcuate fasciculus</td>
<td></td>
<td>36, 11</td>
<td>15/15</td>
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<td>Authors</td>
<td>Description</td>
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<td>Minami et al. (2003)</td>
<td>All WM regions bilaterally</td>
<td>41, 9 10 18–55</td>
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<td>Sun et al. (2003)</td>
<td>Anterior cingulate gyrus</td>
<td>27, 8 18/12 26, 8 12/7</td>
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<tr>
<td>Wang et al. (2003)</td>
<td>Superior and middle cerebellar peduncles. <em>D unchanged</em></td>
<td>28, 7 29/0 26, 6 20/0</td>
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<tr>
<td>Wolkin et al. (2003)</td>
<td>Inferior frontal WM anisotropy inversely proportional to SANS score in schizophrenia cases. No comparison group</td>
<td>41, 9 10/0</td>
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<tr>
<td>Kumra et al. (2004)</td>
<td>Bilateral frontal WM in plane of anterior and posterior commissures (i.e. ventral), right occipital WM in same plane</td>
<td>17, 2 9/3 16, 2 6/3 15–19 12–16</td>
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<tr>
<td>Hoptman et al. (2004)</td>
<td>In schizophrenia, impulsivity correlated with decreased FA in some areas, including right ventromedial prefrontal WM, and increased FA in other areas</td>
<td>39, 7 25/0 24–51</td>
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<tr>
<td>Hubl et al. (2004)</td>
<td>Arcuate fasciculus, uncinate fasciculus, inferior longitudinal fasciculus, corpus callosum</td>
<td>Temporoparietal arcuate fasciculus and anterior left corpus callosum greater in schizophrenia subjects with auditory hallucinations than in controls</td>
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<tr>
<td>Nestor et al. (2004)</td>
<td>Uncinate fasciculus; FA correlates with memory performance in schizophrenia only</td>
<td>41, 7 14/0 42, 7 14/0 17–55 17–55</td>
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<td>Okugawa et al. (2004)</td>
<td>Middle cerebellar peduncles. <em>D unchanged</em></td>
<td>Less difference in subjects on higher dosage of neuroleptics 30, 7 12/13 30, 4 11/10</td>
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<tr>
<td>Wang et al. (2004b)</td>
<td>Bilateral cingulum bundle, especially left</td>
<td>Posterior cingulum bundle 29, 6 21/0 26, 6 20/0 22–53 19–57</td>
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<tr>
<td>Jones et al. (2005)</td>
<td>Right superior temporal gyrus, left cerebellum. <em>D unchanged</em></td>
<td>All other areas. <em>D unchanged</em> 34 14/0 34 14/0 22–53 19–57</td>
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<tr>
<td>Kubicki et al. (2005)</td>
<td>FA: anterior and middle cingulum bilaterally, anterior and posterior superior occipito-frontal fasciculus, internal capsule bilaterally, fornix, corpus callosum, right inferior occipito-frontal fasciculus, left arcuate fasciculus</td>
<td>All other regions 18–55 21/0 18–55 21/0</td>
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<tr>
<td>Okugawa et al. (2005)</td>
<td>Middle cerebellar peduncle. <em>D unchanged</em></td>
<td>30, 7 12/13 29, 4 11/10 [continues overleaf]</td>
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<td>Study</td>
<td>Regions of white matter with decreased fractional anisotropy or decreased magnetization transfer</td>
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<td>Schizophrenia sample</td>
<td>Non-psychiatric sample</td>
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<td>Price et al. (2005)</td>
<td>Genu and splenium of corpus callosum in first episode patients. <em>D unchanged</em></td>
<td>Age (av, S.D.) 25 14/6 18–49</td>
<td>Age (av, S.D.) 28 11/18 20–40</td>
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<tr>
<td>Szeszko et al. (2005)</td>
<td>Left internal capsule, left middle frontal gyrus WM and left superior temporal gyrus WM</td>
<td>Age (av, S.D.) 27 5 6/4 29–40</td>
<td>Age (av, S.D.) 29 6 7/6 26–36</td>
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<td>Brambilla et al. (2005)</td>
<td>Increased diffusivity throughout corpus callosum. Correlates with positive symptoms rostrally</td>
<td>Age (av, S.D.) 41 12 42/25</td>
<td>Age (av, S.D.) 40 11 37/33 26–36</td>
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<tr>
<td>Kitamura et al. (2005)</td>
<td>Frontal WM. <em>λ₂</em> and <em>λ₅</em> increased</td>
<td>Parietal WM. <em>λ₂</em> and <em>λ₅</em> unchanged</td>
<td>31 5 6/0 24–38 32 4 6/0 26–36</td>
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<td></td>
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<tr>
<td>Jones et al. (2006)</td>
<td>Left superior longitudinal fasciculus. Greater difference at younger age. <em>D unchanged</em></td>
<td>Right cingulum, right uncinate. Other nonsignificant differences difficult to interpret because of age effects</td>
<td>34 9 14/0 34 10 14/0 19–57</td>
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<tr>
<td>Kuroki et al. (2006)</td>
<td>Fornix. <em>D increased</em></td>
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<td>40 9 24/0 41 9 31/0 24–52 23–54</td>
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<td>Hao et al. (2006)</td>
<td>Multiple, including ventral prefrontal bilaterally and right middle frontal gyrus WM. First episode with ≤6 wk antipsychotic exposure</td>
<td>Multiple, including left dorsal prefrontal</td>
<td>24 5 12/9 25 5 10/11 18–42 19–33</td>
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<td>Buchsbaum et al. (2006a)</td>
<td>Frontal WM (ventral &gt; dorsal, under age 60 yr &gt; over age 60 yr), rostral corpus callosum, cingulate grey and WM, superior longitudinal fasciculus</td>
<td>Most other regions</td>
<td>42 13 44/19 42 20 32/23 20–73 18–80</td>
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<td>Buchsbaum et al. (2006b)</td>
<td>Shorter frontal thalamocortical projections by diffusion tractography, lower anisotropy in ventral tracts</td>
<td>No difference in length of ventral tracts on right side. No difference in anisotropy of dorsal tracts</td>
<td>43 12 83/20 44 15 28/13 18–29</td>
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<td>Federspiel et al. (2006)</td>
<td>Decreased intervoxel coherence in deep WM, mostly prefrontal and temporal, left anterior limb of internal capsule</td>
<td>Increased intervoxel coherence in right anterior thalamic peduncle, right optic radiation, and left posterior external capsule. No differences in superficial WM</td>
<td>23 3 8/4 23 3 8/4 18–29</td>
<td></td>
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<tr>
<td>Lim et al. (2006)</td>
<td>Multiple correlations of FA in different regions with different cognitive domains in schizophrenia</td>
<td></td>
<td>36 10 22/3</td>
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</table>

WM, White matter; FA, fractional anisotropy; SANS, Scale for the Assessment of Negative Symptoms; WCST, Wisconsin Card Sorting Test; MT, magnetization transfer.
decreases that included dorsal prefrontal white matter (Federspiel et al., 2006; Lim et al., 1999; Minami et al., 2003), underlying a cortical region implicated in functional imaging studies of cognition in schizophrenia (Callicott et al., 2003; Weinberger et al., 1986). None of the DTI studies of schizophrenia involved elderly subjects, except for the large study by Buchsbaum et al. (2006a), who reported that decreases in frontal anisotropy were enhanced when subjects aged > 60 yr were removed from the sample. According to Jones et al. (2006), by middle age, differences in FA between schizophrenia and comparison subjects start to become less evident with age.

As noted above, decreases in FA may be the result of alterations in myelin. A subtle axonopathy, e.g. as part of a slow dying-back process, might be consistent with the reported loss of anisotropy and with the loss of NAA signal in white matter, with relative preservation of normal histology (see below). For example, it appears that in amyotrophic lateral sclerosis, DTI may be more sensitive than histological examination for detecting abnormalities in the suprabulbar portions of the corticospinal tracts (Toosy et al., 2003), which usually appear normal on myelin stains.

Although a number of studies describe decreased anisotropy in the uncinate fasciculus, or in ventral frontal white matter, where it terminates, Highley et al. (2002) report normal size and axon number in the uncinate fasciculus at autopsy. The methodology did not allow myelin changes to be ruled out, but the discrepancy between normal axonal number and decreased anisotropy could also be explained by disorganization of the fasciculus. This possibility is supported by tractography evidence of shorter frontal fibre bundles, which could indicate dispersion of fibre tracts before they reach their targets (Buchsbaum et al., 2006b).

Resolution of these issues will require stereological evaluations of Verhoeff myelin stains in the white matter of the dorsal prefrontal region and found no difference from non-psychiatric subjects (Dwork et al., 2005). Falkai et al. (1999) found no evidence for astrocytosis in the white matter of the premotor cortex or the subventricular zone of the third ventricle, which suggests that, at least in these regions, a demyelinating process is unlikely.

Highley et al. (2002) reported normal size and axon number in an autopsy study of the uncinate fasciculus in elderly subjects with schizophrenia. In the same sample, the anterior commissure was of normal size, but there was a 31% decrease in fibre density in the female schizophrenia subjects compared with controls, while there was no effect of diagnosis among the males (Highley et al., 1999b). In the corpus callosum, fibre density was decreased among females with schizophrenia but not among males (Highley et al., 1999a). In the fornix, there was a 32% increase in fibre density on the left side in males with schizophrenia (Chance et al., 1999). These studies found a loss of fibres with age in most subregions of the corpus callosum, but not in the uncinate fasciculus, anterior commissure, or fornix. In other studies of the corpus callosum of middle-aged (Casanova et al., 1989) and elderly (Nasrallah et al., 1983) subjects, schizophrenia was not associated with a loss of fibre density.

Ultrastructural studies of white matter in schizophrenia are lacking, but there are several reports on oligodendroglial and myelin morphology in frontal cortical area BA 10. An electron microscopic study of BA 10 biopsies found lipofuscin deposits in oligodendroglial cytoplasm and increased numbers of electron-dense granules in neuronal cytoplasm, axon–oligodendrocyte interfaces, and myelin sheaths (Miyakawa et al., 1972). An electron microscopic study of autopsy material (Uranova et al., 2001) purported to show subtle abnormalities in oligodendroglia and oligodendrocytes in the white matter underlying Brodmann’s area (BA) 9, and a 28% decrease when oligodendrocytes were identified by immunoreactivity for 2’,3’-cyclic nucleotide-3’-phosphodiesterase (CNPase). However, in the younger sample from the Stanley Consortium, Uranova et al. (2004) found an effect of schizophrenia on density of oligodendroglia in this region only in the cortex, not in the white matter. Marner and Pakkenberg (2003), comparing eight schizophrenia subjects and nine controls with a mean age of 60 yr, found no difference in the total length of myelinated axons in the prefrontal white matter, nor in the diameters of these axons. In a large series of elderly, chronically institutionalized schizophrenia subjects, we performed detailed histological evaluations of Verhoeff myelin stains in the white matter of the dorsal prefrontal region and found no difference from non-psychiatric subjects (Dwork et al., 2005). Falkai et al. (1999) found no evidence for astrocytosis in the white matter of the premotor cortex or the subventricular zone of the third ventricle, which suggests that, at least in these regions, a demyelinating process is unlikely.

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### Table 2. Post-mortem studies of cerebral white matter

<table>
<thead>
<tr>
<th>Study</th>
<th>Regions investigated</th>
<th>Findings in schizophrenia</th>
<th>Schizophrenia sample</th>
<th>Non-psychiatric sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age (av, s.d.) (range)</td>
<td>Age (av, s.d.) (range)</td>
</tr>
<tr>
<td>Nasrallah et al. (1983)</td>
<td>Corpus callosum</td>
<td>No difference in density of axons or glia in anterior or posterior portions</td>
<td>69, ~11 n = 18</td>
<td>64, 11 n = 11</td>
</tr>
<tr>
<td>Casanova et al. (1989)</td>
<td>Corpus callosum</td>
<td>No difference in fibre density in anterior, middle, or posterior portions</td>
<td>15, 12 10/1</td>
<td>50, 16 10/3</td>
</tr>
<tr>
<td>Falkai et al. (1999)</td>
<td>Grey matter (entorhinal cortex and subiculum) and WM (premotor cortex, subventricular zone of the third ventricle and next to inferior horn)</td>
<td>No evidence for astrocytosis</td>
<td>54, ~8 14/19</td>
<td>53, 12 13/13</td>
</tr>
<tr>
<td>Highley et al. (1999a)</td>
<td>Corpus callosum</td>
<td>Normal size</td>
<td>67, ~16 15/11</td>
<td>70, ~15 15/14</td>
</tr>
<tr>
<td></td>
<td>Decrease fibre density among females with schizophrenia</td>
<td>74 0/10</td>
<td>64 0/11</td>
<td></td>
</tr>
<tr>
<td>Highley et al. (1999b)</td>
<td>Anterior commissure</td>
<td>No difference in fibre density among the males</td>
<td>65 10/0</td>
<td>64 10/0</td>
</tr>
<tr>
<td></td>
<td>31% decrease in fibre density in the female schizophrenia subjects compared with controls</td>
<td>72, 18 0/8</td>
<td>73, 14 0/10</td>
<td></td>
</tr>
<tr>
<td>Chance et al. (1999)</td>
<td>Fornix</td>
<td>No difference in fibre density on the left side among males with schizophrenia, no difference in total number of fibres</td>
<td>62,15 16/0</td>
<td>67,13 19/0</td>
</tr>
<tr>
<td>Highley et al. (2002)</td>
<td>Uncinate fasciculus</td>
<td>Normal size</td>
<td>78, 12 0/13</td>
<td>72,13 0/14</td>
</tr>
<tr>
<td>Hof et al. (2002)</td>
<td>BA 9 cortex and WM</td>
<td>Decrease in density of oligodendrocytes in cortical layer III and WM</td>
<td>80, 3 2/2</td>
<td>80, 4 2/2</td>
</tr>
<tr>
<td>Hof et al. (2003)</td>
<td>BA 9 cortex and WM</td>
<td>Decrease in number and density of oligodendrocytes in cortical layer III and WM</td>
<td>77, 6 3/4</td>
<td>79, 6 4/3</td>
</tr>
<tr>
<td>Marner and Pakkenberg (2003)</td>
<td>Prefrontal WM</td>
<td>No difference in the total length of myelinated axons nor in the diameters of the axons</td>
<td>60, 14 8/0</td>
<td>60, 14 9/0</td>
</tr>
<tr>
<td>Uranova et al. (2004)</td>
<td>BA 9 cortex and WM</td>
<td>Decrease density of oligodendrocytes in cortical layer VI but not in the WM</td>
<td>45, 13 9/6</td>
<td>48, 11 9/6</td>
</tr>
<tr>
<td>Dwork et al. (2005)</td>
<td>Dorsal prefrontal WM</td>
<td>No difference from nonpsychiatric subjects in myelin histology</td>
<td>79, 11 52/40</td>
<td>62, 12 12/16</td>
</tr>
<tr>
<td>McCullumsmith et al. (2007)</td>
<td>Anterior cingulate WM</td>
<td>Decreased mRNA for MAG; CNPase; QKI; and transferrin</td>
<td>75, 12 29/12</td>
<td>79, 12 13/21</td>
</tr>
<tr>
<td>Mancevski et al. (2006)</td>
<td>Dorsal prefrontal WM</td>
<td>Correlation of myelin histology with cognitive function in schizophrenia subjects</td>
<td>79, 12 46/35</td>
<td></td>
</tr>
<tr>
<td>Beasley et al. (in press)</td>
<td>Anterior cingulate WM</td>
<td>Decreased mRNA for MAG; MBP; and CNPase; decreased levels of MBP protein but not CNPase</td>
<td>51, 14 18/20</td>
<td>52, 14 18/20</td>
</tr>
</tbody>
</table>

WM, White matter; MAG, myelin-associated glycoprotein; CNPase, 2',3'-cyclic nucleotide-3'-phosphodiesterase; QKI, quaking homologue; MBP, myelin basic protein.
myelin sheaths of cortical layer VI of BA 10 and the caudate nucleus in schizophrenia. These included decreased cross-sectional areas of nuclei and decreased fraction of cytoplasmic volume occupied by mitochondria, but not the electron-dense granules or lipofuscin described in the biopsies (Miyakawa et al., 1972). The non-specific findings of these studies are somewhat compromised by a failure to note whether the examiners were masked to diagnosis. None of these studies described evidence of demyelination, and none measured the thicknesses of myelin sheaths, which could be reduced in the case of remyelination or altered by aberrant regulation of myelination (e.g. as hypothesized in the case of an abnormality or insufficiency of neuregulin 1; see below).

In the only reported study of mRNA in white matter (McCullumsmith et al., 2007), expression of myelin-associated glycoprotein [MAG; transmembrane glycoprotein of oligodendrocytes, largely localized to the periaxonal collar and believed to be involved in signal transduction between the axon and myelin sheath (Schachner and Bartsch, 2000)], CNPase (cytoplasmic protein of oligodendrocytes, with unknown function), quaking homologue [QKI, regulates alternative splicing of several myelin-related genes (Aberg et al., 2006a; Wu et al., 2002)], and transferrin (iron transport protein expressed by oligodendrocytes) were down-regulated in the anterior cingulate white matter of 41 elderly, medicated and unmedicated schizophrenia subjects, compared with 34 elderly non-psychiatric subjects. Similarly, in a small, middle-aged sample, we found decreased mRNA for MAG, MBP, and CNPase, and decreased levels of MBP protein, but not CNPase, in anterior cingulate white matter (Beasley et al., in press).

Studies of myelin- and oligodendrocyte-related proteins and mRNA levels in grey matter are more numerous (Table 3). Flynn et al. (2003) found substantial decreases in immunoreactivity for CNPase and MAG in prefrontal cortex. Hakak et al. (2001) demonstrated down-regulation of mRNA for CNPase, MAG, myelin and lymphocyte protein, gelsolin, and transferrin, all of which are expressed predominantly in oligodendrocytes, and for ErbB3, a receptor for neuregulin (see below) in BA 46 of elderly schizophrenia subjects. Similar results were obtained in BA 9 in a younger sample (Tkachev et al., 2003). Aberg et al. (2006a) demonstrated down-regulation of mRNA for proteolipid protein 1, MAG, and transferrin in frontal cortex, and proposed that this was regulated by expression of the QKI 7-kb splice variant, which is also down-regulated (Aberg et al., 2006b). Dracheva et al. (2006) found, in an elderly sample, that mRNA for MAG, CNPase, SRY (sex determining region Y)-box 10 (SOX10; oligodendrogial transcription regulator), claudin11 (CLDN11, essential for the formation of myelin tight junctions), and peripheral myelin protein 22 (PMP22) was reduced in the hippocampus and anterior cingulate cortex but not in the putamen of patients with schizophrenia, while transcripts for MBP and myelin-associated oligodendrocyte basic protein (MOBP), both involved in compaction of the myelin sheath, were unaffected. Expression of CNPase, the only protein examined in this study, was decreased in the hippocampus but not in the putamen.

The aforementioned abnormalities of myelin-related proteins and mRNA, although studied in grey matter, have undoubtedly contributed to assumptions or speculation that the decreases in FA and MT, observed in MRI studies, are the result of abnormalities in myelin. This line of thought is further supported by genetic studies. Myelination-related genes whose polymorphisms have been associated with schizophrenia include Nrg1 (Harrison and Weinberger, 2005), which is involved (at least in peripheral nerve) in regulating the extent of wrapping of the myelin sheath around the axon (Michailov et al., 2004). Although previous reports involved non-coding regions, association of psychosis with a missense mutation of the Nrg1 gene was recently discovered (Walss-Bass et al., 2006). Studies of white matter in these individuals have not yet been reported. A genetic association of schizophrenia was found with an exonic polymorphism of CNPase, an allele that is less expressed than its counterpart allele in the cerebral cortex of normal heterozygous individuals (Peirce et al., 2006). Schizophrenia has also been associated with a specific haplotype in the region of the QKI gene and, in a different population of schizophrenia patients, with altered patterns of expression of QKI splice variants. Expression of all QKI splice variants was elevated in subjects treated with typical neuroleptics (Aberg et al., 2006b).

While the biology of oligodendrocytes in grey matter appears to be similar to that of oligodendrocytes in white matter, there may be differences that are poorly understood; for example, Graeber et al. (2002) refer to the satellite oligodendrocytes that surround neurons as an ‘enigma’ (p. 150). Thus, while white-matter myelin may be abnormal in schizophrenia, direct evidence for this is very limited, and such an abnormality may or may not underlie the loss of anisotropy seen with DTI. It should also be remembered that axonal abnormalities, such as the slow dying-back of axonotrophic lateral sclerosis (motor neuron disease) (Coleman and Ribchester, 2004), are associated with loss of myelin, and demyelinating diseases, such as
<table>
<thead>
<tr>
<th>Study</th>
<th>Regions investigated</th>
<th>Findings in schizophrenia</th>
<th>Schizophrenia sample</th>
<th>Non-psychiatric sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyakawa et al. (1972)</td>
<td>BA 10</td>
<td>No abnormalities by light microscopy. Lipofuscin deposits and other, subtle abnormalities by electron microscopy (see text)</td>
<td>25–45</td>
<td>3/2</td>
</tr>
<tr>
<td>Uranova et al. (2001)</td>
<td>Cortical layer VI of BA 10 and caudate nucleus</td>
<td>Subtle abnormalities in oligodendroglia and myelin sheaths by electron microscopy</td>
<td>60, 15</td>
<td>9/13</td>
</tr>
<tr>
<td>Flynn et al. (2003)</td>
<td>Prefrontal cortex</td>
<td>Decreased immunoreactivity for CNPase and MAG</td>
<td>31, 10</td>
<td>28/2</td>
</tr>
<tr>
<td>Hakak et al. (2001)</td>
<td>BA 46</td>
<td>Decreased mRNA for CNPase, MAG, myelin and lymphocyte protein, gelsolin, transferrin, and ErbB3</td>
<td>72, 12</td>
<td>9/3</td>
</tr>
<tr>
<td>Tkachev et al. (2003)</td>
<td>BA 9</td>
<td>Down-regulation of mRNA for PLP1, CLDN11, MOG, ErbB3, transferrin, OLIG1, OLIG2, SOX10, and some MBP transcripts. No difference for NRG1 or markers of immature oligodendrocytes</td>
<td>44</td>
<td>9/6</td>
</tr>
<tr>
<td>Aberg et al. (2006a,b)</td>
<td>Frontal cortex</td>
<td>Down-regulation of mRNA for proteolipid protein 1, MAG, transferrin and QKI splice variants 7 kb and 7 kkb</td>
<td>55, 17</td>
<td>32/23</td>
</tr>
<tr>
<td>Dracheva et al. (2006)</td>
<td>Hippocampus</td>
<td>Reduced mRNA for MAG, CNPase, SOX10, CLDN11, PMP22</td>
<td>76, 10</td>
<td>13/11</td>
</tr>
<tr>
<td></td>
<td>Anterior cingulate cortex</td>
<td>Reduced mRNA for MAG, CNPase, SOX10, CLDN11, PMP22</td>
<td>77, 10</td>
<td>18/12</td>
</tr>
<tr>
<td></td>
<td>Caudate</td>
<td>Reduced mRNA for MAG, CNPase, SOX10, CLDN11, PMP22</td>
<td>76, 10</td>
<td>13/10</td>
</tr>
<tr>
<td></td>
<td>Putamen</td>
<td>No changes in gene or protein expression</td>
<td>76, 10</td>
<td>13/11</td>
</tr>
</tbody>
</table>

CNPase, 2',3'-cyclic nucleotide-3'-phosphodiesterase; MAG, myelin-associated glycoprotein; PLP1, proteolipid protein 1; CLDN11, claudin 11; MOG, myelin oligodendrocyte glycoprotein; OLIG 1, 2, oligodendrocyte transcription factor 1, 2; SOX10, sex-determining region Y-box 10 transcription factor; NRG1, neuregulin 1; QKI, quaking homologue; MBP, myelin basic protein; MOBP, myelin-associated oligodendrocyte basic protein.
Ageing, myelin, and ApoE genotype

Myelination of the human brain continues into adulthood (Yakovlev and Lecours, 1967), and by late middle age there begins a process of demyelination (Marner et al., 2003; Tang et al., 1997). In rhesus monkeys, age-related demyelination is accompanied by evidence of remyelination, at least in cerebral cortex, where numerical densities of oligodendrocytes (Peters et al., 1991; Peters and Sethares, 2004), grouping of oligodendrocytes (Peters, 1996), and frequency of paranodal profiles, short internodes, and thinly myelinated internodes (Peters and Sethares, 2003) all increase with age. Some of these changes, as well as a loss of axons, are also observed in the anterior commissure (Sandell and Peters, 2003), corpus callosum (Peters and Sethares, 2002), and optic nerve (Sandell and Peters, 2002) of elderly rhesus monkeys. Sloane et al. (2003) found increasing calpain activation with age in rhesus white matter, accompanied by increased levels of intact and degraded CNPase but decreased levels of MAG [possibly explaining observations by Peters and colleagues of impaired adherence of myelin sheaths to axons, a process in part mediated by MAG (Kursula, 2001)]; this pattern of protein expression may be common to early demyelination of various aetiologies (Aboul-Enein et al., 2003). An interesting question is why these monkeys, like humans (Marner et al., 2003; Tang et al., 1997), undergo a loss of axons in white matter, while axonal numbers are maintained in the simian cortex. Sandell and Peters (2003) suggest a dying-back process that affects distal axons in white matter but not proximal axons in cortex. This explanation is quite plausible; equally plausible is the possibility that axonal damage is secondary to primary demyelination. White-matter oligodendrocytes could be more vulnerable than cortical ones to age-related stressors, or distal axons could be more vulnerable than proximal ones to damage secondary to demyelination.

In humans, imaging (reviewed in Bartzokis, 2004; Bartzokis et al., 2006) and post-mortem studies (Ansari and Loch, 1975; Berlet and Volk, 1980; Chia et al., 1983; Marner et al., 2003; Meier-Ruge et al., 1992; Miller et al., 1980; Svennerholm et al., 1991, 1997; Tang et al., 1997; Wender et al., 1991; Wiggins et al., 1988; Yakovlev and Lecours, 1967) indicate a loss of white matter and its myelin content with ageing. Lintl and Braak (1983) demonstrated an age-associated increase in intra-cortical myelin (in the stria of Gennari) in the first three decades, followed by a linear decrease with age over the next seven decades, consistent with the predictions of Yakovlev and Lecours (1967) that the end-point of cortical myelination would be pathologically or senile demyelination. Kemper (1994), reviewing data from the atlas of Kaes (1907), found pronounced senile loss of myelin in association cortices, but not in primary sensory or motor cortices. Presumably, remyelination also increases with age, as in rhesus monkeys, but this remains to be proven histologically. Preliminary data from the anterior nucleus of the thalamus indicate an increase in oligodendrocytes with normal ageing that is not seen in schizophrenia (W. Byne, personal communication), suggesting that a normal process of demyelination and remyelination may be disrupted by schizophrenia.

It is frequently stated (e.g. Bartzokis, 2004) that the latest axons to be myelinated are the first to be demyelinated. The evidence is consistent with this assumption, but it is not conclusive. The most specific statement that can be made about the effect of ageing on white matter, based on quantitative histology, is that there is a significant loss of myelinated fibres, preferentially affecting those of small calibre (Marner et al., 2003; Pakkenberg et al., 2003; Tang et al., 1997). According to Yakovlev and Lecours (1967) and their citations of Flechsig (1920), the latest white-matter fibres to be myelinated are the connections between thalamus and association cortex, long cortical association fibres, and commissural fibres, with myelination of the corpus callosum gradually extending from the splenium rostrally. Kemper (1994) was of the opinion that the material in Yakovlev’s collection showed age-related pallor confined to corticocortical fibres. Among the commissures of the rhesus monkey, the greatest proportion of small-diameter fibres is in the genu of the corpus callosum, connecting frontal association areas (Lamantia and Rakic, 1990). DTI shows that in normal human ageing, reduced anisotropy in the corpus callosum is primarily in the genu (Head et al., 2004), or at least spares the splenium (Ota et al., 2006). Salat et al. (2005) found age-related decreases in anisotropy in frontal white matter and the genu of the corpus callosum, but also in the posterior limb of the internal capsule [with differences between young and
middle-aged adults; similarly Schneiderman et al. (in press) found a decrease in anisotropy of the posterior limb between adolescence and adulthood. The posterior limb of the internal capsule, containing mostly corticospinal fibres and general somatic projections from thalamus to postcentral gyrus, completes myelination in the first few years of life (Yakovlev and Lecours, 1967), and reaches a plateau of anisotropy at 5–18 months of age (Morriss et al., 1999), with no further increase between childhood and early adulthood (Suzuki et al., 2003).

Myelination, demyelination, and remyelination are probably all affected by genotype for apolipoprotein E (apoE). In young adults, the ε4 allele is associated with an abnormal pattern of cortical activation during a recall task, without deficits in performance of the task (Scarmeas et al., 2005). Some studies find impaired cognitive function in middle-aged and older adults possessing an ε4 allele, while others do not, and there is controversy over whether such abnormalities represent early Alzheimer’s disease (AD) (reviewed in Savitz et al., 2006). Presence of an ε4 allele is associated with increased risk and earlier onset of AD. In a sample of 29 cognitively normal adults with a mean age of 65 yr, the presence of an ε4 allele was associated with a localized decrease in white-matter anisotropy in the ventral parahippocampal region, but not 5 mm or 10 mm dorsal to this (Nierenberg et al., 2005). The localized effect in an age group at risk for AD suggests that this white-matter change may reflect senile degeneration in the entorhinal and transentorhinal cortex [Braak stages I–II (Braak and Braak, 1991)], rather than a generalized effect of the ε4 allele on myelin. Kalus et al. (2006) found localized loss of intervoxel coherence in this region in subjects with mild cognitive impairment (mean age 76 yr), presumably independent of genotype. On the other hand, using T2 relaxation time as a measure of myelin integrity, Bartzokis et al. (2006) found that the apoE ε4 allele was associated with decreased integrity and an exaggerated correlation of decreased integrity with age in frontal white matter and genu of corpus callosum (regions without apparent vulnerability in early AD) among normal adults aged 55–75 yr, while an ε2 allele was protective.

Homozgyosity for ε4 is associated with AD-related white-matter abnormalities on MRI (Bronge, 2002), and with a mean age of onset for schizophrenia that is 10 yr earlier than with other genotypes (Kampman et al., 2004). As noted by Bartzokis et al. (2004), the essential role of apoE in the recycling of lipids and cholesterol could be crucial to myelin repair, and the influence of genotype on this process could explain its influence on the clinical course of a variety of brain insults.

Onset of schizophrenia and the natural course of myelination

Benes and colleagues have noted that the molecular layer of the subiculum and pre- and parasubiculum is myelinated in the second and third decades of life (Benes, 1989; Benes et al., 1994), and they suggest that maturation of the connections subserved by these fibres is required for the onset of schizophrenia (Benes, 1989, 2004; Benes et al., 1994). In a slightly different interpretation of this phenomenon, Bartzokis (2002) suggests that schizophrenia may result from interference with myelination at this time. In schizophrenia, subicular apical dendrites, which extend into the molecular layer, have decreased densities of dendritic spines (Rosoklija et al., 2000) and decreased immunoreactivity for microtubule-associated proteins 2 and 5 (Arnold et al., 1991; Rosoklija et al., 2005). mRNA for spinophilin is reduced in these neurons (Law et al., 2004). These findings suggest that the afferent axons may also be abnormal. However, the question is unresolved, with only one relevant study published. Chambers and Perrone-Bizzozero (2004) compared optical density of MBP immunoreactivity in 16 schizophrenia subjects (10 males, mean age 52 yr; 6 females, mean age 70 yr) and 14 non-psychiatric subjects (9 males, mean age 51 yr; 5 females, mean age 70 yr). Among the females, optical density was significantly lower in the schizophrenia group, while among the males, there was no significant difference between groups. Unfortunately, this study cannot provide a definitive conclusion about the state of myelination of the subicular/presubicular molecular layer, since the number of subjects is small, and optical density of MBP immunoreactivity is not a sensitive method for evaluating the status of myelin [which perhaps explains the small variance that these investigators report, while Benes et al. (1994) illustrate considerable variability among control subjects, even within a given age group].

DTI reveals widespread areas of white-matter change between adolescence and adulthood (Schneiderman et al., in press), any of which could be a candidate for a developmental abnormality of myelination in schizophrenia. Indeed, extension of these studies to schizophrenia has revealed complex patterns of differences in effects of age on FA (Schneiderman et al., 2006, and personal communication). These important studies are somewhat limited by cross-sectional design and modest sample size;
longitudinal follow-up to demonstrate maturational changes in individuals would be invaluable.

The various presentations of metachromatic leukodystrophy, an autosomal recessive defect in aryl sulfatase A that results in widespread demyelination, suggests that brain functions in the process of development may be particularly vulnerable to disruption by demyelination. The late infantile form of metachromatic leukodystrophy presents in the first 2 yr of life with motor difficulties. The juvenile form presents between ages 4 yr and 12 yr with behavioural and speech difficulties, while the adult form presents after puberty with psychiatric symptoms that are frequently mistaken initially for schizophrenia. The psychotic presentation of the adult-onset form is frequently cited as evidence for a role of myelin pathology in the aetiology of schizophrenia (e.g. Bartzokis, 2002; Hyde et al., 1992). However, we would caution against over-interpretation of this clinical phenomenon. The adult onset form of globoid cell leukodystrophy, a sphingolipidosis with similar gross pathology (due to a defect in the next step of sphingolipid metabolism), presents with motor difficulties. Both diseases, while characterized by loss of myelin, are caused by enzymatic deficiencies that also have other effects.

**Myelin integrity and cognitive function in healthy humans and monkeys**

The relationship between cognitive function and myelin integrity has been studied histologically in the rhesus monkey. Demyelination and axonal degeneration in the anterior commissure increase with age. Both processes presumably lead to a loss of myelinated axons, and the number of myelinated axons was significantly correlated with cognitive function between ages 5 and 20 yr. In older monkeys, aged 25–35 yr, the number of myelinated fibres was uniformly decreased to the minimum level found in the younger group, and there was no correlation with cognitive function, which was well-preserved in some of the older animals (Sandell and Peters, 2003). However, degenerative changes of cortical myelin in frontal area 46 (Peters and Sethares, 2002) and primary visual cortex (Peters et al., 2000) were correlated with cognitive impairment at all ages, although at least in the visual cortex, there was no loss of fibres (Nielsen and Peters, 2000).

In a study of 47 children, aged 5–18 yr, there was a significant correlation between IQ and FA in several brain areas, including frontal, parietal, occipito-temporal-parietal, and corticospinal tracts (Schmithorst et al., 2005). In a series of 23 children, working memory was significantly correlated with FA in dorsal left fronto-parietal, ventral left frontal, and left temporo-occipital white matter and in rostral corpus callosum, while reading correlated with FA in left temporal white matter (Nagy et al., 2004). In both studies, anisotropy in these regions also correlated with age, suggesting that deficits were the result of failed or delayed development. Young and middle-aged adults with dyslexia also show decreased FA in left temporal white matter (Klingberg et al., 2000), suggesting persistence of a developmental deficit involving temporal white matter that can still be detected years later by DTI. An even more striking example of developmental variability comes from two studies of healthy Scottish subjects (Deary et al., 2006; Shenkin et al., 2003) who had received IQ tests (Moray House Test) in 1932, at age 11 yr. A total of 69 healthy subjects were examined at ages 80 or 83 yr. Current FA in the centrum semiovale was significantly correlated with IQ at age 11 yr, as well as with current measures of cognitive function and reading ability. (The centrum semiovale is a large region, dorsal to the entire body of the lateral ventricle. More detailed localization would be of great interest.) The remarkable feature of these studies is that normal correlates of cognitive functional abilities are detectable by DTI years after these abilities are established, and indeed, years after they were measured. Long-term longitudinal studies of DTI are not yet available. While the studies cited would suggest that early variations persist, especially in the case of those related to reading ability (generally believed to be among the most stable of cognitive functions), we would point out that this is not necessarily the case, and that the histological basis of a deficit of FA might change. Theoretically, for instance, neuronal pathology could first give rise to a functional deficit without any structural abnormality in white matter. Subsequently, this abnormality could lead to decreased FA due to structural changes in the distal axon, as part of a dying-back axonopathy that eventually might result in loss of myelin.

Significant correlations have been reported between cognitive decline in normal ageing and decreased FA in all levels of centrum semiovale (Charlton et al., 2006) and in rostral corpus callosum (Persson et al., 2006b). However, Shenkin et al. (2005), in a study of 105 non-demented individuals aged 76–82 yr, found no significant correlations of FA in frontal white matter or centrum semiovale with any cognitive measure, including reading ability. Studies that did not include measures of cognitive decline found a significant, negative correlation between age and FA.
in frontal white matter or rostral corpus callosum, but not in posterior regions (Head et al., 2004; Ota et al., 2006; Pfefferbaum et al., 2005; Salat et al., 2005) whereas posterior deficits in FA have been associated with early-stage dementia (Head et al., 2004), and with an apoE e4 allele in a sample of non-demented individuals aged 50–79 yr (Persson et al., 2006a). [Presumably, these posterior deficits in white matter are related to the posterior cortical deficits in resting metabolism and activation that have long been recognized in Alzheimer’s disease (Ingvar et al., 1975).] Since cognitive function and frontal and rostral callo- sal FA are all correlated with ageing, it is difficult to determine whether age-related decline in anterior FA is independently related to cognitive decline. After Charlton et al. (2006) controlled for age and reading ability, the only significant correlation that remained was between working memory and FA in middle and posterior centrum semiovale. It seems plausible that a developmental component of frontal FA contributes to a static component of cognitive function, while age-related loss of frontal FA has little relationship with cognitive function.

In a small autopsy study of elderly subjects with no cognitive impairment, mild cognitive impairment, or AD (Wang et al., 2004a), there was a significant negative correlation between cognitive impairment and immunoreactivity for MBP in white-matter homogenates from the middle frontal gyrus, and a negative correlation of MBP with age among the unimpaired subjects.

Myelin integrity and cognitive function in schizophrenia

A few studies have examined the relationship between white-matter integrity and cognitive function or symptomatology and schizophrenia. In an autopsy study of elderly, chronically institutionalized schizophrenic patients, dorsal prefrontal myelin ratings (from left or right hemisphere, selected randomly) were associated with severity of cognitive dysfunction [evaluated by review of medical records (Ortakov et al., 1999)] at the onset of schizophrenia (typically ~50 yr before death) and during the last years of life, but not with the intervening change (Mancevski et al., 2006). Age at death and neuropathological evidence for vasculopathy, infarction or AD were all associated with lower myelin ratings, greater cognitive impairment at the end of life, and greater progression of cognitive impairment over the course of illness, but not with severity of cognitive impairment at the onset of illness. Thus, as suggested above for healthy subjects, normal variability early in life may contribute to a deficit of white-matter integrity and a static component of cognitive deficit, or decreased cognitive reserve. Whereas in healthy individuals this may correspond only to a few points of IQ, in schizophrenia it is manifested by mild but clinically evident deficits on most items of the adapted Clinical Dementia Rating scale (Ortakov et al., 1999).

Several DTI studies of younger (see Table 1 for ages) schizophrenia subjects found correlations between anisotropy and cognitive measures. Hoptman et al. (2002) found, in a group of male schizophrenia subjects, that in right ventral frontal white matter, but not right dorsal or left, impulsiveness correlated with decreased FA. In a subsequent voxelwise study, the correlation with impulsiveness was confirmed, and other regions were also involved (Hoptman et al., 2004). These two studies did not include healthy subjects, but the result is generally consistent with normal involvement of ventral prefrontal cortex in impulsiveness. Kubicki et al. (2002) found that in patients, but not in comparison subjects, FA of the right uncinate fasciculus at the level of the anterior commissure correlated inversely with measures of attention and verbal abstraction, and FA of the left with immediate recall, but neither side was correlated with performance on the Wisconsin Card Sorting Test (WCST). Nestor et al. (2004) found that in patients but not comparison subjects, WCST performance was inversely correlated with FA in the left cingulum bundle, while FA in the uncinate fasciculi was related to memory functions and general intelligence. Lim et al. (2006), in a whole-brain voxelwise study, found significant correlations (r² ≥ 0.41), between three cognitive dimensions and FA in various regions of white matter. Verbal declarative memory was positively correlated with FA in both hippocampi. Attention was positively correlated with FA bilaterally in anterior cingulate and prefrontal regions and white matter adjacent to the caudate nucleus. Executive function was positively correlated with FA in the anterior cingulate region bilaterally, the corpus callosum, and widespread areas in the left hemisphere. This summary of the findings is not exhaustive. Correlations were found in the expected regions, as well as others, possibly reflecting correlations among performances in a number of cognitive domains. On all of the tests in all of these studies there were significant positive correlations with frontal FA, except for the WCST. However, in the studies that employed the WCST, the frontal region of interest was limited to the uncinate fasciculus, which is situated far ventrally, while functional imaging demonstrates activation of the
dorsolateral prefrontal cortex during this task (Callicott et al., 2003; Weinberger et al., 1986).

Although correlations of cognitive performance with FA in the uncinate fasciculus and cingulum bundle could be explained by the neuroanatomical localization of the specific tasks in healthy people, these correlations were found only in the schizophrenia subjects, in whom mean values of FA in these regions were depressed. This is apparently not a measurement issue; performance was impaired in schizophrenia, but variance in performance was very similar among schizophrenia and healthy comparison subjects (Nestor et al., 2004). This raises the possibility that, rather than a static, developmental element of diminished cognitive reserve, the components of FA in these two regions that correlate with specific cognitive tasks are caused by processes related to schizophrenia itself.

A theoretical model

Characterization of white-matter abnormalities in schizophrenia is a formidable undertaking that is still in its early stages. While many imaging studies indicate the presence of abnormalities, only a handful have examined correlations with cognitive function. There are no studies of the longitudinal course of FA, and there is none of elderly subjects with schizophrenia. There are only a few autopsy studies, and most are small. Thus, the findings that must be explained by a model will undoubtedly change over the next few years.

For now, we believe that a model should explain the following phenomena:

1. There are deficits of white-matter integrity that are specifically related to schizophrenia.
2. Schizophrenia-specific white-matter deficits become less prominent with advancing age.
3. Schizophrenia-specific white-matter deficits are related to schizophrenia-specific cognitive deficits that are permanent and progressive, often resulting in dementia.
4. There is normal developmental variability in white-matter integrity that contributes a static component of cognitive variability both to individuals who remain healthy and to those who develop schizophrenia.
5. Myelin integrity normally declines with age through a process of demyelination and remyelination.
6. Oligodendrocyte density in some areas of grey matter increases with age in healthy humans and monkeys.

We propose a model (Figure 1) in which a deficit of myelin in schizophrenia arises from a partial or complete failure of myelination in late adolescence and early adulthood. The concept of ‘last myelinated, first demyelinated’ would predict that the fibres that fail to myelinate in schizophrenia would be the first to demyelinate with age in healthy individuals, while schizophrenia subjects would have less of this myelin to lose at the same age. Healthy ageing individuals, undergoing more demyelination than ageing individuals with schizophrenia, would respond with more remyelination; hence, shorter internodes requiring more oligodendrocytes. Remyelination could also be pathologically impaired in schizophrenia, but in our proposed model, the efficacy of normal remyelination or its decrement in schizophrenia would be insufficient to amount to a significant contribution.
to the myelin deficit.) The adverse consequences of failed myelination in schizophrenia could be myriad, including greater vulnerability of the axon to injury, greater metabolic requirements of the neuron, impaired transport of neurotrophic factors, and trans-synaptic effects on axonal targets. These effects could already be manifest at the onset of clinical disease, which may follow several years of failing myelination, and they would become more severe over time, but they would not necessarily entail further deficits of myelin. A normal, earlier-developing, stable variability in white-matter integrity, corresponding to a component of variability among individuals in natural cognitive endowment, would be superimposed on this process.

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Statement of Interest

None.

References


Garey LJ, Ong WY, Patel TS, Kanani M, Davis A, Mortimer AM, Barnes TR, Hirsch SR (1998). Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. Journal of Neurology, Neurosurgery and Psychiatry 65, 446–453.

Glantz LA, Lewis DA (2000). Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Archives of General Psychiatry 57, 65–73.


Young KA, Manaye KF, Liang C, Hicks PB, German DC (2000). Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia. Biological Psychiatry 47, 944–953.