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Linking white and grey matter in schizophrenia: oligodendrocyte and neuron pathology in the prefrontal cortex

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Neuronal circuitry relies to a large extent on the presence of functional myelin produced in the brain by oligodendrocytes. Schizophrenia has been proposed to arise partly from altered brain connectivity. Brain imaging and neuropathologic studies have revealed changes in white matter and reduction in myelin content in patients with schizophrenia. In particular, alterations in the directionality and alignment of axons have been documented in schizophrenia. Moreover, the expression levels of several myelin-related genes are decreased in postmortem brains obtained from patients with schizophrenia. These findings have led to the formulation of the oligodendrocyte/myelin dysfunction hypothesis of schizophrenia. In this review, we present a brief overview of the neuropathologic findings obtained on white matter and oligodendrocyte status observed in schizophrenia patients, and relate these changes to the processes of brain maturation and myelination. We also review recent data on oligodendrocyte/myelin genes, and present some recent mouse models of myelin deficiencies. The use of transgenic and mutant animal models offers a unique opportunity to analyze oligodendrocyte and neuronal changes that may have a clinical impact. Lastly, we present some recent morphological findings supporting possible causal involvement of white and grey matter abnormalities, in the aim of determining the morphologic characteristics of the circuits whose alteration leads to the cortical dysfunction that possibly underlies the pathogenesis of schizophrenia.

Keywords: myelin, myelin-related genes, development, anterior cingulate cortex, cingulum bundle

WHITE MATTER AND COGNITIVE FUNCTION

The role of white matter in neural circuit integrity may be appreciated in terms of supporting neural functioning. Most neurons in the brain necessitate adequate myelination of their axons in order to maintain functional processing at all levels of neural systems, from autonomic processes and sensorimotor integration, to mood and thought. The importance of myelination for cognitive functioning becomes apparent in diseases that are known to be caused or affected by deficiencies in myelin, where patients show deficits in intellectual, social and emotional functioning (Dwork et al., 2007; Schmahmann et al., 2008). Leukodystrophies and leukoencephalopathies, diseases characterized by progressive degeneration of the white matter, if diagnosed in late adolescence or early adulthood can present with psychotic symptoms sometimes indistinguishable from those of schizophrenia (Davis et al., 2003; Denier et al., 2007; Walterfang et al., 2005). Likewise, patients with multiple sclerosis who display cognitive and psychiatric symptoms frequently have white matter lesions in the frontal and temporal lobes, which are the brain regions most implicated in schizophrenia (Davis et al., 2003).

Schizophrenia is a severe psychiatric illness that affects close to 1% of the population worldwide. The diagnosis is generally established at first onset of the symptoms, which occurs in most cases in early adulthood. The disease is characterized by a number of mental abnormalities that result in a distortion of perception and expression of reality. There are prominent sensory symptoms, most frequently taking the form of auditory and visual hallucinations, although such sensations can affect any sensory modality. In addition to hallucinations, the patients may experience paranoid delusions, present with disorganized thoughts and speech, and a variable degree of social and occupational dysfunction. There is a considerable degree of inheritability of the disease and prenatal causes, such as insult to the brain during embryonic development, have also been considered to play a key role in the expression of the disease at a later time (see Fallon et al., 2003).

Schizophrenia has been shown to exhibit myelin deficiencies and changes in white matter volume in the brain (Davis et al., 2003; Dwork et al., 2007; Karoutzou et al., 2008; Segal et al., 2007b; Sokolov, 2007; Walterfang et al., 2006). The myelin hypothesis in schizophrenia was first presented by Hakak et al. (2001) after their pivotal finding of altered expression of myelin-related genes in human postmortem tissue (Hakak et al., 2001). Myelin-related gene expression levels have matched the observations made on white matter abnormalities by diffusion tensor imaging (DTI), and were later confirmed in several other studies. Since the first suggestions of a myelin-related pathophysiology underlying schizophrenia, there have been numerous and extensive reports and reviews on the myelin hypothesis (Davis et al., 2003; Dwork et al., 2007; Karoutzou et al., 2008; Segal et al., 2007b; Sokolov, 2007; Walterfang et al., 2006).

Substantial deficits in myelination occur in schizophrenia, which is interesting to consider in light of previous hypotheses that the disease results from abnormal brain development (Lewis and Levitt,

2002; Rapoport et al., 2005; Weinberger, 1986, 1987) and altered neuronal circuitry (Selemon and Goldman-Rakic, 1999), particularly in the prefrontal cortex (PFC). Neuropathologic findings in both white matter and grey matter suggest that myelin alterations in the anterior cingulate cortex (ACC) may underlie some of the behavioral deficits related to prefrontal dysfunction. We discuss some of the white matter findings and relate these to grey matter pathologies in schizophrenia, elucidating a possible impact that white matter abnormalities have on neuronal morphology and function.

IMAGING AND NEUROPATHOLOGIC FINDINGS IN SCHIZOPHRENIA

IMAGING STUDIES

Fractional anisotropy (FA), a measure of the directionality of water movement within the spaces in-between axons, provides an indication of white matter tract directionality and, by measuring the strength of the direction vector of water diffusion, possibly of tract integrity or coherence. A major advantage of this approach is that it can be used to study changes in schizophrenia *in vivo*, allowing investigation of different stages of the disease. *In vivo* DTI studies have revealed decreased FA in several major white matter tracts in schizophrenia (Buchsbaum et al., 1998, 2006; Kubicki et al., 2007; Lim et al., 1999; Shergill et al., 2007), including the cingulum (Kubicki et al., 2003; Wang et al., 2004). In addition, positron emission tomography (PET) imaging has demonstrated increased relative metabolic rates in white matter in schizophrenia, which may represent white matter inefficiency or defects resulting in increased metabolic needs (Buchsbaum et al., 2007), in contrast to findings in the grey matter which have shown decreases in regional cerebral blood flow in the ACC (Tamminga et al., 1992).

Although previous DTI studies have shown decreases in FA in the cingulum bundle as well as in the overlying cingulate gyrus in patients with schizophrenia (Fujiwara et al., 2007; Kubicki et al., 2003; Kumra et al., 2005; Sun et al., 2003; Wang et al., 2004; White et al., 2008), the findings have been somewhat inconsistent, due in large part to small subject samples and different methods of identifying particular brain regions of interest (Kubicki et al., 2007). Segal and collaborators recently investigated the volume and FA in the cingulate gyrus in a large group of subjects with chronic schizophrenia along with a group of patients with recent-onset schizophrenia and healthy control subjects matched for age and sex (Segal, 2008; Segal et al., 2007a). The anterior cingulate gyrus was traced and segmented into axial portions allowing detection of localized changes. Volume was calculated for the anterior cingulate gyrus, and average FA values were calculated for each segment looking separately at grey and white matter. A significant decrease in the overall grey matter volume was found in the anterior cingulate gyrus in persons with schizophrenia. In both grey and white matter, persons with recent-onset schizophrenia had the highest FA in several regions, and persons with chronic schizophrenia had the lowest (**Figure 1**). These results demonstrate both white and grey matter abnormalities in the cingulate gyrus in schizophrenia (Segal, 2008), which may reflect abnormalities in neuron spacing or columnar organization.

MRI studies of the grey matter have revealed regionally reduced cortical volumes in schizophrenia (Honea et al., 2005, 2008; Nesvag et al., 2008; Okugawa et al., 2007), including the ACC (Baiano et al., 2007; Wang et al., 2007). Magnetic transfer imaging (MTI) assessment of macromolecular structural integrity enables separate analysis of white and grey matter, which may help to elucidate early neuropathological changes. Foong et al. (2001) found MTI changes in the grey matter of frontal and temporal areas, while white matter abnormalities were observed only in temporal areas.

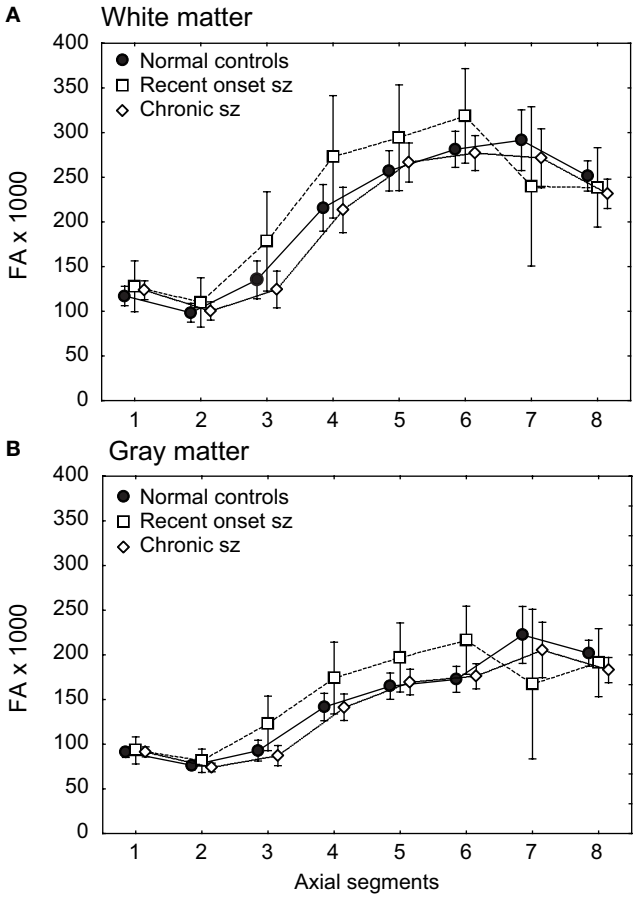

FIGURE 1 | Human DTI along rostrocaudal axial segments of the entire cingulate gyrus, spanning from area 32 (segment 1) to area 23 (segment 8). (A) FA values showing a significant region × diagnosis effect in the cingulate white matter, with patients with recent-onset schizophrenia displaying the highest FA in most segments, followed by control subjects and then patients with chronic schizophrenia (ANCOVA $F_{14,567} = 2.42$, $p = 0.003$). **(B)** The same pattern was noted in cingulate grey matter, also with a significant region × diagnosis effect (ANCOVA $F_{14,567} = 3.01$, $p < 0.001$). Vertical bars indicate 95% confidence intervals and values are computed for the age covariate at its mean. Normal controls ($n = 38$), recent-onset schizophrenia ($n = 6$), chronic schizophrenia ($n = 41$); sz, schizophrenia; FA, fractional anisotropy.

OLIGODENDROCYTE AND MYELIN STUDIES

In attempts to localize and identify a cellular correlate of the white matter changes observed by brain imaging *in vivo*, oligodendrocytes have come to be an important focus of investigation. Analyses of the number, densities and distribution patterns of oligodendrocytes can be performed in both the white and grey matter. Stark et al. (2004) found decreased oligodendrocyte densities in cingulate area 24 but not in the adjacent paracingulate area 32, and Hof et al. (2003) found

decreased densities of oligodendrocytes in the prefrontal area 9 of the superior frontal gyrus in subjects with schizophrenia. In contrast, in a subsequent study, Hof and coworkers evaluated the degree of oligodendrocyte clustering in the anterior cingulum bundle, but found no differences using postmortem tissue from chronic schizophrenics versus age-matched controls (Segal et al., 2009). These results suggest that more subtle oligodendrocyte or myelin anomalies may underlie the structural deficits observed by brain imaging in the cingulum bundle in schizophrenia. On the ultrastructural level, electron microscopy studies of oligodendrocytes in the PFC have demonstrated apoptotic oligodendrocytes, irregularities of mitochondria in oligodendrocytes and damaged myelin in area 10 in schizophrenic brains (Uranova et al., 2001, 2004).

GREY MATTER AND NEURON STUDIES

Postmortem studies, assessing the gyrification index, have found reductions in cortical folding in schizophrenia (Kulynych et al., 1997). Studies on changes in neuronal densities in different cortical regions in schizophrenia have been conflicting, and no definite pattern of neuronal density alterations has yet been established. These differences in observation may in part be due to differences in methodological approaches and procedures and the cortical regions studied. Some postmortem studies of the ACC and dorsolateral PFC (DLPFC) have suggested a decrease in neuronal density. Benes reported a lower neuronal density (mainly in layer II) in areas 24 and 10, primarily of small interneurons (Benes et al., 1991), which suggested an alteration in intrinsic neuronal circuits (Benes, 2000). Other investigators have shown increased neuronal density in areas 9 and 46, without increased absolute numbers of neurons in patients with schizophrenia (Selemon et al., 1995, 1998). This implied that cortical volume in select cortical regions is reduced in schizophrenia, possibly because of reduced neuropil. Goldman-Rakic and coworkers proposed that an altered brain connectivity plays a critical role in the development of schizophrenia (Selemon and Goldman-Rakic, 1999). In other studies on subcortical regions, observations have been made of reductions in the size and total neuron numbers, but not in neuronal density, in the putamen and the amygdala (Kreczmanski et al., 2007).

Cytoarchitectural studies have analyzed neuronal arrangements in terms of interneuronal distances, or mean cell spacing (Casanova et al., 2005, 2008) showing that mean cell spacing was reduced in area 9 in schizophrenic patients, which would imply a higher neuronal density. Rajkowska and coworkers found that in area 9, there was a downward shift in neuronal sizes, accompanied by increases in the density of "small neurons" in layer II, interpreted as GABAergic interneurons, while there was a decrease in the density of "very large neurons" in layer III, presumably pyramidal neurons, in patients with schizophrenia. Concomitant morphological studies at the single neuron level have demonstrated impoverished dendritic structures of pyramidal neurons (Broadbelt et al., 2002) and loss of dendritic spines in schizophrenia (Garey et al., 1998; Glantz and Lewis, 2000; Sweet et al., 2009), as well as in non-human primate models (Selemon et al., 2007).

Another interesting finding is an anomalous distribution of the so-called interstitial white matter neurons in schizophrenia. These interstitial neurons have been suggested to be remnants of subplate neurons that normally undergo programmed cell death during brain maturation (Chun and Shatz, 1989). However, in certain species including human, these white matter interstitial neurons are to some degree normally found in healthy adults (Kostovic and Rakic, 1980). The interstitial white matter neurons have been found to be increased in prefrontal white matter (Akbarian et al., 1996; Anderson et al., 1996) and temporal white matter (Rioux et al., 2003) in subjects with schizophrenia, supporting further the presence of a neurodevelopmental abnormality in schizophrenia (Weinberger, 1986, 1987) (See **Table 1** for a summary of imaging, and grey and white matter studies in schizophrenia.).

THE INVOLVEMENT OF ACC IN SCHIZOPHRENIA

THE CINGULATE GYRUS AND THE CINGULUM BUNDLE

The ACC has been studied in many neuropathologic investigations of schizophrenia. From a topographical viewpoint, the ACC consist of Brodmann area 24, and includes the subgenual area 25, and according to some authors also the paracingulate prefrontal area 32. In the human, area 24 can be subdivided along its rostrocaudal and dorsoventral extent, through which it shows gradients in cytoarchitecture as well as topography in its afferent and efferent projections (Ongür et al., 2003; Palomero-Gallagher et al., 2008; Vogt et al., 1995), and area 32 extends dorsocaudally as a dorsal strip (32′) overlying area 24 (**Figure 2**). The cingulum bundle is the major coherent white matter tract of the cingulate gyrus, radiating superiorly from the corpus callosum to the cingulate cortex. The ACC receives processed multimodal sensory information from insular, temporal, parietal association cortices, and emotional information from the amygdala and the orbitofrontal cortex (Jones and Powell, 1970). The multimodal sensory input enables the ACC to respond to stimuli with motivational significance, activating motor and visceromotor responses, including vocalizations. For details on cingulate circuitry, see Beckmann et al. (2009), Iversen (1984), Kunishio and Haber (1994), Van Hoesen et al. (1993), Vogt and Pandya (1987) and Vogt et al. (1987).

THE ROLE OF ACC IN BEHAVIOR WITH IMPLICATIONS FOR SCHIZOPHRENIA

The first observation that the ACC had a role in emotional and visceromotor behavior was from non-human primate studies. Electrical stimulation of the ACC in monkeys generates changes in blood pressure, heart rate, respiratory rate, and agitation and vocalizations (Devinsky et al., 1995; Jürgens et al., 1967; Neafsey, 1990; Smith, 1945). Primate lesion studies have shown aggressiveness, emotional blunting, and impaired infant-mother interactions, further indicating that the ACC has an important role in emotional and social functions (Devinsky et al., 1995; Glees et al., 1950; Mirsky et al., 1957). However, these early lesion studies commonly involved more than just area 24 or area 32 and often included the parts of the OFC, and later confirmation studies have shown various effects in monkeys (Devinsky et al., 1995; Hadland et al., 2003). In the human, different observations have been made from tumors, strokes, seizures and electrical stimulation studies involving the ACC, but these have been quite variable (Devinski and Luciano, 1993; Devinsky et al., 1995). For example, surgical interventions of the ACC have focused on management of pain, chronic depression and obsessive-compulsive behavior (Devinsky et al., 1995). It is likely that the social aspects of the ACC that have been observed are related to its connections with the OFC. For an overview of the

Table 1 | Examples of neuropathological observations on the human cerebral cortex and underlying white matter in schizophrenia.

Parameter	Method	Observations in schizophrenia	References
IMAGING STUDIES			
White matter fractional anisotropy	DTI	Decreased FA in the cingulum bundle	Kubicki et al. (2003)
		Decreased FA in the cingulum bundle	Sun et al. (2003)
		Decreased FA in the cingulum bundle	Wang et al. (2004)
		Decreased FA in the frontal WM	Kumra et al. (2005)
Myelin water fraction	MRI	Reduced myelin water fraction in frontal WM	Flynn et al. (2003)
White matter metabolism	PET	Increased in the cingulum bundle	Buchsbaum et al. (2007)
Gyrification index	MRI	Reduction in cortical folding in frontal regions	Kulynych et al. (1997)
Sulcal patterning	MRI	Shallower sulcal depth in the parietal operculum	Csernansky et al. (2008)
Cortical volume	MRI	Reduced volume of frontal lobes	Andreasen et al. (1986)
		Reduced volume of the ACC	Baiano et al. (2007)
		Reduced volume of the ACC	Koo et al. (2008)
		Cortical thinning of prefrontal and temporal cortices	Nesvag et al. (2008)
		Cortical thinning of ACC, temporal and parietal cortices	Narr et al. (2005)
		Progressive grey matter loss starting in the parietal cortex and progressing towards temporal cortex and DLPFC	Thompson et al. (2001)
Grey matter metabolism	rCBF	Decreased rCBF in ACC	Tamminga et al. (1992)
	PET	Decreased glucose metabolic rates in the ACC	Haznedar et al. (2004)
Macromolecular structure integrity	MTI	Alterations in frontotemporal GM and temporal WM	Foong et al. (2000)
OLIGODENDROCYTE AND MYELIN STUDIES			
Oligodendrocyte density in white matter	Stereology	Decreased density in the WM of SFG	Hof et al. (2003)
		Unaltered density in the cingulum bundle	Segal et al. (2009)
Oligodendrocyte density in grey matter	Stereology	Decreased density in area 24 but not in area 32	Stark et al., (2004)
		Decreased density in the SFG	Hof et al. (2003)
Oligodendrocyte morphology	EM	Apoptotic oligodendrocytes in area 10	Uranova et al. (2001)
Myelin sheaths	EM	Damaged myelin in area 10	Uranova et al. (2001)
Gene expression of myelin-related genes	Microarrays association analysis	Decreased expression of myelin-associated glycoprotein (MAG), myelin and lymphocyte protein (MAL), 2′,3′-cyclic nucleotide 3′-phosphodiestase (CNP), gelsolin, transferrin and HER3 (neuregulin receptor) in the DLPFC	Hakak et al. (2001)
	Association analysis	Association of 10 single nucleotide polymorphisms from six myelin-related genes	Jungerius et al. (2008)
Protein expression of myelin-related genes		Decreased expression of CNP in GM of anterior PFC	Flynn et al. (2003)
GREY MATTER AND NEURON STUDIES			
Capillary lengths	Stereology	No differences in are 24 and area 9	Kreczmanski et al. (2005)
Neuronal density	2D morphometric analysis*	Decreased in area 24 and area 10	Benes et al. (1991)
	3D morphometric analysis*	Increases in area 9 and area 46	Selemon et al. (1995, 1998)
Interstitial white matter neurons	2D analysis	Increased neurons in prefrontal white matter	Akbarian et al. (1996) and Anderson et al. (1996)
Neuronal distribution	Stereology	Decreased mean cell spacing in area 9	Casanova et al. (2005, 2008)
Neural soma size	3D analysis*	Smaller mean neuronal somas in area 9	Rajkowska et al. (1998)
Neuronal integrity	Golgi stains	Decreased number of dendrites in area 32	Broadbelt et al. (2002)
		Decreased dendritic spine density in DLPFC	Glantz and Lewis (2000), Kolluri et al. (2005) and Sweet et al. (2009)
Synaptic proteins	Synaptophysin	Alterations in synaptic protein expression	Glantz and Lewis (1997) and Eastwood and Harrison (1995)

This table is not a comprehensive summary of all neuropathologic findings in schizophrenia. Rather, it gives examples of some of the latest morphological observations in which the myelin hypothesis may have an impact, in relation to some of the classical neuropathologic findings.
WM, white matter; GM, grey matter; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; SFG, superior frontal gyrus; FA, fractional anisotropy; DTI, diffusion tensor imaging; MTI, magnetic transfer imaging; MRI, magnetic resonance imaging; rCBF, regional cerebral blood flow; PET, positron emission tomography; EM, electron microscopy
**Biased to tissue orientation and limited sampling.*

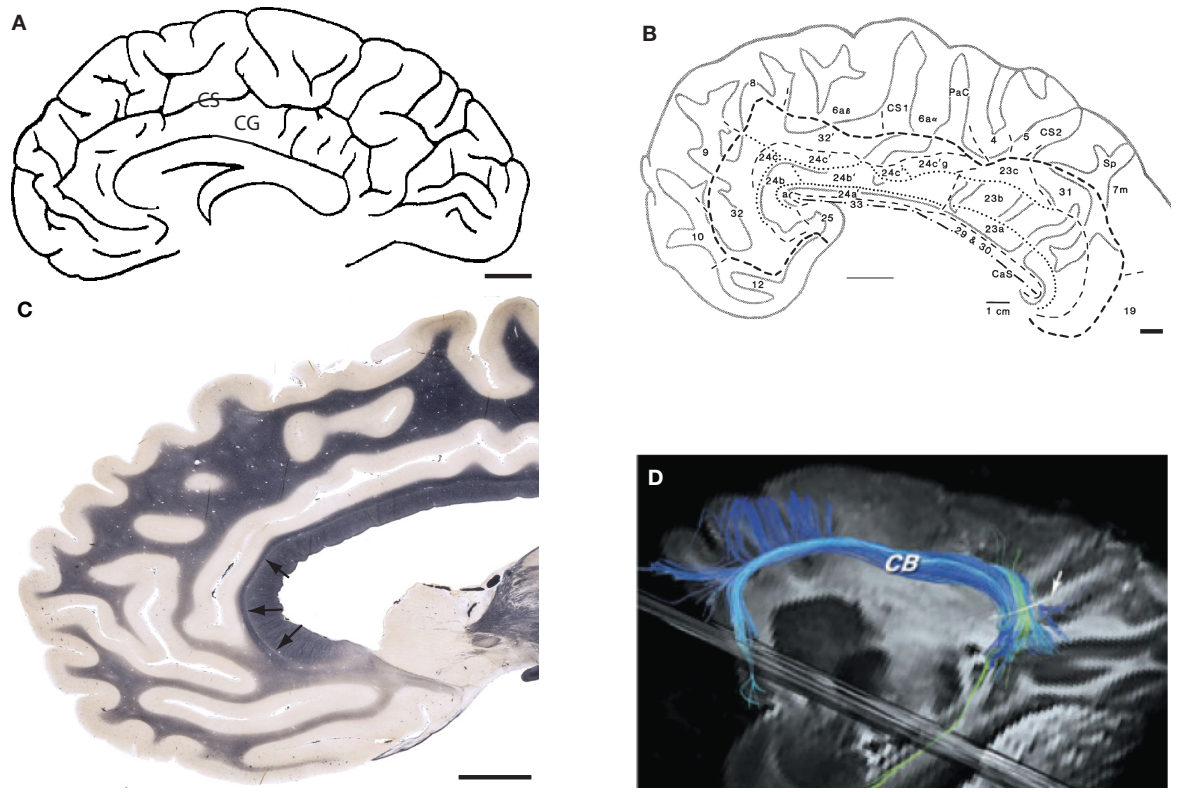

FIGURE 2 | The cingulate cortex and cingulum bundle. (A) Medial surface view of the human brain, depicting the cingulate gyrus (CG) and the cingulate sulcus (CS). **(B)** Human flat map of the cingulate cortex and surrounding areas. Note that the anterior cingulate is composed of the subgenual area 25, the paracingulate area 32, and six cytoarchitecturally different subregions of area 24 (24a,b,c,a′,b′,c′, respectively). **(C)** Human sagittal myelin stain showing the cingulate cortex and the cingulum bundle (arrows) as a thin fiber tract overlying the corpus callosum. **(D)** The cingulum bundle in the rhesus monkey, as visualized with DTI. Panels **(A,B)** modified from Vogt et al. (1995), and panel **(D)** from Schmahmann et al. (2007), with permissions. Scale bars 1 cm.

ACC in social function, see Amodio and Frith (2006), Bush et al. (2000), Rudebeck et al. (2008) and Rushworth et al. (2007a,b). It is noteworthy that both the sensory integration and social processing modalities are pertinent to the presumed ACC dysfunction in schizophrenia. It is however important to keep in mind that social and emotional functions are separate entities though they commonly interact.

BRAIN MATURATION AND MYELINATION

MYELINATION SEQUENCES

During ontogeny, the cognitive development of children and young adults depends closely on the progressive myelination of cortical axons (Casey et al., 2005; Fuster, 2002; Gibson and Petersen, 1991; Paus, 2005). As first shown by Flechsig in 1901, and later by Yakoklev in human postmortem myelin preparations (Flechsig, 1901; Yakovlev and Lecours, 1967), the regions that are myelinated first include the spinal cord and brainstem, and then myelination continues dorsally towards the frontal cortex, with proximal pathways myelinating prior to distal pathways, sensory pathways prior to motor pathways, and downstream projection pathways prior to association pathways (Volpe, 2000) and prefrontal regions myelinating the last (Lenroot and Giedd, 2006). Although initiated prenatally in humans, most tracts and regions become myelinated during the first year of life, and myelination continues into the second and third decade of life in humans (**Figure 3**). These early reports have been confirmed and further refined with modern brain imaging techniques (Ballesteros et al., 1993; Knickmeyer et al., 2008; Lenroot and Giedd, 2006; Miller et al., 2003; Mukherjee and McKinstry, 2006; Mukherjee et al., 2001, 2002; Paus et al., 2001; Sowell et al., 2003; Volpe, 2000). In addition, the number of oligodendrocytes drastically increases after birth through maturity (O'Kusky and Colonnier, 1982). It is this increase in oligodendrocytes and myelination that accounts for the large increase in white matter volume observed during the first years of life (Knickmeyer et al., 2008; Lenroot and Giedd, 2006).

The PFC is the last region of the brain to mature (Fuster, 2002). The volume of prefrontal white matter increases through childhood and early adolescence, and is not complete until early adulthood (Paus et al., 2001). As such, myelination *per se* can be used as an index of cortical maturation (Fuster, 2002). In the human cingulum bundle, the onset of myelination is around gestational week 38 and is fully myelinated at 1 year of age in humans (Gilles et al., 1983). It should be kept in mind however that when adulthood is reached, the cortical areas 24, 25 and 32 are poorly myelinated (Ongür et al., 2003), although the underlying cingulum bundle is highly myelinated.

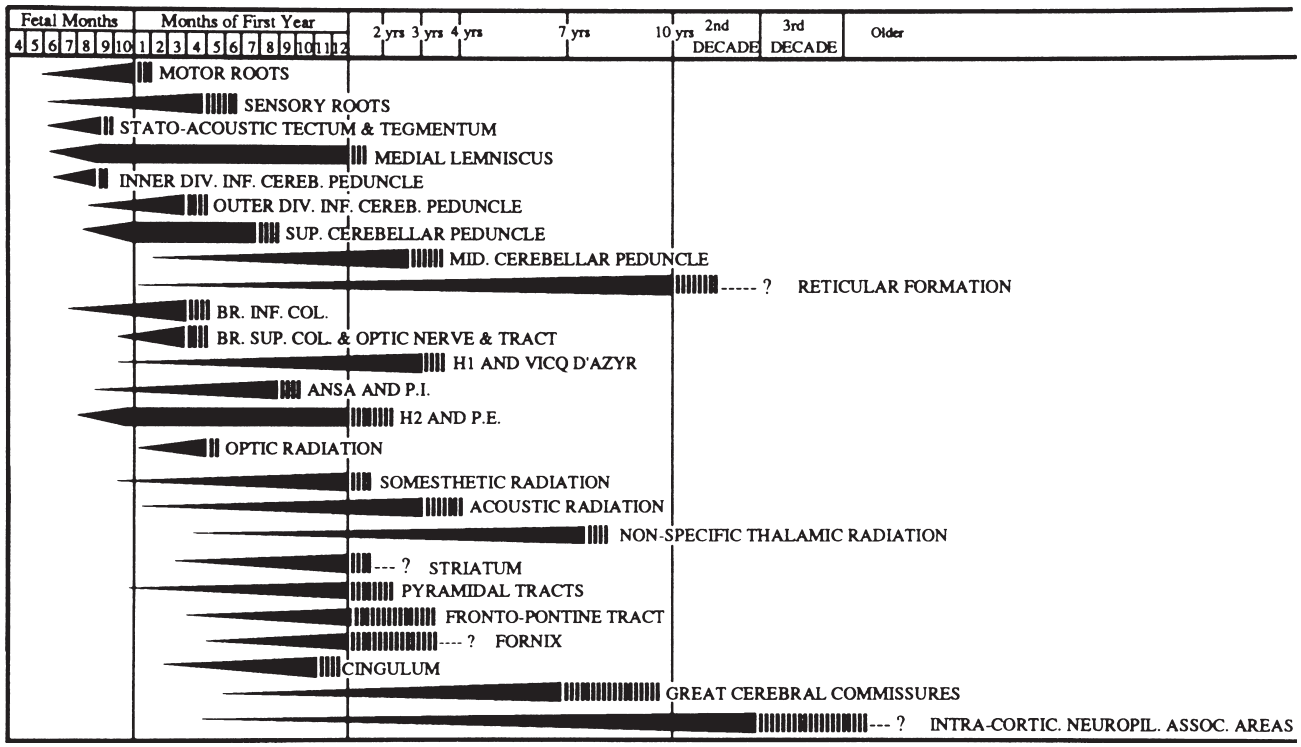

FIGURE 3 | Myelination during brain maturation in the human. From Yakovlev and Lecours (1967), with permission.

This brain maturation process of myelination and white matter volume expansion occurs simultaneously with a grey matter volume reduction (Pfefferbaum et al., 1994), and an increase in synaptogenesis which is followed by synaptic pruning and elimination (Huttenlocher, 1979). For example, Pfefferbaum showed with MRI that the volume of cortical grey matter decreases starting at 5 years of age in the human, while the white matter volume continues to increase through the third decade of life (Pfefferbaum et al., 1994). This has been confirmed and extended to include an analysis of the progression of white and grey matter changes through the complete human lifespan, in which frontal and parietal grey matter volumes peak at around 10–12 years of age and temporal grey peaks at 16–18 years of age (Thompson et al., 2005), and the white matter volume does not start to decline until after the age of 50 (**Figure 4**) (Sowell et al., 2003). The classic work of Huttenlocher (1979) showed that in the human medial PFC, the peak synaptic density occurs at 3–4 years of age, and starts to decline at mid-to-late adolescence. The pruning of axonal connections during brain development and maturation may be necessary for adequate formation of appropriate neuronal circuits. Thus, there is an interplay between progressive and regressive events that occur during brain maturation (Gogtay et al., 2004; Lenroot and Giedd, 2006; Sowell et al., 2003, 2004; Toga et al., 2006). In summary, the overall brain development and maturation occurs at several levels: (i) axonal, with wiring and myelination; (ii) dendritic, with arborization and spine formation; (iii) synaptic, with synaptogenesis and pruning; (iv) neuronal, with postnatal overshoot of neurons and programmed cell death; and (v) glial, with oligodendrocyte, astrocyte, and microglia maturation.

BRAIN MATURATION AND SCHIZOPHRENIA

It is possible that the regionally specific remodeling of grey and white matter that takes place into the third decade of life underlies some of the structural and functional changes that leads to the development of psychiatric disorders such as schizophrenia. The fact that the PFC matures last and that myelination is not complete until late adolescence may be significant, as the timing coincides with the typical onset of symptoms in schizophrenia. This suggests that a dysfunctional myelination process could underlie the pathogenesis of schizophrenia. Also several other psychiatric diseases, such as anxiety, mood, and personality disorders, first manifest themselves during early adulthood, possibly reflecting aberrations in brain maturation mechanisms (Paus et al., 2008). In fact, Paus and others discusses that "an exaggeration of typical adolescent changes…has occurred in patients with schizophrenia" (Keshavan et al., 1994). In fact, several of the observed neuropathologic findings in schizophrenia, such as reductions in frontal grey matter volumes (Baiano et al., 2007; Sporn et al., 2003), reductions in prefrontal metabolism (Andreasen et al., 1992), and reductions in plasma membrane phospholipid levels (Pettegrew et al., 1991) are "consistent with an exaggeration of the changes that occur in typical development" (Paus et al., 2008). Imaging work by Thompson and coworkers have also related brain maturation with the development of schizophrenia (Gogtay et al., 2008; Thompson et al., 2001).

However, it is interesting to note the lack of neurological comorbities in schizophrenia in comparison with other more typical white matter diseases. In dysmyelinating and hypomyelinating diseases such as the leukoencephalopathies, the effects of a myelin

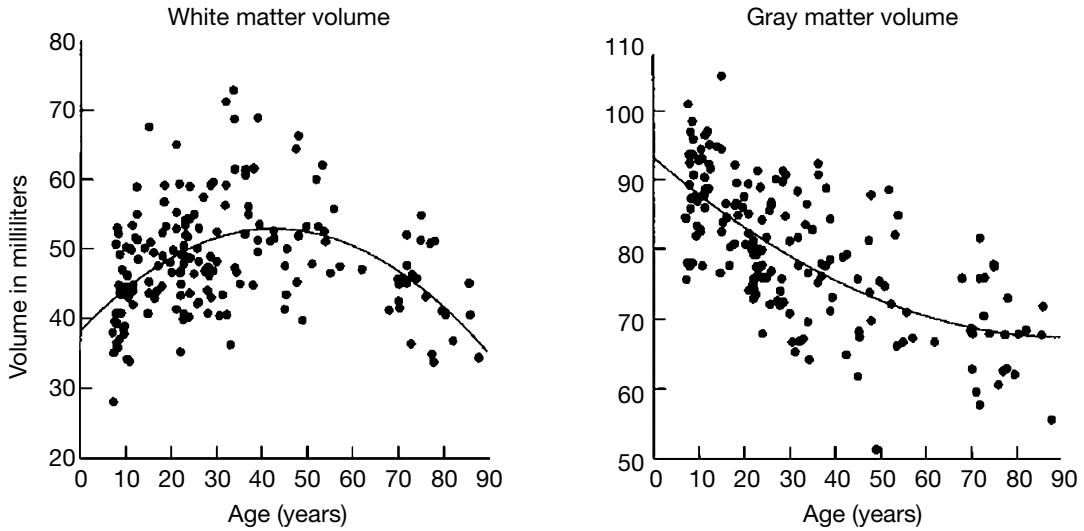

FIGURE 4 | Grey matter and white matter volumes in healthy subjects assessed with MRI. From Sowell et al. (2003), with permission.

deficiency may be striking and fatal (see reviews by Lyon et al., 2006; Schmahmann and Pandya, 2007; Schmahmann et al., 2007, 2008; Walterfang et al., 2005). If the myelin hypothesis holds true, and myelin deficiencies prove to be one of the central causes of the development of schizophrenia, one might argue and question why classic schizophrenia patients show so few neurologic symptoms. Several other white matter abnormalities often generate disturbances at the neuron level, such as seizures and/or psychomotor developmental delays. Why patients with schizophrenia do not particularly exhibit similar neurologic comorbidities, such as seizures or sensorimotor deficits, is unknown. It may be that only specific pathways become myelin-deficient, such as the late developing and poorly myelinated regions of the PFC, leading to the generation of behavioral symptoms seen in schizophrenia. Since the diverse circuits in the brain do not mature at the same time, if there is a developmental insult, this may affect only a certain population of neurons undergoing myelination, and result in a pathway-specific deficiency.

GENETICS

GENETIC ASSOCIATION OF OLIGODENDROCYTE AND MYELIN-RELATED GENES IN SCHIZOPHRENIA

In a groundbreaking study using gene microarray analysis to examine gene expression levels in postmortem samples from schizophrenia patients (Hakak et al., 2001), it was found that the expression of six myelin-related genes predominantly expressed in oligodendrocytes, including the myelin-associated glycoprotein (MAG), myelin and lymphocyte protein (MAL), 2′,3′-cyclic nucleotide 3′-phosphodiestase (CNP), gelsolin, transferrin and HER3 (ErbB3) was significantly decreased in the DLPFC in postmortem schizophrenic brains. The decreased expression of oligodendrocyte-related gene products was later confirmed and extended to other brain areas, implying that there is a pathology of oligodendrocytes underlying schizophrenia (Dracheva et al., 2006; Hakak et al., 2001; Haroutunian et al., 2006, 2007; Katsel et al., 2005a,b, 2008; McCullumsmith et al., 2007; Tkachev et al., 2003). Genetic linkage studies have also implicated myelin-related loci in schizophrenia (Bailer et al., 2000; Levinson et al., 1998) although linkage studies are now considered somewhat controversial in complex psychiatric disorders. This molecular pathology, showing a reduced myelin-related gene expression, has been shown in the DLPFC, hippocampus, superior temporal cortex, and the cingulate gyrus (Katsel et al., 2005b; McCullumsmith et al., 2007; Sugai et al., 2004). These results from gene expression studies led to genetic association studies, to clarify whether reduced expression of oligodendrocyte and myelin genes in schizophrenia represents an early event in the etiology of the disorder, or merely result from treatment with no direct causative relation to the disorder. Much evidence, including whole genome association studies, have identified myelin- and oligodendrocyte-related genes as susceptibility genes for schizophrenia.

One of the most promising schizophrenia-related genes is neuregulin 1 (*NRG1*) gene (Stefansson et al., 2002, 2003; Williams et al., 2003). NRG1 and the NRG1-receptor ERBB4 are involved in several aspects of nervous system development including oligodendrocyte development (Calaora et al., 2001; Corfas et al., 2004; Sussman et al., 2005). Several lines of studies support genetic association of *NRG1* with schizophrenia (Munafo et al., 2006), and associated endophenotypes (Bramon et al., 2008; Mata et al., 2009). A genetic locus–locus interactive analyses between *NRG1* and *ERBB4* genes provided evidence for a significant interaction between the *NRG1* Icelandic schizophrenia risk haplotype and *ERBB4* (Norton et al., 2006), suggesting that *NRG1* may mediate its effects on schizophrenia susceptibility through functional interaction with *ERBB4*. Given the emerging role of NRG1 and ERRB4 in oligodendrocyte development, it is possible that alterations in *NRG1* and *ERBB4* affect oligodendrocytes, leading to schizophrenia.

Reticulin 4 (*RTN4*, also known as NOGO) is a myelin-associated protein that inhibits the outgrowth of neurites and nerve terminals. Novak et al. (2002) reported over-expression of *RTN4* in the brains of people with schizophrenia and also evidence for genetic association between a marker in the 3′UTR of the gene. Several groups

have subsequently failed to replicate these genetic findings (Chen et al., 2004; Covault et al., 2004; Gregorio et al., 2005; Xiong et al., 2005), however, a moderately large study (Woo and Crowell, 2005) demonstrated modest evidence for association (Chen et al., 2004). Interestingly, three rare non-synonymous variants have recently been reported in the RTN4 receptor in schizophrenia cases but not in controls (Sinibaldi et al., 2004).

Additional genes showing reduced expression have been analyzed in genetic association studies. These genes include *OLIG2* and *CNP1*. Olig2 is a basic helix-loop-helix (bHLH) oligodendrocyte transcription factor that, together with Olig1 is sufficient and necessary for the formation of oligodendrocytes (Ross et al., 2003; Sauvageot and Stiles, 2002). Association analysis revealed strong evidence for association for this gene. Of six informative single nucleotide polymorphisms (SNPs) analyzed, four showed genetic association (Georgieva et al., 2006), which has been further confirmed in Chinese (Huang et al., 2008), but not Japanese (Usui et al., 2006), cohorts. *CNP1*, encodes CNPase, which is important for process formation of oligodendrocytes (Hakak et al., 2001). The *CNP1* gene maps to a region in which there is a previously reported significant linkage to schizophrenia in a single large pedigree. Significant association of a functional SNP was observed, and interestingly, this SNP is shown to be associated with low CNPase expression using allelic expression analysis in human brain (Peirce et al., 2006). This association was replicated in Caucasian (Voineskos et al., 2008), but not in Asian, cohorts (Tang et al., 2007; Usui et al., 2006). There have also been reports of genetic association between schizophrenia and myelin-oligodendrocyte glycoprotein (MOG; (Liu et al., 2005), proteolipid protein 1 (Qin et al., 2005), claudin 5 (Sun et al., 2004) and gelsolin (Xi et al., 2004). The gene encoding QKI, the quaking homologue KH domain RNA binding, is located in 6q25-27, and this region had been shown to be a susceptibility locus for schizophrenia as identified in a large pedigree from northern Sweden (Lindholm et al., 2001). Some evidence of genetic association was reported in this population (Aberg et al., 2006a,b), but this was not observed in a Chinese sample (Huang et al., 2009). Another gene reported to be associated with schizophrenia is *MAG*. MAG is a MAG that plays important roles in myelination. Support for a role for MAG in schizophrenia susceptibility has been reported in both family based and case control studies in Han Chinese populations, but still controversial.

Finally, *PTPRZ1*, a gene encoding receptor protein tyrosine phosphatase beta (RPTPβ) is a new and promising candidate gene for schizophrenia (Buxbaum et al., 2008). RPTPβ is expressed in oligodendrocytes, and appears to modulate ERBB4 signaling. Association analysis of *PTPRZ1* showed highly significant association of this gene to schizophrenia in this first study, however, this association was not replicated in a Japanese cohort (Ito et al., 2008).

MOUSE MODELS OF WHITE MATTER DYSFUNCTION

Transgenic mouse models may serve as vehicles for studying the morphological and anatomical abnormalities that may result from a genetic defect affecting myelination. Some recent mouse models of white matter dysfunction have emerged during the last few years, which may serve as putative animal models for schizophrenia. The evidence described above are beginning to provide enough construct validity for mice with disruption of oligodendrocyte and myelin-associated genes as animal models for schizophrenia, and several knockout mice for oligodendrocyte and myelin-related genes have been investigated.

For example, CNPase knockout mice show no obvious delay in myelination and oligodendrocyte development, but develop ataxia and motor deficits at 4 months and die (Lappe-Siefke et al., 2003). A detailed histological analysis found axonal loss in these mice, a feature observed in schizophrenia. As NRG1 regulates oligodendrocyte development through ERB receptors on oligodendrocytes, Corfas and colleagues generated a mouse expressing a dominant negative ERB receptor in oligodendrocytes, and found oligodendrocyte and myelin abnormalities in this line. These mice showed reduced locomotion and social dysfunction, with increased dopamine signaling and hypersensitivity to amphetamine, reflecting aspects of the disorder (Roy et al., 2007). In the same way, mice deficient in Rtn4r have been studied, and altered locomotor activity (Hsu et al., 2007) and reduced working memory function (Budel et al., 2008) were observed. The transmembrane protease Bace1 is a key molecule that regulates NRG1 signaling and myelination (Hu et al., 2006). Savonenko et al. (2008) reported that Bace1-null mice show schizophrenia-related phenotypes in multiple behavioral domains, including deficits in prepulse inhibition and novelty-induced hyperactivity, hypersensitivity to a glutamatergic psychostimulant, cognitive impairments, and deficits in social recognition. Fgfr2 is expressed in oligodendrocytes and involved in the formation of myelin membranes and Kaga et al. (2006) generated conditional knockout mice of this gene and found that conditional knockout mice are hyperactive and that dopamine receptor antagonist abolished this abnormality.

The MAG knockout model is another relevant mouse model of myelin deficits, in light of the studies that found decreased expression of MAG in schizophrenia (Hakak et al., 2001; McCullumsmith et al., 2007; Tkachev et al., 2003). MAG is known to interact with neuronal membranes where it helps maintain the periaxonal space of myelin sheaths (Li et al., 1994), is involved in initiation of myelination (Montag et al., 1994), and has been shown to inhibit neurite outgrowth and impair axonal regeneration (Quarles, 2009). This has led to the hypothesis that MAG promotes maturation, maintenance and survival of myelinated neurons (Quarles, 2009). MAG knockout mice may therefore have disruptions in normal myelinated tract development that are reflected in altered anisotropy or fiber length density. Several studies have described developmental abnormalities in the MAG knockout model but have not demonstrated a dysfunctional phenotype (Li et al., 1994; Loers et al., 2004; Weiss et al., 2000, 2001). Behavioral studies of these mice showed fairly subtle abnormalities. Mice missing the *Mag* gene are less proficient than wild-type mice in maintaining balance on a rotating cylinder and display hyperactivity and impaired hindlimb reflex extension (Pan et al., 2005). However, the mutant mice showed no differences in spatial learning and memory or in swimming speed, as demonstrated in a Morris water maze (Montag et al., 1994).

Another mouse model recently used in research on schizophrenia is the QKI model or "Quaking" mutant (Haroutunian et al., 2006; Lauriat et al., 2008). Qk^{v} is an autosomal recessive mutation in mice that leads to severe dysmyelination of the CNS due to defects in oligodendrocyte maturation and RNA metabolism of myelin

components, and all isoforms of QKI (QKI5, 6, 7) are deleted in the mice with this mutation. The "quaking" mice show reduced number of myelin lamellae, lack of myelin sheath compaction, and abnormalities in the structure of nodal regions. In addition to that, alterations of dopamine system parameters, including increased dopamine metabolism and increased dopamine D_2 receptor binding, have been observed (Nikulina et al., 1995). Homozygous mice that survive to adulthood exhibit a characteristic tremor or "quaking" (Sidman et al., 1964), with abnormal composition and structure of myelin (Baumann and Pham-Dinh, 2001). As a homozygote, this mouse has traditionally been used in epilepsy research in virtue of its myelin and conduction abnormalities, whereas the heterozygote has a milder form of white matter dysfunction, and has been used as a putative schizophrenia model (Aberg et al., 2006a,b). The *QKI* gene product is an mRNA binding protein involved in determination of glial fate and oligodendrocyte differentiation (Ebersole et al., 1996; Larocque and Richard, 2005) and has been implicated in schizophrenia in several studies (Chenard and Richard, 2008; McCullumsmith et al., 2007; McInnes and Lauriat, 2006), in addition to the genetic studies cited above.

Mice treated with cuprizone, a drug that induces demyelination, demonstrated altered behavior including hyperactivity, sensorimotor gating anomalies, and memory alterations (Franco-Pons et al., 2007). Interestingly, these defects lasted after the discontinuation of cuprizone treatment, suggesting developmental insults to oligodendrocytes and myelin might contribute to schizophrenia. Zhang et al. found that the atypical antipsychotic, quetiapine, promoted the differentiation of oligodendrocyte lineage cells and prevented cortical demyelination and the concomitant spatial working memory impairment induced by cuprizone (Xu et al., 2009; Zhang et al., 2008).

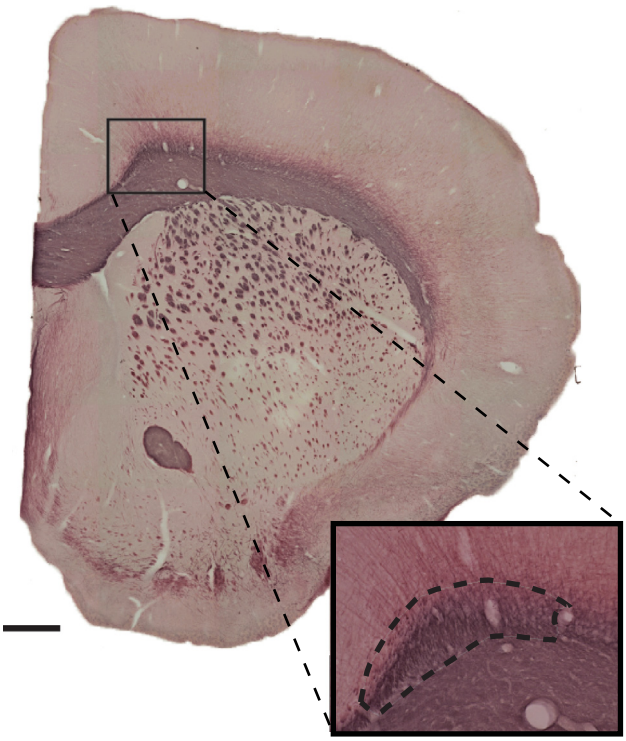

FIGURE 5 | Low magnification photomicrograph of a myelin Black Gold stain of a wild-type mouse. Inset depicts the outlined cingulum bundle for analysis of fiber length density. Scale bar 50 μm.

RECENT MORPHOLOGICAL FINDINGS FROM TRANSGENIC MICE

To date, two mouse models have been investigated for morphological alterations: the MAG model and the QKI model. Hof and coworkers examined two measures of white matter integrity in the MAG knockout model (Höistad et al., 2008; Segal, 2008). The cingulum bundle was examined using both DTI to examine white matter coherence as well as histological techniques to measure myelinated fiber length density. Diffusion anisotropy imaging was performed in adult MAG knockout mice, measuring the FA in a region of the cingulum bundle. At matched histological levels, using sections stained for myelin with Black Gold (Schmued and Slikker, 1999), myelinated fiber length density, defined as fiber length per unit of white matter volume was evaluated (**Figure 5**). The MAG knockout model displayed no alterations in either FA or fiber length density in the cingulum bundle (Segal, 2008). Thus, the effects of dysmyelination in the MAG model may be very subtle and may require ultrastructural studies to pinpoint the precise neuropathologic alterations.

We also performed morphological analysis of regional overall changes in cytoarchitecture in the ACC of the MAG and QKI mouse models (Höistad et al., 2008). Using stereologic methods, the number, density and spatial distribution patterns of neurons and oligodendrocytes were investigated. The effects of dysmyelination on neuron and oligodendrocyte numbers and densities in the ACC in these models revealed slight decreases in the overall volume of the ACC. Both the MAG and the QKI mouse models displayed lower total neuron numbers, but no difference in estimates of neuronal density, and differences in oligodendrocytes in the ACC were observed only as a trend in the QKI model. Thus, the QKI model may prove to be a more valuable model of myelin deficiencies than the MAG model, especially considering the absence of changes in the FA and fiber length density in this model.

Furthermore, we analyzed the dendritic structure of pyramidal neurons in these mouse models to assess whether disrupted myelination of axonal pathways that provide inputs to the neocortex severely affect the dendritic integrity of target neurons, resulting in dendritic attrition, loss of dendritic spines, and alterations in spine morphology. This permits an evaluation of the effect of abnormal myelination on the structure and function of pyramidal neurons in select regions relevant to schizophrenia, for example the medial PFC. The hypothesis we are investigating is elucidating potential morphological effects on target neurons, as a consequence of myelin deficiencies in the afferent axonal tracts (Segal et al., 2007b). Single pyramidal neurons were injected with a fluorescent dye and then analyzed morphometrically.

In the MAG model, analyses of pyramidal neurons in layers II and III in the PFC have shown that in young mice (3 months) the basal dendrites showed a reduced level of dendritic branching compared to their wild-type littermates (Segal et al., 2007b), while less remarkable effects were observed on the apical branches. This may suggest that the dendritic tree of the MAG mice is undergoing a selective pathology that may be related to alterations in

specific axonal pathways influencing principally the basal dendrites, and as such possibly of thalamic origin. These data imply that a disturbance in the organization of myelin, due to impaired expression of MAG, may result in alterations in morphology of layers II and III pyramidal cells, particularly with respect to basal dendritic integrity. Such alterations may lead to abnormalities of specific white matter tracts and affect the prefrontal circuits. Preliminary observations of spine densities in young MAG mice have so far not revealed differences between knockout and control mice (Segal et al., 2007b). However spine pathology may be more prominent in aged mice as a function of aging *per se*.

In the QKI model, analyses of pyramidal neurons in layers II and III in the ACC of old mice showed shorter dendritic lengths of both apical and basal dendrites (Höistad et al., 2008). The apical dendrites displayed shorter dendritic lengths distal from the soma, fewer numbers of branch radial intersections, and fewer higher order branches, whereas no differences were observed in the basal dendrites (**Figures 6A–D**). Preliminary observations of spine densities in the QKI mouse has suggested that dendritic spines are in fact more numerous in QKI mice compared to control littermates (**Figures 6E–H**). This may reflect compensatory mechanisms similar to sprouting. These observations are in line with our stereologic findings, which demonstrate that the QKI mice exhibit lower total neuron numbers and lower volumes of the ACC than control mice.

The preliminary evidence presented in **Figure 6** on the QKI model, suggests possible support for the viability of the hypothesis that myelin deficiencies may have morphological effects on target neurons, although the extent of these effects are not fully analyzed. We are aware of the fact that the relationship between disrupted myelin and changes in spine densities may not appear as a direct or causal one. It remains plausible that deficits in myelination may cause significant alterations in connectivity of select components of the afferent systems to cortical neurons, and as a result, a partial differentiation of those targets, which may alter the spine densities and spine morphologies. Comparably, detrimental changes in spine densities have been found during aging and in stress conditions (Duan et al., 2003; Radley et al., 2008).The possibility that myelin and oligodendrocyte changes impact on the integrity of the pyramidal neuron dendritic tree fits well within the general context of the effects of white matter disruption in the brain.

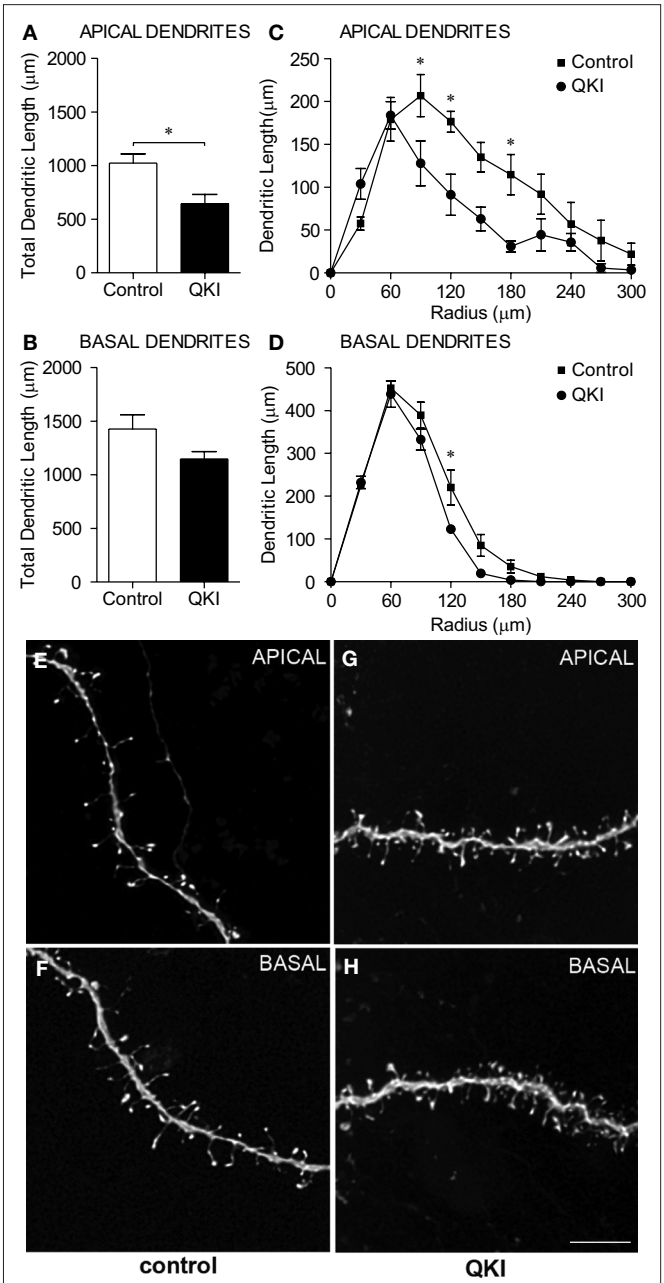

FIGURE 6 | Dendritic arbors and spines in the control and QKI mouse model. (A,B) Arbor analysis showing total dendritic lengths in apical and basal dendrites, $*p < 0.05$, Student's *t*-test. **(C,D)** Dendritic lengths in apical and basal dendrites, as a function of the radial distance from the cell soma, $*p < 0.05$, two-way ANOVA with Bonferroni's *post hoc* test (Höistad et al., 2008). **(E–H)** Dendritic segments of Lucifer yellow-filled neurons in the medial PFC were scanned at high resolution on a confocal laser scanning microscope. 3-Dimentionally reconstructed dendritic segments, 50–100 µm from the cell soma, show hyperspiny dendrites on both the apical and basal branches in the QKI mouse. Scale bar 5 µm.

FUTURE DIRECTIONS

Evidence from very different lines of research supports the premise that dysfunction of oligodendrocytes is a critical factor in the development of schizophrenia. The precise role oligodendrocytes hold in the cascade of malfunctions that results in the constellation of deficits seen in the disease is still unknown. Layers II and III pyramidal neurons in the ACC may be the targets of axonal pathways affected in schizophrenia. Quantitative information on neuronal integrity in mouse models is important for understanding downstream effects of myelin genetic abnormalities, and to assess the validity of models in the context of observable neuropathologic changes in human brains. These studies need to be extended to additional models reflecting the genetic complexity of schizophrenia, and electron microscopy studies should be used further to assess structural aberrations in oligodendrocytes and myelin sheaths, as well as immunogold approaches to study synaptic integrity by visualizing pre- and postsynaptic proteins. Correlative morphology and density analyses of dendritic spines will help clarify plastic changes in responses to myelin challenges.

The data obtained in transgenic mice will offer critical correlates to neuropathologic features that can be analyzed in postmortem human materials. Combined analysis of human specimen and relevant mouse models offers a unique opportunity to investigate myelin deficits that have a clinical impact. As a result of such combined approaches, a model of schizophrenia with characterized molecular defects that can be used for developing therapeutic approaches will hopefully emerge.

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