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Multimodal white matter imaging to investigate reduced fractional anisotropy and its age-related decline in schizophrenia

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Abstract

We hypothesized that reduced fractional anisotropy (FA) of water diffusion and its elevated aging-related decline in schizophrenia patients may be caused by elevated hyperintensive white matter (HWM) lesions, by reduced permeability-diffusivity index (PDI), or both. We tested this hypothesis in 40/30 control/patient participants. FA values for the corpus callosum were calculated from high angular resolution diffusion tensor imaging (DTI). Whole-brain volume of HWM lesions was quantified by 3D-T2w-fluid-attenuated inversion recovery (FLAIR) imaging. PDI for corpus callosum was ascertained using multi b-value diffusion imaging (15 b-shells with 30 directions per shell). Patients had significantly lower corpus callosum FA values, and there was a significant age-by-diagnosis interaction. Patients also had significantly reduced PDI but no difference in HWM volume. PDI and HWM volume were significant predictors of FA and captured the diagnosis-related variance. Separately, PDI robustly explained FA variance in schizophrenia patients, but not in controls. Conversely, HWM volume made equally significant contributions to variability in FA in both groups. The diagnosis-by-age effect of FA was explained by a PDI-by-diagnosis interaction. Post hoc testing showed a similar trend for PDI of gray matter.

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Contributions

PK designed experiments, performed data analyses and wrote the manuscript. JC designed the experiment, collected data, performed data analysis and contributed to writing the manuscript. SNW performed data analyses and contributed to writing the manuscript. LMR designed experiments, performed data analyses and contributed to writing the manuscript. BP performed data analyses and contributed to writing the manuscript. SAW performed data analyses and contributed to writing the manuscript.

KN collected data, performed data analyses and contributed to writing the manuscript. RPM designed statistical approaches and performed statistical analyses. WTC designed experiments and contributed to writing the manuscript. FM collected data and contributed to writing the manuscript. HM performed data analysis and contributed to writing the manuscript. LEM designed experiments, performed data analyses and wrote the manuscript.

Conflict of interest disclosure

The authors have no conflicts of interest to disclose.

Our study demonstrated that reduced FA and its accelerated decline with age in schizophrenia were explained by pathophysiology indexed by PDI, rather than HWM volume.

Keywords

Permeability; Diffusivity; Advanced DTI; Hyperintense white matter lesions

1. Introduction

Fractional anisotropy (FA) of water diffusion, measured using diffusion tensor imaging (DTI), reflects the "integrity" of the cerebral white matter (Pfefferbaum et al., 2000; Song et al., 2003; Song et al., 2005; Kochunov et al., 2007), and is widely used in psychiatric and neurological research (Kanaan et al., 2005; Mori et al., 2007; Friedman et al., 2008; Kochunov et al., 2012b; Nazeri et al., 2012). It has emerged as one of the more sensitive and replicable imaging biomarkers for schizophrenia (Mori et al., 2007; Friedman et al., 2008; Glahn et al., 2011; Perez-Iglesias et al., 2011; Kochunov et al., 2012b; Nazeri et al., 2012; Alba-Ferrara and de Erausquin, 2013). In addition, schizophrenia patients have been shown to have an accelerated rate of aging-related decline in FA values compared with controls in some studies (Mori et al., 2007; Friedman et al., 2008; Kochunov et al., 2012b; Wright et al., 2014), but not others (Jones et al., 2006). The biology of reduced FA values and its potential accelerated decline with age in schizophrenia patients remains unknown. The specific aspects of the white matter integrity decline that FA is indexing in schizophrenia patients are insufficiently understood. We hypothesized that reduced FA and its accelerated decline with age in patients with schizophrenia may be caused by two distinct biological mechanisms. The first mechanism is the elevation of T2-hyperintense white matter (HWM) lesions; it would suggest cerebrovascular causes of reduced FA values. The second mechanism is indexed by a novel permeability-diffusivity index (PDI); it would suggest that reduced FA in patients may be due to a difference in the membrane permeability (Kochunov et al., 2013a).

First, we hypothesized that reduced FA values in schizophrenia patients may be due to increases in the HWM volume as measured by fluid-attenuated inversion recovery (FLAIR) imaging. Supportive of this hypothesis are findings of elevated HWM volume in psychiatric disorders (Swayze et al., 1990; McDonald et al., 1999; Sassi et al., 2003; Zanetti et al., 2008), including schizophrenia (wayze et al., 1990; McDonald et al., 1999; Sassi et al., 2003; Zanetti et al., 2008), and particularly in older patients (Persaud et al., 1997; Lubman et al., 2002; Zanetti et al., 2008). HWM volume is an important neuroimaging marker of white matter integrity that is sensitive to focal demyelination (Kochunov et al., 2008; McGuire et al., 2013a), caused by ischemia and/or neuroinflammation (Fazekas et al., 1993; Geurts et al., 2005; Galluzzi et al., 2008; Wardlaw et al., 2013). During aging, the rise in HWM regions that occurs is associated with a reduction in FA values (Kochunov et al., 2007; Kochunov et al., 2008; MacLulich et al., 2009). Hypertension and other cerebrovascular disorders have been determined to be the risk factors for both the accelerated rise in HWM and decline in FA (Kochunov et al., 2009a; Kochunov et al., 2010; Kochunov et al., 2011c; Kochunov et al., 2012a). This aging-related change in white matter integrity occurs concurrently with decline in the overall cerebral integrity (Kochunov et al., 2008), cerebral blood flow (Kraut

et al., 2008) and glucose metabolism (Kochunov et al., 2009b). Patients with schizophrenia have twice the rate of hypertension, cardiovascular, and metabolic illnesses compared with normal aging (Tsuang and Woolson, 1978; Brown, 1997; Hennekens et al., 2005; Saha et al., 2007; Kirkpatrick et al., 2008; Ito and Barnes, 2009; Jeste et al., 2011). Therefore, reduced FA values in schizophrenia patients may be a reflection of the reduced white matter health due to neuroinflammatory, vascular, and other possible systemic pathologies found in schizophrenia that could be indexed by HWM.

Second, we hypothesized that schizophrenia-related FA deficits might be explained by differences in the membrane permeability of the white matter tissue of schizophrenia patients. FA values are calculated by fitting a multivariate, Gaussian, mono-exponential decay model to the DTI data, which is typically collected with a single diffusion weighting value (non-zero b-value) (Basser and Pierpaoli, 1996). This approximation is successful at modest diffusion weighting (up to $\sim 1000 \text{ s/mm}^2$), but becomes less accurate at higher b-values where signal decay behaves as a bi-exponential function of b-values (Assaf and Cohen, 1998; Clark et al., 2002; Wu et al., 2011a; Wu et al., 2011b). Sukstanskii and colleagues proposed a model that explained the behavior of the diffusion signal at higher b-values by the presence of permeable cellular membranes (Sukstanskii et al., 2003; Sukstanskii et al., 2004). Using this model, a PDI was derived and was shown to be theoretically sensitive to membrane permeability within the range of the normal physiological values observed in cerebral white matter (Sukstanskii et al., 2004; Kochunov et al., 2013a). A further rationale for estimating the membrane permeability is presented in Section 2. In the first application of this measure in humans, we compared PDI values for 26 schizophrenia patients with those measured from an equal number of healthy controls. There, we observed that patients had significantly lower PDI values in cerebral white and gray matter, and the effect size on PDI measurements was significantly stronger than in FA values (Kochunov et al., 2013a).

We tested both hypotheses in the mid-sagittal band of the corpus callosum, including its three subdivisions (genu, body, and splenium). This region was chosen because it consistently shows the largest schizophrenia-related white matter deficits (Kubicki et al., 2008; Henze et al., 2012; Kochunov et al., 2012b; Lee et al., 2013). It has a simpler, parallel commissural fiber architecture that has no intravoxel crossing (Aboitiz et al., 1992). Presence of intravoxel crossing fibers reduces FA values, and therefore testing this hypothesis in the corpus callosum simplifies interpretation of the biological mechanisms underlying the lower FA values in patients. Whether crossing fibers would affect PDI is unknown, but they are assumed to be a factor; therefore, PDI is also measured at the corpus callosum. The corpus callosum is a consistent anatomical landmark that is spatially limited in the left-to-right dimension. This makes the corpus callosum a target for multi b-value imaging experiments that may take a long ($\sim 80 \text{ s/slice}$) time to collect (Kochunov et al., 2013a). In addition, HWM lesions are most prevalent in the frontal and parietal lobes, thereby affecting the integrity of axonal fibers that decussate in the corpus callosum (Kochunov et al., 2009a; McGuire et al., 2013a). Therefore, we chose the whole brain HWM volume as the global, macroscopic marker of cerebrovascular and inflammatory white matter health, and assessed its potential contribution to FA. We performed this multimodal

white matter study by specifically excluding subjects who were diagnosed with diabetes or with neurological and cardiovascular disorders.

2. Methods

2.1. Participants

Participants comprised 40 (23 males, age=41.9±12.9 years) healthy controls and 30 schizophrenia patients (21 males, age=40.1±12.1 years). PDI data from 26/26 controls/patients, collected in the early stage of this study, were used to develop the PDI protocol (Kochunov et al., 2013a). Table 1 presents additional clinical and demographic information for the entire sample. All participants were evaluated with the Structured Clinical Interview for DSM-IV. Patients were those with a current Axis I schizophrenia diagnosis. Controls had no Axis I psychiatric diagnosis. With the exception of seven medication-free participants, all schizophrenia patients were on antipsychotic medications. Exclusion criteria included illicit substance and alcohol abuse and dependence, any heart disorder or major neurological diagnosis, or events such as head trauma, seizure, stroke or transient ischemic attack, and diagnosis for type-2-diabetes and hypertension.

2.2. Imaging and data analysis protocols

All imaging was performed at the University of Maryland Center for Brain Imaging Research using a Siemens 3T TRIO MRI (Erlangen, Germany) system and 32-channel phase-array head coil. Three white-matter-related imaging protocols were applied to each subject: high-angular resolution diffusion imaging (HARDI) DTI for FA, 3D FLAIR for HWM, and multi b-value diffusion imaging (MBI) for PDI.

2.2.1. HARDI protocol—The details of this imaging protocol are described elsewhere (Kochunov et al., 2011b). In short, diffusion tensor data were collected using a single-shot, echo-planar, single refocusing spin-echo, T2-weighted sequence with a spatial resolution of 1.7×1.7×3.0 mm. The sequence parameters were as follows: echo time (TE)/repetition time (TR)=87/8000 ms, field of view (FOV)=200 mm, axial slice orientation with 50 slices and no gaps, 64 isotropically distributed diffusion-weighted directions, two diffusion weighting values ($b=0$ and 700 s/mm²) and five $b=0$ images. These parameters were calculated using an optimization technique that maximizes the contrast-to-noise ratio for FA measurements (Jones et al., 1999). The total scan time was about 9 min/participant. The HARDI data were eddy-current corrected and fitted with a DTI model to extract FA values. Multi-subject analysis of FA values was performed using a tract-based spatial statistics (TBSS) method, distributed as a part of the FMRIB Software Library (FSL) package (Smith et al., 2006). The population-based, 3D, DTI cerebral white matter tract atlas, developed at Johns Hopkins University and distributed with the FSL package (Wakana et al., 2004), was used to calculate population average FA values along the spatial course of the corpus callosum (Kochunov et al., 2011a; Kochunov et al., 2012c). Axial and radial diffusivities were also explored.

2.2.2. 3D-FLAIR protocol—T2-weighted, three-dimensional (3D), high-resolution (isotropic 1-mm), FLAIR data were collected using a turbo-spin-echo sequence with the

following parameters: TR/TE/TI/flip angle/echo train length (ETL) = 5 s/353 ms/1.8 s/180°/221. This 3D-FLAIR protocol was designed to overcome the limitations of a two-dimensional, thick-slice (5- to 10-mm) clinical FLAIR protocol and to permit a more accurate determination of smaller lesions and accurate tracing of the lesion boundaries. Measurement of the volume of the HWM lesions from FLAIR images is described elsewhere (Kochunov et al., 2010; McGuire et al., 2013b). Briefly, FLAIR images were preprocessed by removal of non-brain tissue using the FSL brain extraction tool (BET) (FMRIB). Next, FLAIR images for individual subjects were registered to their corresponding T1-weighted images, and the T1-weighted images were then registered to a common Talairach-atlas-based stereotactic frame using the FSL FMRIB's Linear Image Registration Tool (FLIRT) global normalization transformation. Next, all images were corrected for radio frequency (RF) inhomogeneity artifact using the FSL BET method with default parameters. HWM regions were then manually delineated in 3D-space using in-house software (<http://ric.uthscsa.edu/mango>) by an experienced neuroanatomist with high intra-rater test-retest reproducibility and without knowledge of participants' diagnostic status (McGuire et al., 2013a). Total volume of the HWM regions across the whole brain white matter was the primary HWM measure. The total scan time was 12 min/participant.

2.2.3. MBI protocol—The MBI protocol was developed based on q-space protocols for in-vivo mapping of water diffusion in the brain (Clark et al., 2002; Wu et al., 2011b). This protocol consisted of 15 shells of b-values (b=250, 500, 600, 700, 800, 900, 1000, 1250, 1500, 1750, 2000, 2500, 3000, 3500 and 3800 s/mm²; diffusion gradient duration=47ms, diffusion gradient separation=54 ms). Thirty isotropically distributed diffusion-weighted directions were collected per shell, including 16 b=0 images. Three dummy scans preceded the data collection to establish the steady state. The highest b-value (b=3800 s/mm²) was chosen because the signal-to-noise ratio (SNR) for the corpus callosum in the average diffusion image (SNR=6.1±0.7), measured in five healthy volunteers (ages 25–50 years) during protocol development, approached the empirically selected lower limit of SNR=5.0. The b-values and the number of directions per shell were chosen for improved fit of the bi-exponential model and SNR (Jones et al., 1999). The imaging data were collected using a single-shot, echo-planar, single refocusing spin-echo, T2-weighted sequence with a spatial resolution of 1.7×1.7×4.6 mm and seven slices prescribed in sagittal orientation to sample the midsagittal band of the corpus callosum (Fig. 1). The sequence control parameters were TE/TR=120/1500 ms with FOV=200 mm. The total scan time was about 10 min/participant.

2.3. Permeability-diffusivity model

The details of permeability-diffusivity modeling are presented elsewhere (Kochunov et al., 2013b). The permeability-diffusivity model addresses a limitation of the standard DTI-FA model, which assumes a single pool of anisotropically diffusing water (Fig. 1S, see supplement). However, diffusion signal behaves as a bi-exponential function of b-values, representing two 'pools' of water, unrestricted and restricted (Assaf and Cohen, 1998; Clark et al., 2002; Wu et al., 2011a; Wu et al., 2011b). The DTI-FA signal is therefore an average of the fractional contribution from both pools (Assaf and Cohen, 1998; Clark et al., 2002; Wu et al., 2011a; Wu et al., 2011b). Importantly, the two diffusion pools cannot be ascribed to physically separate compartments such as the extracellular and intracellular spaces

(Hwang et al., 2003; Yablonskiy et al., 2003; Schwarcz et al., 2004; Stokes et al., 2012). Instead, the two-pool approximation provides a better description of the complex signal decay behavior in the presence of a permeable cellular membrane (Sukstanskii et al., 2003; Sukstanskii et al., 2004). Parameters derived from the bi-exponential modeling, such as PDI, should therefore be sensitive to the membrane's permeability, as supported by theoretical modeling (Sukstanskii et al., 2003; Sukstanskii et al., 2004; Kochunov et al., 2013b). In short, diffusion images were pre-processed to perform a region-of-interest (ROI) based fit for a two-compartment diffusion model (eq. 1) that assumes that intravoxel signal is formed by a contribution from two compartments (Clark et al., 2002; Sukstanskii et al., 2003; Panagiotaki et al., 2009; Wu et al., 2011b):

$$S(b) = S_0 \cdot (M_u \cdot e^{-b \cdot D_u} + (1 - M_u) \cdot e^{-b \cdot D_r}) \quad (1)$$

$$PDI = D_r / D_u \quad (2)$$

where $S(b)$ is the average diffusion-weighted signal for a given b-value, averaged across all directions. M_u is the fraction of the signal that comes from the compartment with unrestricted diffusion. The term $(1 - M_u)$ is the fraction of the signal that comes from the compartment with restricted diffusion. The PDI was calculated as the ratio of D_u and D_r (eq. 2), which are the apparent diffusion coefficients of the unrestricted and restricted compartment, respectively. This model assumes that the diffusion signal is produced by two quasi-pools of anisotropically diffusing water. D_u is a mean unrestricted diffusivity of the water molecules that are away from the axonal membranes. The water near the membrane and passing through channel pores of the membrane is characterized by restricted mean diffusivity (D_r). Our previous measurements showed that the unrestricted and restricted pools are about the same size in the corpus callosum ($M_u = 55 \pm 3.1\%$), and showed no patient-control differences ($p > 0.5$). The main parameter of this model is the permeability-diffusivity index (PDI) calculated as the ratio of D_r/D_u . An increase in membrane permeability via activated ion channels should increase water exchange and thus D_r , resulting in higher PDI. Conversely, reduced active permeability should reduce PDI. The diffusion-weighted image for each of the b-values, $S(b)$, were calculated for the four white matter ROIs: the whole corpus callosum, and the genu, body, and splenium subdivisions (Fig. 1S, see supplement).

Segmentation of the corpus callosum was performed based on the contrast in the FA values between corpus callosum and the nearby gray matter and cerebrospinal fluid (Fig. 1S, see supplement). To perform this segmentation, voxel-wise FA, radial, and axial diffusivity images for each subject were created using Camino software (<http://cmic.cs.ucl.ac.uk/camino>) (Alexander et al., 2011). There were no significant patient-control differences in the volumes of any ROI ($p > 0.4$). The bi-exponential diffusion model (eq. 1) was fitted for the white matter of the corpus callosum and its three subdivisions, using non-linear, least square fitting, implemented in the [R] package (R-Development-Core-Team, 2009) (Fig. 1S, see supplement).

2.4. Statistical analysis

Group differences in the imaging and clinical measures were compared using two-tailed *t*-tests. Effects of accelerated aging in FA values were tested using the model of age, diagnosis (DX), and age-by-diagnosis interaction (eq. 3).

$$FA = A + \beta_{age} \cdot age + \beta_{DX} \cdot DX + \beta_{age \cdot DX} \cdot age \cdot DX \quad (3)$$

Next, we tested if there were explanatory effects of HWM and PDI on FA values using the model in eq. 4.

$$FA = A + \beta_{HWM} \cdot HWM + \beta_{PDI} \cdot PDI \quad (4)$$

The significance of the difference in the explanatory power of two models was evaluated by comparing the change in r^2 using the analysis of variance (ANOVA) test. Finally, we evaluated the full linear model that included prediction of age, HWM, PDI, and their interaction with diagnosis (5).

$$FA = A + \beta_{age} \cdot age + \beta_{DX} \cdot DX + \beta_{age \cdot DX} \cdot age \cdot DX + \beta_{HWM} \cdot HWM + \beta_{HWM \cdot DX} \cdot HWM \cdot DX + \beta_{PDI} \cdot PDI + \beta_{PDI \cdot DX} \cdot PDI \cdot DX \quad (5)$$

All modeling was performed with the [R] package (R-Development-Core-Team, 2009), using the linear effects model library and the maximum likelihood estimation algorithm (Pinheiro et al., 2008).

3. Results

There were no significant group differences in age, gender, body-mass index, or current smoking status, but controls showed a significantly higher number of years of education than patients (14.7 ± 2.3 vs. 12.6 ± 2.1 ; $p = 0.002$) (Table 1). Patients had significantly lower FA values ($p = 0.02$) and significantly reduced PDI ($p = 0.0002$) for the corpus callosum (Fig. 1). The volume of HWM was log-transformed to achieve normality, and showed no significant group difference ($p = 0.75$) (Fig. 1). Regionally, significantly reduced FA values were observed for the genu, and reduced PDI values were observed for all three compartments of the corpus callosum (Table 2). There were no significant differences in the axial or radial diffusivity (Table 2).

Testing of the age-and-diagnosis model (eq. 3) explained about 30% of the variance in FA values and revealed the age-by-diagnosis interaction to be the only significant predictor (Table 3). Patients showed twice the aging-related decline in FA compared with controls ($\beta = -1.2 \pm 0.3 \cdot 10^{-3}$ vs. $-0.5 \pm 0.3 \cdot 10^{-3}$ FA/year for patients and controls, respectively) (Fig. 2). Age-by-diagnosis interactions were significant for genu ($p = 0.03$) and body ($p = 0.01$), and trending toward significance for splenium ($p = 0.07$) (Table 3).

Testing of the HWM and permeability-diffusivity model (eq. 4) showed that HWM and PDI independently predicted variability in FA values (Table 3). Post hoc analyses showed that the aging-related trends for HWM volumes were equally significant for both groups (Fig. 2).

The age-related trends for PDI of the corpus callosum were only significant for patients (Fig. 2). Overall, the HWM and permeability-diffusivity model (eq. 4) explained a significantly larger proportion of variance in FA values than the age and diagnosis model (eq. 3) (Table 3).

Testing of the combined model (eq. 5) demonstrated that after accounting for HWM and PDI, the contributions from diagnosis and age were no longer significant (Table 4). The HWM volume contributed to average FA values equally in both groups (no significant HWM by diagnosis interaction), while PDI was specifically associated with schizophrenia ($\beta_{\text{PDI} \times \text{Dx}} = 1.5 \pm 0.6$; $p = 0.02$). Fig. 3 shows that the PDI by diagnosis interaction reflected a contribution from PDI to FA in patients.

We observed no significant differences between smokers and non-smokers in FA, HWM, or PDI imaging measurements in either group (all $p > 0.3$). There were no significant differences in imaging measurements for 23 medicated vs. 7 unmedicated patients (all $p > 0.3$). In patients on antipsychotic medications, correlations between chlorpromazine-equivalent dose and FA, HWM, or PDI imaging measurements were not significant (all $p > 0.6$).

4. Discussion

We performed a multi-modal assessment of white matter integrity to gain a better understanding of the biological processes that contribute to the reduced FA values in schizophrenia patients (Mori et al., 2007; Friedman et al., 2008; Kochunov et al., 2012b). DTI-FA has become a primary clinical measure of white matter, and has been used in many clinical research projects despite an inadequate understanding of its underlying biology. We demonstrated that HWM volume and PDI combined to explain a significantly higher proportion of FA variance than diagnosis and age. Further, the variance in FA due to age, diagnosis, and diagnosis-by-age interaction was fully accounted for by the HWM volume and a PDI-by-diagnosis interaction. Moreover, the accelerated decline in FA observed in schizophrenia patients was explained by decline in PDI. Overall, we observed that the rise in HWM volume contributed to lower FA values equally in patients and controls. The group differences in HWM volume did not explain the reduced FA or its accelerated decline in patients. Conversely, PDI was strongly associated with FA in patients where it explained nearly half (46%) of the FA variance. This suggests that PDI may be incorporating a more malleable component of the white matter integrity that makes it more sensitive to schizophrenia-related deficits (Kochunov et al., 2013a).

FA deficits in schizophrenia are reported in the untreated, first episode, and chronic patients (Szeszko et al., 2005; Friedman et al., 2008; Perez-Iglesias et al., 2013; Peters et al., 2013), and deficits in cerebral white matter FA values are among the most replicated neuroimaging findings in schizophrenia (Alba-Ferrara and de Erausquin, 2013; White et al., 2013). Furthermore, aging-related decline in FA values and other cerebral integrity measurements may be accelerated in schizophrenia, as reported by studies with sample sizes sufficiently large enough to detect age-by-diagnosis interactions (Mori et al., 2007; Nenadic et al., 2011; Schneiderman et al., 2011; Kochunov et al., 2013b; Koutsouleris et al., 2013; Wright et al.,

2014). Importantly, the impact of accelerated aging may not be fully realized because schizophrenia patients have a shorter (by 20 years) average lifespan, even after accounting for suicide (Tsuang and Woolson, 1978; Brown, 1997; Saha et al., 2007; Kirkpatrick et al., 2008). Yet the physiological cause of FA abnormalities in schizophrenia is still unknown. We hypothesized that the age-related increase in HWM lesions could partially explain the reduced FA values in schizophrenia patients because of increased cardiovascular risks and possible neuroinflammation associated with this disorder (Tsuang and Woolson, 1978; Brown, 1997; Hennekens et al., 2005; Saha et al., 2007; Kirkpatrick et al., 2008; Ito and Barnes, 2009; Jeste et al., 2011). HWM volume is a highly sensitive marker of reduced cerebrovascular health (Kochunov et al., 2009a; Kochunov et al., 2010; Kochunov et al., 2011c; Kochunov et al., 2012a; Wardlaw et al., 2013), and schizophrenia is associated with an elevated incidence of hypertension, diabetes mellitus, hypercholesterolaemia, and smoking. These factors can raise the risk of small cerebral vessel disease in patients leading to elevated HWM volume (Wardlaw et al., 2013). In this context, the finding of no group difference in HWM volume may in part be due to our recruitment strategy, which specifically excluded subjects with diabetes, hypertension, and other neurological and major medical conditions. In addition, patients and controls were approximately matched on body-mass index and smoking status. In normal aging, an increase in HWM volume parallels a decline in FA values because both measurements index white matter integrity (Raz et al., 1998; Gunning-Dixon and Raz, 2000, 2003; Bastos Leite et al., 2004; Kochunov et al., 2007; Kochunov et al., 2009b; Kochunov et al., 2009c). Moreover, the age-related rise in HWM volume shares common genetic variance with reduced FA (Kochunov et al., 2012a). Our findings replicated the expected negative relationship between FA and HWM volume. This trend was the same in both groups, however, and it did not account for patient-control differences in FA, thereby suggesting other causes need to be sought.

In contrast, PDI robustly accounted for both the diagnosis and accelerated aging trends in FA in patients. One may think that this is not surprising since the FA and PDI were derived from related imaging techniques. However, the two datasets were collected using different diffusion sequences. FA used a single b-value DTI sequence and the PDI data were derived from a q-space sequence that used 15 b-values. We observed only a marginal correlation between PDI and FA in normal controls. Instead, the high correlation between PDI and FA in schizophrenia patients (Fig. 3) may provide new insight to the FA deficit, especially considering that PDI accounted for about half of the FA variance in patients. Moreover, the PDI-by-diagnosis interaction fully accounted for the accelerated decline in FA values with age in schizophrenia, and direct regression of PDI from both groups led to equality of aging trends in the residual FA values between the groups.

That said, the limitation of this investigation is that the mechanisms by which PDI values differ by group are still unknown, and necessitate further investigations. Our main finding, that accelerated aging decline in FA values in patients is being explained by aging-related PDI decline, is challenging to interpret because the biophysical causes of deviations from the pattern of Gaussian diffusion in the biological tissue are poorly understood. Our results indicate that the patient-control differences in the behavior of the unrestricted and restricted water pools explain the patient-control aging differences in the FA values, but offer no biophysical mechanism to explain this phenomenon. One possible explanation is based on

the work by Sukstanskii and colleagues (Sukstanskii et al., 2004) and others (Grinberg et al., 2011) on the impact of cellular membrane permeability on diffusion-signal behavior. Cellular membranes are actively permeable via ionic and water pumps. Higher active permeability increases the proportion of water across channel pores, which should increase water diffusivity in the restricted compartment (D_r) and thus result in higher PDI.

The altered cellular permeability may also be likely to be present in the cerebral gray matter of schizophrenia patients. An advantage of the permeability-diffusivity model is that it can be applied to gray matter. In an ad-hoc analysis, we explored the patient-control differences in PDI-aging trends by fitting the permeability-diffusivity model to data collected from the cingulate gray matter overlying the corpus callosum (Fig. 2S, see supplement). We observed that gray matter PDI was significantly lower ($p=10^{-4}$) and showed a significant negative correlation with age in patients ($r=-0.37; p=0.04$), but not in controls ($r=-0.21; p=0.20$) (Fig. 2S, see supplement). Gray matter PDI measurements were unrelated to the HWM volume burden in either group ($p>0.3$), suggesting that the finding of a PDI correlation with FA in patients may reflect the sensitivity of both indices to a malleable component of schizophrenia instead of being due to a direct biophysical linkage. Schizophrenia is associated with structural abnormalities in ion channel proteins and reduced densities of trans-membrane ion channels (Freedman et al., 2000; Meyer et al., 2001; Huffaker et al., 2009; Blasius et al., 2011; Smolin et al., 2011; Smoller et al., 2013). FA measurements in white matter and PDI measurements in both white and gray matter are perhaps both sensitive to these abnormalities. While we are unable to fully explain the biophysical phenomenon of this empirical observation, we hope that further development of this model will lead to a better understanding of the causes of cerebral integrity deficits in schizophrenia. Our findings should encourage the exploration of more advanced diffusion imaging techniques, including recently proposed methods for direct measurements of cellular permeability and inter-compartmental exchange rates (Nilsson et al., 2013).

Overall, we observed that the commonly reported accelerated aging decline in FA values in schizophrenia can be explained by reduced PDI. We also observed that HWM volume contributed to reduced FA values equally in both groups. The patient-control difference in PDI has captured most of the diagnosis-related variance in the FA values, suggesting that PDI deficits are sensitive to schizophrenia white matter pathophysiology. Our understanding of the essential role of the white matter in the pathophysiology of schizophrenia is rapidly evolving, supported by imaging techniques including DTI, but also new techniques that probe the underlying pathology (Cronenwett and Csernansky, 2013; Du et al., 2013). Results from this comprehensive white matter imaging experiment suggest that PDI should be considered as another important white matter integrity measure to complement the FA white matter measures in aiding our effort to understand the fiber connectivity dysfunction in schizophrenia. Finally, antipsychotic medications and the high rate of smoking in schizophrenia patients may confound our observations. We observed no significant association between smoking or medication levels and the three neuroimaging measurements (all $p>0.7$). The analyses of aging trends performed in this study were limited by the cross-sectional nature of the data. Additional research will be needed to understand the biological underpinnings of the findings reported here.

The design of this study does not allow for determination on how the results may be related to the etiology of schizophrenia. Furthermore, our findings are empirical and should stimulate additional methodological development of the permeability-diffusivity model. For instance, the permeability-diffusivity model cannot fully explain the positive correlation between FA and PDI in patients. Further development of the permeability-diffusivity model may include terms that account for the exchange between two compartments and terms to account for diffusion anisotropy. At present, the permeability-diffusivity model also does not account for crossing fibers, and it remains to be determined how crossing fibers may influence this model. Therefore, using the corpus callosum overcame this limitation, since the corpus callosum has a simple architecture with no crossing fibers (Aboitiz et al., 1992). These developments will undoubtedly require the collection of more imaging data and therefore longer imaging times. Fortunately, the new multiplex DTI sequences, including those distributed by the Human Connectome Project (Feinberg et al., 2010; Moeller et al., 2010), can accelerate collection of imaging data by two- to eight-fold, making these developments practical (<20 min).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Underpinnings of accelerated aging in white matter in schizophrenia were evaluated
- Rise in FLAIR lesions and reduction in axonal permeability were considered predictors
- FLAIR lesion predicted white matter aging equally in patients and controls
- Accelerated aging in schizophrenia was explained by changes in axonal permeability
- Aging decline in activity of ion-channels is suspected in schizophrenia patients

Fig. 1.

Patient-control differences on primary imaging measures. The whole-brain fractional anisotropy (FA) value was calculated by averaging across the entire tract-based spatial statistics (TBSS) white matter skeleton and presented for comparison only. Group-wise significance was calculated using a two-tailed *t*-test.

Fig. 2.

Age-related trends for the corpus callosum fractional anisotropy (FA) values (top left), whole brain hyperintense white matter (HWM) volume (top right) and permeability-diffusivity index (PDI) (bottom). FA showed a significant negative correlation with age in both groups in the corpus callosum(CC) (patients: $r = -0.48$, $p = 0.01$; controls: $r = -0.37$; $p = 0.01$), but the downward slope was significantly steeper for the patients ($\beta = -1.2 \pm 0.3 \cdot 10^{-3}$ vs. $-0.5 \pm 0.3 \cdot 10^{-3}$ FA/year, for patients and controls respectively). The logarithm of HWM volume showed a significant age-related rise in both groups (patients: $r = 0.39$; $p = 0.04$ vs. controls: $r = 0.37$; $p = 0.02$). PDI showed a significant negative correlation in patients ($r = -0.38$; $p = 0.04$) but not in controls ($r = -0.26$; $p = 0.11$).

Fig. 3.

Plots of fractional anisotropy (FA) versus permeability-diffusivity index (PDI) for corpus callosum (CC) for patients and controls. FA was highly correlated with PDI in patients, but not controls (patients: $r=0.68$, $p=0.0001$; controls: $r=0.22$, $p=0.17$).

Table 1

Participants' demographic and clinical information.

	Sex (F:M)	Age, range (years)	Age of onset (years)	Duration of illness (years)	CPZ equivalent	BMI	Current smokers	Years of education completed
Patients	(9:21)	40.1±12.1, 20–59	18.2±7.4	19.3±13.4	781.3±666.5	28.8±5.0	45%	14.7±2.3
Controls	(17:23)	41.9±13.1, 20–62	N/A	N/A	N/A	27.4±5.6	33%	12.6±2.1
Group difference, <i>p</i> -value	0.50	0.60	N/A	N/A	N/A	0.25	0.23	0.002

All values are provided as average ± standard deviation; average antipsychotic medication dose in chlorpromazine (CPZ) equivalence (mg) for 23 medicated patients. BMI: body-mass index. Group-wise significance was calculated using a two-tailed *t*-test or χ^2 test.

Table 2

Schizophrenia patient (SZ) – normal control (NC) differences on the fractional anisotropy (FA), permeability-diffusivity index (PDI) and axial (D_{axial}) and radial (D_{radial}) diffusivity measurements for three sub-regions of corpus callosum.

	Genu			Body			Splenium		
	FA	D_{axial}	D_{radial}	PDI	FA	D_{axial}	D_{radial}	PDI	PDI
SZ	.71±.05	1.37±0.09	5.1±0.6	4.2±0.11	.63±.06	1.42±0.08	5.0±0.5	3.2±.7	4.9±0.7
NC	.73±.03	1.41±0.08	4.9±.4	5.2±.08	.66±.04	1.45±0.08	4.9±.4	3.7±.6-1 0	4.8±.5
<i>P</i> -value	0.03	0.10	0.40	0.0003	0.07	0.07	0.35	0.0021	0.12

All values are provided as average ± standard deviation. Group-wise significance was calculated using a two-tailed *t*-test. See Fig. 1 for results for the whole corpus callosum. The axial (D_{axial}) and radial (D_{radial}) diffusivity are provided in mm^2/s units and their values are scaled by 1000. PDI values are scaled by 100.

Table 3

Results (beta value $\pm$ standard deviation) of the regression modeling of contributing factors to fractional anisotropy (FA) in corpus callosum (CC) and its subdivisions, using age and diagnosis (equation 3) and hyperintensive white matter (HWM) volume + permeability-diffusivity index (PDI) (equation 4) models.

Models		CC	CC genu	CC body	CC splenium
Age + Diagnosis Model (eq 1)	$\beta_{Age} \pm SD$ (<i>p</i> -value)	-4.7 $\pm$ 3.5 (0.17)	-7.9 $\pm$ 3.9 (0.04)	-2.2 $\pm$ 5.5 (0.71)	-4.4 $\pm$ 3.5 (0.22)
	$\beta_{Dx} \pm SD$ (<i>p</i> -value)	-.02 $\pm$.02 (0.31)	-.002 $\pm$.02 (0.5)	.004 $\pm$.05 (0.16)	-.012 $\pm$.021 (0.58)
	$\beta_{Age \times Dx} \pm SD$ (<i>p</i> -value)	-11.3 $\pm$ 5.0 (0.02)	-13.2 $\pm$ 6.0 (0.03)	-19.6 $\pm$ 8.0 (0.01)	-1.1 $\pm$ 0.5 (0.07)
	<i>F</i> (3,68) value (<i>p</i> -value)	9.7 (1.9$\cdot$10⁻⁵)	14.2 (2.7$\cdot$10⁻⁷)	6.9 (0.0003)	7.8 (0.0001)
	$\beta_{HWM} \pm SD$ (<i>p</i> -value)	-0.013 $\pm$ 0.003 (0.0007)	-0.014 $\pm$ 0.004 (0.001)	-.008 $\pm$.006 (0.18)	-0.009 $\pm$ 0.004 (0.005)
HWM + PDI Model (eq 2)	$\beta_{PDI} \pm SD$ (<i>p</i> -value)	2.00 $\pm$.48 (1.3$\cdot$10⁻⁵)	1.62 $\pm$.34 (1.410$\cdot$10⁻⁵)	1.9 $\pm$.51 (2.310$\cdot$10⁻⁵)	1.1 $\pm$.3 (.0003)>
	<i>F</i> (2,69) value (<i>p</i> -value)	17.5 (7.2$\cdot$10⁻⁷)	20.5 (1.0$\cdot$10⁻⁸)	12.7 (2.0$\cdot$10⁻⁵)	13.5 (1.1$\cdot$10⁻⁵)
	Comparison of variance explained by two models (eq 3 vs. eq 4)	7.6$\cdot$10⁻⁵	0.002	0.003	0.001

The significance of the difference in the explanatory power between the two models was explored using analysis of variance (ANOVA) test. The *p*-values of each term or test are in parentheses. Significant associations (*p*<0.05) are in bold font.

Table 4

Results for the full regression model (equation 5) that modeled variability in fractional anisotropy (FA) values of the corpus callosum (CC) and its three subdivisions using diagnosis, age (age and age $\times$ diagnosis), hyperintensive white matter volume (HWM) (HWM and HWM $\times$ diagnosis), and permeability diffusivity index (PDI) (PDI and PDI $\times$ diagnosis).

	Full model	CC	CC genu	CC body	CC splenium
Diagnosis effects	$\beta_{Dx} \pm SD$ (<i>p</i> -value)	-0.05 $\pm$ 0.06 (0.31)	-0.06 $\pm$ 0.05 (0.26)	-0.04 $\pm$ 0.08 (0.26)	-0.06 $\pm$ 0.07 (0.26)
Age effects	$\beta_{Age} \pm SD$ (<i>p</i> -value)	-1.7 $\pm$ 3.6 (0.62)	4.3 $\pm$ 4.6 (0.32)	1.3 $\pm$ 5.6 (0.84)	1.2 $\pm$ 5.7 (0.89)
	$\beta_{Age \times Dx} \pm SD$ (<i>p</i> -value)	-6.9 $\pm$ 5.5 (0.28)	-8.1 $\pm$ 7.4 (0.24)	-1.2 $\pm$ 8.4 (0.94)	-1.3 $\pm$ 0.9 (0.12)
HWM effects	$\beta_{HWM} \pm SD$ (<i>p</i> -value)	-0.9 $\pm$ 4.1 (0.03)	-1.4 $\pm$ 0.5 (0.009)	-0.7 $\pm$ 0.7 (0.15)	-0.6 $\pm$ 0.7 (0.33)
	$\beta_{HWM \times Dx} \pm SD$ (<i>p</i> -value)	2.6 $\pm$ 6.9 (0.91)	2.6 $\pm$ 6.9 (0.92)	0.7 $\pm$ 1.9 (0.91)	0.9 $\pm$ 1.1 (0.58)
PDI effects	$\beta_{PDI} \pm SD$ (<i>p</i> -value)	0.34 $\pm$ 0.64 (0.60)	0.56 $\pm$ 0.55 (0.71)	0.63 $\pm$ 0.75 (0.42)	0.45 $\pm$ 0.73 (0.54)
	$\beta_{PDI \times Dx} \pm SD$ (<i>p</i> -value)	1.5 $\pm$ 0.6 (0.02)	1.5 $\pm$ 0.7 (0.04)	2.2 $\pm$ 0.9 (0.04)	2.3 $\pm$ 1.0 (0.03)
	$F(7,64)$ value (<i>p</i> -value)	7.5 (5.410⁻⁷)	10.5 (1.010⁻⁸)	5.2 (8.010⁻⁵)	5.2 (2.710⁻⁵)

The *p*-values are in parentheses. Significant associations (*p*<0.05) are in bold font. Note that diagnosis and age effects were no longer significant after HWM and PDI effects were taken into account.