Psychiatry Research: Neuroimaging ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

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

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ARTICLE INFO

Article history:
Received 3 January 2014
Received in revised form
18 April 2014
Accepted 8 May 2014

Keywords:
Permeability
Diffusivity
Advanced DTI
Hyperintensive white matter lesions

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 mater. 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.

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, 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., 2013).

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 (Swayze 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

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http://dx.doi.org/10.1016/j.pscychresns.2014.05.004
0925-4927/

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 neuroinflamation (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; Maclullich 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', 2010', 2011c', 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 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, 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', 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., 2013). 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., 2013).

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 s/slice) time to collect (Kochunov et al., 2013). 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 $\pm$ 12.9 years) healthy controls and 30 schizophrenia patients (21 males, age=40.1 $\pm$ 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., 2013). 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 $\times$ 1.7 $\times$ 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/mm^2) and five b=0 images. These parameters were calculated using an optimization technique

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 $\pm$ 12.1, 20–59	18.2 $\pm$ 7.4	19.3 $\pm$ 13.4	781.3 $\pm$ 666.5	28.8 $\pm$ 5.0	45%	14.7 $\pm$ 2.3
Controls	(17:23)	41.9 $\pm$ 13.1, 20–62	N/A	N/A	N/A	27.4 $\pm$ 5.6	33%	12.6 $\pm$ 2.1
Group difference, *p*-value	0.50	0.60	N/A	N/A	N/A	0.25	0.23	0.002

All values are provided as average $\pm$ 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.

Please cite this article as: Kochunov, P., et al., Multimodal white matter imaging to investigate reduced fractional anisotropy and its age-related decline in schizophrenia. Psychiatry Research: Neuroimaging (2014), http://dx.doi.org/10.1016/j.pscychresns.2014.05.004