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Accelerated white matter aging in schizophrenia: role of white matter blood perfusion

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ABSTRACT

Elevated rate of age-related decline in white matter integrity, indexed by fractional anisotropy (FA) from diffusion tensor imaging, was reported in patients with schizophrenia. Its etiology is unknown. We hypothesized that a decline of blood perfusion to the white matter may underlie the accelerated age-related reduction in FA in schizophrenia. Resting white matter perfusion and FA were collected using pseudo-continuous arterial spin labeling and high-angular-resolution diffusion tensor imaging, respectively, in 50 schizophrenia patients and 70 controls (age = 18–63 years). Main outcome measures were the diagnosis-by-age interaction on whole-brain white matter perfusion, and FA. Significant age-related decline in brain white matter perfusion and FA were present in both groups. Age-by-diagnosis interaction was significant for FA ($p < 0.001$) but not white matter perfusion. Age-by-diagnosis interaction for FA values remained significant even after accounting for age-related decline in perfusion. Therefore, we replicated the finding of an increased rate of age-related white matter FA decline in schizophrenia and observed a significant age-related decline in white matter blood perfusion, although the latter did not contribute to the accelerated age-related decline in FA. The results suggest that factors other than reduced perfusion account for the accelerated age-related decline in white matter integrity in schizophrenia.

1. Introduction

An increased rate of age-related decline in white matter (WM) integrity has been demonstrated in schizophrenia patients in several (Friedman et al., 2008; Kochunov et al., 2012b; Mori et al., 2007), but not all studies (Chiapponi et al., 2013). The accelerated rate of WM change coincides with schizophrenia patients' increased rates in somatic diseases such as cardiovascular illnesses, hypertension, and diabetes (Hennekens et al., 2005), all which are known to increase in occurrence with normal aging. Schizophrenia patients also have an increased mortality rate and shorter (by as much as 20 years) average life span, even after accounting for suicide (Brown, 1997; Kirkpatrick et al., 2008; Saha et al., 2007; Tsuang and Woolson, 1978). The finding of accelerated decline in WM integrity was one of the first pieces of evidence of the abnormally higher rate of the aging process in the brain structure of schizophrenia patients. Its biological basis is obscure.

Declining cerebrovascular health is a risk factor for WM integrity during normal aging (He et al., 2005; Kennedy and Raz, 2009; Kochunov et al., 2011; Maclullich et al., 2009; Nitkunan et al., 2008) and schizophrenia is associated with an increased rate of cardiovascular illnesses (Hennekens et al., 2005). Cerebral WM is perfused via long penetrating arterioles that originate at the surface of the brain (Brown and Thore, 2011). This renders WM more vulnerable than gray matter (GM) for small vessel disorders (Kochunov et al., 2011, 2012a; Wardlaw et al., 2013). Associative WM tracts, which show the highest rate of accelerated aging in schizophrenia (Kochunov et al., 2012b), are especially susceptible to declining vascular health because of their location in the watershed areas (Minkner et al., 2005). In addition, oligodendrocytes of the associative frontal WM are among the most metabolically active neural cells, which contribute to the high vulnerability to hypoperfusion in these WM areas (Bartzokis et al., 2004). Therefore, an increased rate of age-related decline in WM perfusion, if found in schizophrenia, may impact oligodendrocytes and WM integrity,

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and provide an explanation to the accelerated decline of the WM integrity in schizophrenia patients.

Perfusion refers to microcirculation of blood to supply tissues with nutrients and remove metabolic waste, and when measured during resting state, is thought to be coupled with basal glucose usage and metabolism (Biagi et al., 2007). Previous findings of cerebral blood flow (CBF) in schizophrenia concentrated on the reports of cortical differences between patients and controls and the relationship between CBF and symptom severity (Andreasen et al., 1996; Pinkham et al., 2011; Scheef et al., 2010; Vita et al., 1995). We hypothesized that reduced CBF will detrimentally impact WM more than GM, because of less compensatory blood supply. The reduced WM CBF may contribute to the reduced WM integrity, as assessed with diffusion tensor imaging (DTI), in participants with schizophrenia, and drive its accelerated decline with age. Therefore, we tested if WM perfusion contributes to the accelerated age-related decline of WM integrity observed in schizophrenia.

Previously, we compared cerebral WM fractional anisotropy (FA) aging trends in schizophrenia and normal control cohorts, and found that the age-related decline in the whole-brain FA values was approximately twice as fast in patients compared with controls (Kochunov et al., 2012b). The present study pursued 2 aims to follow-up this finding. The primary aim was to test if accelerated age-related decline in WM integrity in participants with schizophrenia, compared with controls, is associated with an increased rate of age-related decline in WM blood perfusion. The secondary aim was to re-examine and replicate the finding of accelerated aging of the cerebral WM in schizophrenia in an independent cohort using a more modern DTI sequence.

2. Methods

2.1. Participants

Fifty (age = 36.9 ± 13.4 years) individuals with schizophrenia and 70 (age = 38.9 ± 13.7 years) healthy controls participated in the study. All participants gave written informed consent approved by the University of Maryland Internal Review Board. All participants were evaluated using the Structured Clinical Interview for the DSM-IV. Patients were individuals with an Axis I diagnosis of schizophrenia or schizoaffective disorder, recruited through the Maryland Psychiatric Research and neighboring mental health clinics. Controls were participants without Axis I psychiatric diagnosis. Controls were recruited through media advertisements. Additional clinical and epidemiologic information is provided in Table 1. Individuals who participated in the previous study of DTI and accelerated aging (Kochunov et al., 2012b) were excluded. The exclusion criteria included hypertension, hyperlipidemia, type 2 diabetes, heart disorders, and major neurologic events, such as stroke or transient ischemic attack. Illicit substance and alcohol abuse and dependence were exclusion criteria. Except for 7 medication-free participants, schizophrenia patients were on antipsychotic medications: 10 were on first-generation antipsychotics and the rest were on either second-generation or combined first- and second-generation antipsychotics.

2.2. Diffusion tensor imaging (DTI)

All imaging was performed at the University of Maryland Center for Brain Imaging Research using a Siemens 3T TRIO MRI (Erlangen, Germany) system equipped with a 32-channel phase array head coil. The high-angular resolution diffusion imaging (HARDI) DTI 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: echo time/repetition time (TE/TR) = 87/8000 ms, field of view = 200 mm, axial slice orientation with 50 slices, and no gaps, 5 b = 0 images and 64 isotropically distributed diffusion weighted directions with b = 700 s/mm^2. These parameters maximized the contrast to noise ratio for FA measurements (Kochunov et al., 2012b). A tract-based spatial statistics method, distributed as a part of FMRIB Software Library (FSL) package, was used for tract-based analysis of diffusion anisotropy (Smith et al., 2006). First, FA images were created by fitting the diffusion tensor to the motion and eddy current diffusion data. Root mean square difference (RMSDIFF) (Smith et al., 2004) was used to estimate the root mean square movement distance between diffusion sensitized and b = 0 images. All data passed quality assurance (QA) control of <3 mm accumulated motion during the scan. There were no differences in the average motion per TR between patients and controls (0.42 ± 0.21 vs. 0.43 ± 0.20, respectively). In the next step, all FA images were globally spatially normalized to the Johns Hopkins University (JHU) atlas that is distributed with the FSL package, version 5.0.1 (Wakana et al., 2004) and then nonlinearly aligned to a group-wise, minimal-deformation target (MDT) brain as detailed elsewhere (Jahanshad et al., 2013). The global spatial normalization was performed using a method distributed with the FSL package (FLIRT) (Smith et al., 2006) with 12 degrees of freedom. This step was performed to reduce the global intersubject variability in brain volumes before nonlinear alignment. The group's MDT brain was identified by warping all individual brain images in the group to each other (Kochunov et al., 2001). The MDT was selected as the image that minimizes the amount of the required deformation from other images in the group. Next, individual FA images were averaged to produce a group-average anisotropy image. This image was used to create a group-wise skeleton of WM tracts. The skeletonization procedure was a morphologic operation, which extracts the medial axis of an object. This procedure was used to encode the medial trajectory of the WM fiber-tracts with 1 voxel thin sheaths. Finally, FA images were thresholded at the level of FA = 0.20 to eliminate non-WM voxels and FA values were projected onto the group-wise skeleton of WM structures. This step accounts for residual misalignment among individual WM tracts. FA values were assigned to each point along a skeleton using the peak value found within a designated range perpendicular to the skeleton. The FA values vary rapidly perpendicular to the tract direction, but vary slowly along the tract direction. By assigning the peak value to the skeleton, this procedure effectively maps the center of the individual WM tracts onto the skeleton. This processing was performed under 2 constraints. First, a distance map was used to establish search borders for individual tracts.

Table 1
Demographic and clinical characteristics

	Sex (female:male)	Age (y)	Age of onset (y)	Duration (y)	BMI	Current smokers
Patients	19/31	36.9 ± 13.4	19.1 ± 8.1	19.1 ± 12.9	30.0 ± 6.2	34%
Controls	29/41	38.9 ± 13.7	N/A	N/A	29.9 ± 5.3	23%
Group difference (*p*-value)	0.55	0.45			0.42	0.18

Key: BMI, body mass index.