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More highly myelinated white matter tracts are associated with faster processing speed in healthy adults

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ABSTRACT

The objective of this study was to investigate whether the estimated myelin content of white matter tracts is predictive of cognitive processing speed and whether such associations are modulated by age. Associations between estimated myelin content and processing speed were assessed in 570 community-living individuals (277 middle-age, 293 older-age). Myelin content was estimated *in-vivo* using the mean T1w/T2w magnetic resonance ratio, in six white matter tracts (anterior corona radiata, superior corona radiata, pontine crossing tract, anterior limb of the internal capsule, genu of the corpus callosum, and splenium of the corpus callosum). Processing speed was estimated by extracting a principal component from 5 separate tests of processing speed. It was found that estimated myelin content of the bilateral anterior limb of the internal capsule and left splenium of the corpus callosum were significant predictors of processing speed, even after controlling for socio-demographic, health and genetic variables and correcting for multiple comparisons. One SD higher in the estimated myelin content of the anterior limb of the internal capsule was associated with 2.53% faster processing speed and within the left splenium of the corpus callosum with 2.20% faster processing speed. In addition, significant differences in estimated myelin content between middle-age and older participants were found in all six white matter tracts. The present results indicate that myelin content, estimated *in vivo* using a neuroimaging approach in healthy older adults, is sufficiently precise to predict variability in processing speed in behavioural measures.

1. Introduction

The highly-myelinated nature of the human brain and the vulnerability of myelin to degeneration, may contribute to our species' susceptibility to age-related neurocognitive disorders. The cognitive domain most associated with myelin is processing speed (PS) (Lu et al., 2011, 2013) – a sensitive indicator of overall cognitive decline (Finkel et al., 2007; Cherbuin et al., 2010). It has been demonstrated that PS is the basic cognitive mechanism that mediates age-related decline in memory (Bunce and Macready, 2005; Lee et al., 2012). PS can be conceptualised as the rate at which cognitive operations are executed, such as planning and initiation of intended motion and is often tested in conjunction with psychomotor speed, which accounts for the speed of the motion itself (Cepeda et al., 2013). Recent longitudinal studies have demonstrated an inverse U-shaped lifespan trajectory of myelin content with a peak at around 30–40 years (Bartzokis et al., 2012). A similar trajectory has been observed in cognitive PS scores across the lifespan (Cerella and Hale, 1994; Bartzokis et al., 2010). Further, a decline in PS is the primary cognitive deficit underlying the rapid cognitive decline seen in demyelinating diseases such multiple sclerosis (Demaree et al., 1999). In addition, myelin loss and PS decline have also been shown to share multiple risk-factors including *APO*E4* genotype (Bartzokis et al., 2007), and lifestyle factors (Anstey et al., 2009; Ramagopalan et al., 2010).

A few studies have made important contributions in this area by using indirect imaging measures such as transverse relaxation rate or diffusion measures such as fractional anisotropy. Such studies on healthy older populations have found that the integrity of white matter regions, especially in frontal areas, are correlated with PS, and that these regions show modest mediation effects on age-related PS decline (Lu et al., 2011, 2013; Salami et al., 2012). These studies have used a maximum of two PS tests and as such are potentially confounded by unwanted variance relating to other cognitive domains (Salthouse et al., 1996). Other

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research using more robust measures of PS have shown more global effects by demonstrating that general factor of white matter fractional anisotropy is able to predict PS in healthy older adults (Penke et al., 2010; Kerchner et al., 2012). However, the measures of white matter integrity used by these studies are unspecific as they index the movement of water molecules which are affected, apart from myelin, by neuronal and glial density and size (Winston, 2012), as well as pathological states such as amyloid beta deposition (Racine et al., 2014).

In addition, few such studies have accounted for hemispheric asymmetries in myelin content of white matter tracts in healthy adults (Toga and Thompson, 2003; Takao et al., 2011). These asymmetries have been shown to be associated with specialisations in language, memory and motor functions, and as such may indeed be implicated in PS (de Schotten et al., 2011; Ocklenburg et al., 2016). For instance, the corpus callosum is the primary tract that facilitates information transfer between hemispheres and asymmetrical myelin content may differentially disrupt speed and efficiency of communication between and within networks. In particular, tracts within the left hemisphere have been repeatedly shown to be more susceptible to age- and pathology-related neurodegeneration (Thompson et al., 2007; Minkova et al., 2017). Accounting for such asymmetries in myelin content will assist in clarifying how tracts within each hemisphere differentially contribute to age-related changes in PS.

Few studies have directly examined the relationship between myelin content and PS in non-clinical populations, and we are not aware of any study using a measure specifically developed for this purpose. This is likely due to the difficulty in measuring myelin levels *in vivo*. Histological myelin measurement is the gold standard, but it can only be performed post-mortem and is therefore not suitable to investigate this question in humans.

Recently, a new measure, the ratio between an individual's structural T1-weighted (T1-w) and T2-weighted (T2-w) image (T1w/T2w), has been proposed as a practical and sensitive measure for *in vivo* myelin content estimation (Glasser and Van Essen, 2011; Ganzetti et al., 2014). Multiple studies have demonstrated that T1w/T2w cortical intensity maps parallel myeloarchitectural maps based on histological samples (Glasser and Van Essen, 2011; Ganzetti et al., 2014, 2015; Glasser et al., 2014; Nieuwenhuys and Broere, 2017). Recently, an immunocytochemistry study of post-mortem brains showed that T1w/T2w values correlate with myelin levels (Nakamura et al., 2017). The T1w/T2w ratio has also been used to estimate *in vivo* myelin degeneration in patients with schizophrenia (Ganzetti et al., 2015; Iwatani et al., 2015), multiple sclerosis (Beer et al., 2016), and bipolar disorder (Ishida et al., 2017). Further, the method has been used to demonstrate that higher estimated myelin within the cerebral cortex is associated with reduced intra-subject variability on speeded tasks (Grydeland et al., 2013).

Although we are not aware of any research investigating the association between sub-cortical myelin content (MYE) as estimated by T1w/T2w, and cognitive performance, we predicted based on the available literature that lower MYE within white matter tracts would be associated with lower PS in cognitively healthy individuals. Moreover, since age-related decrease in brain myelin has been clearly demonstrated (Bartzokis, 2004), we predicted that older individuals would present with lower MYE levels than younger individuals and that this difference would be associated with a slower PS. Thus, the aim of this study was to investigate whether MYE of major white matter tracts was predictive of PS in a large sample of cognitively healthy middle-age and older adults.

2. Materials and method

2.1. Participants

Participants were selected from the MRI sub-study within the PATH Through Life Project (PATH) which has been described in detail elsewhere (Anstey et al., 2012). Briefly, PATH is an ongoing population-based longitudinal study that aims to track the course of cognitive ability, mental health disorders, substance use and dementia across the lifespan. Participants are randomly selected from the electoral roll of the Australian Capital Territory and surrounding regions. Data collection started in 1999 and participants are reassessed every four years.

The PATH study consists of three cohorts: 20–24 years (young adult), 40–44 years (middle-age), and 60–64 (older-age) years at baseline. The focus of this study is on the middle-age (MA) and older-age (OA) cohorts at the third assessment, due to the availability of higher quality T1-w and T2-w MRI scans for both the MA and OA participants at this time-point. Of the 2530 MA and 2550 OA participants recruited into the study, 304 MA and 303 OA participants had complete imaging data at the third assessment. However, an inhouse quality control script and visual inspection revealed an additional 14 scans that were excluded due to poor quality. From this sample, a further 23 participants were excluded due to: epilepsy ($n = 2$), having a history of stroke ($n = 14$), Parkinson's disease ($n = 3$), dementia ($n = 2$) and cognitive impairment ($n = 2$) as defined by a Mini-Mental Status Exam score of less than 25. The final sample available for analysis included 570 participants (277 MA and 293 OA). The selected sample did not differ significantly from the overall MA and OA PATH cohort on sex and education; however, it was significantly younger ($t = 1.967$, $p = .049$).

2.2. Socio-demographic, health and genetic measures

Years of education, alcohol consumption, smoking, physical activity were assessed using self-report. Alcohol consumption was assessed as the number of standard alcoholic drinks consumed per week (Alcohol Use Disorders Identification Test; Babor et al., 2001). Physical activity was assessed as the number of hours per week of mild, moderate and vigorous exercise. To provide an intensity-sensitive continuous score of physical exercise, the three levels of activity were combined using a weighted procedure such that hours of mild physical activity were multiplied by 1, hours of moderate physical activity by 2 and hours of vigorous physical activity by 3 (Lamont et al., 2014). Depressive symptomology was assessed using the Goldberg Depression Score (Goldberg et al., 1988). Seated systolic and diastolic blood pressures (BP) were averaged over two measurements after a 5-min rest and participants were classified as hypertensive if they were on medical therapy for hypertension or if they had an average systolic BP $\geq$ 140 mm Hg or diastolic BP $\geq$ 90 mm Hg. Genomic DNA was extracted using cheek swabs and was used to identify the presence of *APO*E4* genotype (Christensen et al., 2008).

2.3. Measures of cognitive PS

PS was assessed using five different tasks. The Symbol Digit Modalities Test (SDMT; Strauss et al., 2006), was scored as the number of correct matches identified according to the stimulus symbol digit code, within a 90-s period. Simple (SRT) and choice reaction time (CRT) were assessed by giving participants a small box to hold with both hands, with left and right buttons at the top to be depressed by the index fingers. The front of the box had three lights: a red stimulus light under each of the left and right buttons, and a green get-ready light in the middle. For SRT task, participants placed their right hand, on the right button and were asked to press it as quick as possible when they saw the red stimulus light up. For the CRT task, participants were asked to place their right finger on the right button and their left finger on the left button and to press the corresponding button when the left or right red light lit up. There were 4 blocks of 20 trials measuring SRT, followed by two blocks of 20 trials measuring CRT. The mean reaction time was the average across all trials. Trail Making Task Part A (TMT-A; Reitan, 1958) was scored as the amount of time taken to complete the task and the Purdue Pegboard task using both hands (PP; Tiffin and Asher, 1948) was scored as the number of pairs of pins placed into the pegboard device within 30-s.