Brain and Cognition 81 (2013) 131–138

Contents lists available at SciVerse ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Myelin breakdown mediates age-related slowing in cognitive processing speed in healthy elderly men ☆

Po H. Lu [a,*], Grace J. Lee [a], Todd A. Tishler [b], Michael Meghpara [a], Paul M. Thompson [a,c], George Bartzokis [b,c]

[a] Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, United States
[b] Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, United States
[c] Laboratory of Neuroimaging, Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, United States

ARTICLE INFO

Article history:
Accepted 24 September 2012
Available online 27 November 2012

Keywords:
Healthy aging
Cognition
Cognitive processing speed
Myelin
White matter
Magnetic resonance imaging

ABSTRACT

Background: To assess the hypothesis that in a sample of very healthy elderly men selected to minimize risk for Alzheimer's disease (AD) and cerebrovascular disease, myelin breakdown in late-myelinating regions mediates age-related slowing in cognitive processing speed (CPS).

Materials and methods: The prefrontal lobe white matter and the genu of the corpus callosum myelinate later in brain development (late-myelinating white matter; LMWM) and are more vulnerable to breakdown due to the effects of normal aging. An *in vivo* MRI biomarker of myelin integrity (transverse relaxation rates; R_2) of LMWM was obtained for 38 very healthy elderly adult men (mean age = 66.3 years; SD = 6.0; range = 55–76). To evaluate regional specificity, we also assessed a contrasting early-myelinating region (splenium of the corpus callosum; SWM), which primarily contains axons involved in visual processing. CPS was assessed using the Trail Making Test.

Results: LMWM R_2 and CPS measures were significantly correlated ($r = .515$, $p = .0009$), but no significant association between R_2 and CPS was detected in the splenium ($p = .409$). LMWM R_2, but not SWM R_2, was a significant mediator of the relationship between age and CPS ($p = .037$).

Conclusions: In this very healthy elderly sample, age-related slowing in CPS is mediated by myelin breakdown in highly vulnerable late-myelinating regions but not in the splenium.

1. Introduction

Cognitive processing speed (CPS), broadly defined as the speed at which your brain processes information, is one of the measures of mental efficiency or how fast one can execute the mental operations needed to complete cognitive tasks (Salthouse, 2000). Salthouse and others have argued that the age-related slowing in CPS underlies age-associated decrements in other higher-order cognitive functions including memory and executive functioning (Hedden, Lautenschlager, & Park, 2005; Levitt, Fugelsang, & Crossley, 2006; Rabbitt et al., 2007; Salthouse, 1996, 2005; Salthouse & Coon, 1993; Salthouse & Ferrer-Caja, 2003). Age-related changes in CPS have been well-documented in the neuropsychological literature. Cross-sectional (Gottsdanker, 1982; Salthouse, 2000, 2009; Tombaugh, 2004; Wilkinson & Allison, 1989) and longitudinal (Schaie, 2005) studies show that across the lifespan, performance on CPS tasks has a quadratic, inverted-U trajectory, reaching maximum efficiency around the mid-30s then declining thereafter. The biological substrates underlying CPS remain incompletely understood but recent studies have implicated white matter (WM), and more specifically myelin, as the biological basis for this basic cognitive phenomenon (Bartzokis, Lu, et al., 2007; Bucur et al., 2008; Charlton et al., 2006; Deary et al., 2006; Kennedy & Raz, 2009; Lu et al., 2011; Madden et al., 2009; Marner, Nyengaard, Tang, & Pakkenberg, 2003; O'Sullivan et al., 2001; Tuch et al., 2005; Turken et al., 2008; Vernooij et al., 2009).

Axon myelination results in saltatory conduction of action potentials (APs) that increases signal transmission speed by more than 100-fold (Waxman, 1977). Myelination also markedly decreases the refractory time (time needed for repolarization before a new AP can be supported by the axon) by as much as 34-fold (Felts, Baker, & Smith, 1997; Sinha, Karimi-Abdolrezaee, Velumian, & Fehlings, 2006). Thus, intact myelin enhances the integration of information across spatially distributed neural networks supporting cognitive and motor functions (Bartzokis et al., 2001; Fuster, 1999; Lutz, Koeneke, Wustenberg, & Jancke, 2005; Mesulam, 2000; Srinivasan, 1999). The protracted myelination process of the human brain, with myelin content and integrity peaking in the mid-30s followed by breakdown and loss with advancing

☆ This data was presented in part at the 13th annual meeting of the International Conference for Alzheimer's Disease, Paris, France, 2011.

* Corresponding author. Address: Mary S. Easton Center for Alzheimer's Disease Research, 10911 Weyburn Avenue, Suite 200, Los Angeles, CA 90095-7226, United States. Fax: +1 310 794 3148.
E-mail address: plu@mednet.ucla.edu (P.H. Lu).

0278-2626/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bandc.2012.09.006

age, resembles the inverted U pattern that characterizes CPS performance across the lifespan (Bartzokis et al., 2001, 2003; Benes, Turtle, Khan, & Farol, 1994; Ge et al., 2002; Jernigan & Gamst, 2005; Kemper, 1994; Walhovd et al., 2005).

The structural integrity of myelin sheaths can be indirectly measured *in vivo* with magnetic resonance imaging (MRI) by estimating the transverse relaxation rates (R_2, derived from the reciprocal of transverse relaxation time or T_2). Intuitively, relaxometry indices such as R_2 measure how rapidly the MRI signal dissipates, and this rate is markedly sensitive to small changes in the proportion of tissue water (Oldendorf & Oldendorf, 1988). Myelination reduces white matter water content (Ferrie et al., 1999; Paus et al., 2001) and thereby increases R_2; conversely, myelin breakdown increases tissue water and decreases R_2 (Fazekas, Schmidt, & Scheltens, 1998; Takao et al., 1999). Studies using ultrastructural electron microscope reveal that age-related myelin breakdown results in microvacuolations consisting of splits in the myelin sheath layers (Kemper, 1994; Nielsen & Peters, 2000; Peters & Sethares, 2002), which creates microscopic fluid-filled spaces that increase tissue water and thus decrease R_2 (Bartzokis et al., 2004; Peters et al., 1996). Herein, R_2 measures will be referred to as myelin "integrity" and "breakdown."

We specifically chose to analyze the frontal lobe white matter (FWM) and genu of the corpus callosum (GWM), which is comprised of intrahemispheric fibers connecting prefrontal association cortices (Lamantia & Rakic, 1990), because these regions myelinate later in brain development and are maximally affected by the aging process. Age-related myelin breakdown is most pronounced in more vulnerable later-myelinating regions such as FWM and GWM because they contain higher proportions of smaller thinly-myelinated axons (Bartzokis et al., 2004; Marner et al., 2003; Salat et al., 2005) and the myelin sheaths have fewer myelin lamellae (Chia, Thompson, & Moscarello, 1983). Fiber-tracking analysis of DTI data has also shown that the most prominent age-related deterioration of the white matter is observed in association fibers (Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2008) that connect the regions last to complete myelination in the course of development (Flechsig, 1901). The CPS task (Trail Making Test, Reitan & Wolfson, 1985) used in this study was chosen because it assesses a broad range of cognitive, perceptual, and motor processes and are thus more sensitive to the integrity of late-myelinating fiber systems (Turken et al., 2008). In support of our hypothesis, Eckert (2011) recently highlighted the importance of frontal cortex (a late-myelinating region) as a neurobiological predictor of processing speed. In contrast, the splenium of the corpus callosum (SWM) was analyzed as a comparison region because it contains primarily large sensory (visual) axons that tend to be fully and heavily myelinated in childhood (Lamantia & Rakic, 1990; Pandya & Seltzer, 1986; Yakovlev & Lecours, 1967) and are more resistant to the age-related degradation in integrity; therefore, it would not be expected to correlate as well with CPS.

We previously demonstrated that in 152 healthy elderly adults, myelin breakdown was significantly associated with CPS performance in late-myelinating regions but not in the splenium (Lu et al., 2011). However, significant correlations do not infer a causal relationship; therefore, the purpose of the current study was to test the hypothesis that myelin breakdown (as assessed by R_2) mediates the association between age and CPS, thus establishing a potential causal association between myelin and CPS. Specifically, we performed a series of regression and multiple regression analyses, following the general outline for mediation analysis first introduced by Baron and Kenny (1986). Contemporary experts in mediation analysis recommend performing statistical tests to directly test the multiplicative paths (Lockwood & Mackinnon, 1997; MacKinnon & Fairchild, 2009; Preacher & Hayes, 2004) then apply bootstrap resampling to estimate the standard errors of these multiplicative paths. We expected the mediation relationship to be regionally specific, namely that CPS would be mediated by myelin breakdown in LMWM regions but not in the comparison early-myelinating association area of SWM. Our prior work and existing literature have shown that men and women have different rates of age-related decline in both white matter integrity and CPS (Bartzokis, Tishler, et al., 2007; Szeszko et al., 2003); therefore, we examined a male sample in order to reduce heterogeneity due to gender differences in myelination trajectories (Benes et al., 1994) as well as key variables of interest such as cognitive performance (Bornstein, 1985; Jimenez, Mancini-Marie, & Mendrek, 2009; Longenecker, Dickinson, Weinberger, & Elvevag, 2010).

2. Materials and methods

2.1. Subjects

Normal adult male volunteers were between the ages of 55–76. They were recruited from the community and hospital staff for a study of healthy aging. All subjects received written and oral information about the study and signed written informed consents approved by the local institutional review board prior to study participation. Subjects were excluded if they had a history of neurological disorder, psychiatric illness (including drug or alcohol abuse), or head injury resulting in loss of consciousness for more than 10 min. Additional exclusion criteria aimed at reducing risk of underlying AD pathology included family history of AD or other neurodegenerative disorders and failed glucose tolerance test. The subjects were physically very healthy and were excluded if they were obese (defined as body mass index [BMI] of >30 kg/m^2), or if they had a history of diabetes, hypertension, or cardiovascular disease. The participants were independently functioning and had no complaints or evidence of neurocognitive impairment or gross neurological abnormalities on clinical interview and brief neurological examination (GB). Analyses were based on a total of 38 men with mean age of 66.3 (SD = 6.0) and a mean education level of 16.6 years (SD = 2.3); their racial composition was comprised of four Asian (11%), four African–American (11%), and 30 Caucasian (78%) subjects. All participants denied any problems with memory and scored 27 and above (mean = 28.3, SD = 0.99) on the Mini-Mental State Examination (MMSE; (Folstein, Folstein, & McHugh, 1975)).

2.2. Cognitive processing speed (CPS)

Trail Making Test – Parts A and B (Reitan & Wolfson, 1985). Part A of the Trail Making Test (Trails A) assesses speed of visual scanning, information processing, and graphomotor tracking. Subjects are required to rapidly connect 25 consecutively numbered circles. Part B (Trails B) involves the sequencing of numbers and letters of the alphabet in an alternating manner, which requires additional executive functioning processes including set-shifting and cognitive flexibility (Lezak, Howieson, & Loring, 2004). However, prior studies have shown that it is difficult to disentangle the executive component from the speed factor that underlies both conditions, and that both measures primarily reflect cognitive processing speed (Bartzokis et al., 2011; Salthouse, 2011a). Therefore, a composite CPS score was computed by standardizing the scores (time to complete each task) from Trails A and Trails B (both log transformed due to positive skew then multiplied by −1 so that higher *z*-score indicates faster performance), using the means and standard deviations from the present healthy adult sample, then averaging the *z*-scores.