

## Lifespan trajectory of myelin integrity and maximum motor speed

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### Abstract

**Objective:** Myelination of the human brain results in roughly quadratic trajectories of myelin content and integrity, reaching a maximum in mid-life and then declining in older age. This trajectory is most evident in vulnerable later myelinating association regions such as frontal lobes and may be the biological substrate for similar trajectories of cognitive processing speed. Speed of movement, such as maximal finger tapping speed (FTS), requires high-frequency action potential (AP) bursts and is associated with myelin integrity. We tested the hypothesis that the age-related trajectory of FTS is related to brain myelin integrity.

**Methods:** A sensitive in vivo MRI biomarker of myelin integrity (calculated transverse relaxation rates ( $R_2$ )) of frontal lobe white matter (FLwm) was measured in a sample of very healthy males ( $N=72$ ) between 23 and 80 years of age. To assess specificity,  $R_2$  of a contrasting early-myelinating region (splenium of the corpus callosum) was also measured.

**Results:** FLwm  $R_2$  and FTS measures were significantly correlated ( $r=.45$ ,  $p<.0001$ ) with no association noted in the early-myelinating region (splenium). Both FLwm  $R_2$  and FTS had significantly quadratic lifespan trajectories that were virtually indistinguishable and both reached a peak at 39 years of age and declined with an accelerating trajectory thereafter.

**Conclusions:** The results suggest that in this very healthy male sample, maximum motor speed requiring high-frequency AP burst may depend on brain myelin integrity. To the extent that the FLwm changes assessed by  $R_2$  contribute to an age-related reduction in AP burst frequency, it is possible that other brain functions dependent on AP bursts may also be affected. Non-invasive measures of myelin integrity together with testing of basic measures of processing speed may aid in developing and targeting anti-aging treatments to mitigate age-related functional declines. © 2008 Elsevier Inc. All rights reserved.

**Keywords:** Age; Processing speed; Motor; White matter; Oligodendrocyte; Breakdown; Cognition; Dementia; Risk; Neurodegeneration; Alzheimer; Onset; Frontal lobe; Treatment; Prevention

### 1. Introduction

The protracted myelination of the human brain results in roughly quadratic (inverted U) trajectories of myelin content

and integrity reaching a maximum in mid-life and then declining in older age (Bartzokis et al., 2001, 2003; Benes et al., 1994; Ge et al., 2002; Jernigan and Gamst, 2005; Kemper, 1994; Walhovd et al., 2005). Axon myelination results in saltatory conduction of action potentials (AP) that increases (>10-fold) signal transmission speed (Waxman, 1977) and makes it possible to integrate information across the spatially distributed neural networks that support cognitive and motor functions (Bartzokis et al., 2001; Fuster, 1999; Lutz

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et al., 2005; Mesulam, 2000; Srinivasan, 1999). 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 et al., 1997; Sinha et al., 2006). Thus myelin and maintenance of its integrity allows axons to support high-frequency bursts of signals and is necessary for a variety of normal brain processes ranging from high motor speeds, to cortical oscillations and long-term potentiation (LTP) of synaptic transmission (Axmacher et al., 2006; Bartzokis, 2004a; Buzsaki and Draguhn, 2004; Canolty et al., 2006; Kreiman et al., 2006).

Salthouse and others (Hedden et al., 2005; Salthouse, 2000; Schaie et al., 2004) have argued that the age-related decline in cognitive processing speed resources underlies age-related declines in most cognitive functions including memory encoding which depends on high-frequency bursts (up to 200 Hz) to produce LTP of synaptic transmission [(Buhl and Buzsaki, 2005; Yun et al., 2002); for review see (Axmacher et al., 2006)]. In fact, cognitive, sensory, and motor measures of processing speed are all highly related to brain aging and show quadratic-like trajectories over the lifespan, reaching peaks in adulthood (Era, 1988; Hedden and Gabrieli, 2004; Hoyer et al., 2004; Salthouse, 2000; Schaie et al., 2004). The underlying biological substrate of this relationship is not well understood (Hedden and Gabrieli, 2004; Schaie et al., 2004). Peters and others have argued that brain aging may be primarily related to the process of myelin breakdown (Bartzokis et al., 2004, 2006; Braak and Braak, 1996; Marner et al., 2003; Peters et al., 1996, 2001; Peters and Sethares, 2004, 2004; Sloane et al., 2003). To test the hypothesis that processing speed measures are related to myelin integrity (Bartzokis, 2004a, b) we examined one of the simplest and best understood tests of CNS processing speed: maximal finger tapping speed (FTS).

Like many cognitive tasks the FTS task involves a distributed neural network and high-frequency bursts of APs (Lutz et al., 2005). Single cell recordings in monkey brain have demonstrated that firing rates of motor neurons positively correlate with increasing velocity, force, and acceleration necessary to produce faster finger movements (Ashe and Georgopoulos, 1994; Humphrey, 1972) as well as other fast movements such as visual saccades where similar relationships of movement speed and AP frequency (upwards of 300 Hz) are observed (Berthoz et al., 1986; Krauzlis, 2003; Missal et al., 2002). The tight coupling of FTS with AP firing frequency makes the tapping task dependent on intact myelin to reduce axonal refractory time in order for high AP frequencies to be supported by the neural networks (Felts et al., 1997; Sinha et al., 2006). Thus both its distributed nature and dependence on high neuronal firing rates make FTS dependent on the developmental process of myelination (Garvey et al., 2003; Yeudall et al., 1987) and the maintenance of myelin integrity with aging (Bartzokis, 2004a; Bartzokis et al., 2006).

The structural integrity of myelin sheaths can be indirectly measured in vivo with magnetic resonance imaging (MRI)

using transverse relaxation rates ( $R_2$ ), relaxometry measures that are markedly sensitive to small changes in the proportion of tissue water (Oldendorf and Oldendorf, 1988).  $R_2$  is related to the transverse relaxation time ( $T_2$ ) through the simple formula  $R_2 = 1/T_2 \times 1000$ . Myelination decreases water content (increasing  $R_2$ ) while myelin breakdown and loss increases water content (decreasing  $R_2$ ).  $R_2$  measures have been used to assess myelin integrity in development/myelination phase (birth to mid-life) when  $R_2$  increases (Bartzokis et al., 2003; Miot-Noirault et al., 1997) as well as in aging and a variety of myelin-damaging conditions when  $R_2$  decreases (Bartzokis et al., 2003; House et al., 2006; Neema et al., 2007; Takao et al., 1999; Vermathen et al., 2007). Severity of myelin damage and associated  $R_2$  changes are on a continuum that ranges from focal lesions (Neema et al., 2007; Takao et al., 1999; Vermathen et al., 2007) visible to the unaided eye (referred to as T2 “hyperintensities” on radiology reports) to diffuse changes that occur in “normal appearing white matter” detectable only with *quantitative*  $R_2$  measures (Bartzokis et al., 2003; House et al., 2006; Neema et al., 2007; Vermathen et al., 2007). In disease processes such as multiple sclerosis or phenolketonuria myelin destruction is *qualitatively* observable on MRI images but more subtle changes are also detectable quantitatively in “normal appearing white matter” (Neema et al., 2007; Vermathen et al., 2007). Similarly, age-related  $R_2$  changes in normal appearing white matter have been quantitatively demonstrated in healthy aging as well as more pronounced changes associated with genes that increase risk of developing Alzheimer’s disease (AD), pre-AD conditions such as mild cognitive impairment, and AD itself (Bartzokis et al., 2003, 2007; House et al., 2006).

Ultrastructural electron microscopy studies demonstrate that age-related myelin breakdown results in microvacuolations consisting of splits of myelin sheath layers that create microscopic fluid-filled spaces that increase MRI “visible” water and thus decrease  $R_2$  (Bartzokis et al., 2004; Peters et al., 1996). These microvacuolations are ultrastructurally very similar to reversible myelinopathies produced by certain toxins (Jackson et al., 1994; Peters et al., 1996; Peyster et al., 1995; Weiss et al., 1994). Animal studies have confirmed that this type of myelin breakdown can be detected with MRI in circumscribed susceptible white matter regions and that the histopathologic changes produced by toxins as well as the recovery process can be thus tracked by MRI with the unaided eye [(Jackson et al., 1994; Peyster et al., 1995; Qiao et al., 2000; Weiss et al., 1994); reviewed in (Cohen et al., 2000)]. Although  $R_2$  has not been directly correlated with myelin breakdown due to normal aging (as opposed to the reversible toxin-induced myelin breakdown described above), in humans and primates healthy aging is not associated with neuronal loss [(Gomez-Isla et al., 1997); reviewed in (Peters, 2002; Peters et al., 1998)] while the process of age-related myelin breakdown and loss has been thoroughly demonstrated (Kemper, 1994; Marner et al., 2003; Peters et al., 1996, 2001; Peters and Sethares, 2003, 2004; Sloane et al., 2003; Tang et al., 1997). Herein the terms myelin

“integrity” and “breakdown” will be used to refer to  $R_2$  measures (Bartzokis et al., 2006).

Age-related myelin breakdown is a generalized process (Bartzokis et al., 2004; Marner et al., 2003; Peters et al., 1996, 2001; Peters and Sethares, 2003, 2004; Sloane et al., 2003) that is most pronounced in more vulnerable later myelinating regions such as frontal lobe white matter (FLwm) that contain higher proportions of smaller thinly myelinated axons (Bartzokis, 2004a; Grieve et al., 2007; Marner et al., 2003; Salat et al., 2005; Sullivan et al., 2008). It is technically difficult to directly assess myelin breakdown of the *specific* myelin segment(s) limiting the maximal frequency of APs a circuit can support. We therefore chose FLwm to serve as an *in vivo* biomarker for myelin integrity because its vulnerability makes this region a good surrogate for damage prone regions of the FTS circuitry (Jancke et al., 1998; Lutz et al., 2005). The choice was based on the fact that both post mortem as well as our prior imaging data show FLwm is maximally sensitive to differences in myelin integrity due to aging (Bartzokis et al., 2004; Kemper, 1994; Marner et al., 2003) and that highly reliable and reproducible  $R_2$  measures can be obtained from this region (Bartzokis et al., 2003).

We tested the hypothesis that the lifelong quadratic trajectory of myelination and subsequent myelin breakdown is associated with FTS performance across the lifespan. We focused on men because men show consistently higher FTS performance, and we hypothesized that the *highest* possible tapping speed that requires the highest action potential frequencies would be most sensitive to differences in myelin integrity (Homann et al., 2003; Kauranen and Vanharanta, 1996; Reed et al., 2004).

## 2. Methods

### 2.1. Subjects

Healthy adult male volunteers that participated in the study were recruited from the community and hospital staff. Potential 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. The subjects were physically very healthy and were excluded if they were obese (defined as body mass index of (BMI)  $>30 \text{ kg/m}^2$ ), had a history of diabetes or cardiovascular disease or taking medications for such. Only three of the subjects were taking medication for one of the following chronic medical conditions: hypertension, elevated cholesterol, or asthma. The final sample ( $N=72$ ) ranged in age from 23 to 80 years (mean = 56.1, S.D. = 17.1) and their racial distribution was 51 (71%) Caucasian, 13 (18%) Asian, and 8 (11%) African-American. All subjects were functioning independently and had no evidence of neurocognitive impairment on clinical interview and examination with the study principal investigator (GB). In addition, the 44 out of the 72 subjects who were over 55 years of age were admin-

istered the Mini-Mental State Examination by the PI and their scores all fell in the normal range (between 27 and 30; mean = 28.4, S.D. = 0.9). 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.

### 2.2. Fine motor speed

An electronic version of the Finger Tapping device (Western Psychological Services) was used and performance was assessed on the same day the MRI scan was performed. The task requires the subjects to press a button as fast as they can, using their index finger. Subjects alternate between dominant and nondominant hands, and an electronic counter registers the numbers of taps across 10-s trials. Ten trials were administered for each hand. However, 2 of the subjects received only 5 trials; therefore, the average number of taps across the first 5 trials is the dependent variable of interest.

### 2.3. MRI protocol

All subjects were scanned using the same 1.5 T MR instrument, all scans used the same imaging protocol, and scan timing was irrespective of demographic (e.g., age, education) variables. Details of the protocol have been published previously (Bartzokis et al., 2004) and are only summarized here. Two pilot sequences were obtained to specify the location and spatial orientation of the head and the position of the axial image acquisition grid. The axial image acquisition sequence acquired interleaved contiguous slices using a Carr Purcell Meiboom Gill dual spin-echo sequence TR = 2500, TE = 20, 90, 3 mm slice thickness,  $256 \times 192$  view matrix, and 25 cm field of view.

### 2.4. Image analysis

$T_2$  was calculated for each voxel by an automated algorithm from the two signal intensities (TE = 20 and 90) of the robust dual spin-echo sequence that used  $90^\circ$  refocusing pulses to produce gray-scale encoded  $T_2$  maps of the brain (Bartzokis et al., 1994) which were not normalized. The  $T_2$  measures were extracted using a Macintosh configured image analysis workstation. A single rater, who was blind to clinical information, performed all measurements. The image analysis software permitted the rater to delineate the region-of-interest (ROI) using a mouse.

For both ROIs two contiguous slices were chosen for analysis. For analysis of the FLwm a circular ROI sample of supraorbital white matter was placed manually by the rater in the frontal lobe white matter on the second and third contiguous slices above the last image containing orbitofrontal cortex (Bartzokis et al., 2003). For the early-myelinating regions the lower half of the splenium of the corpus callosum (Swm) was chosen. The second and third lowest slices on which the fibers of the splenium connected in the midline were chosen

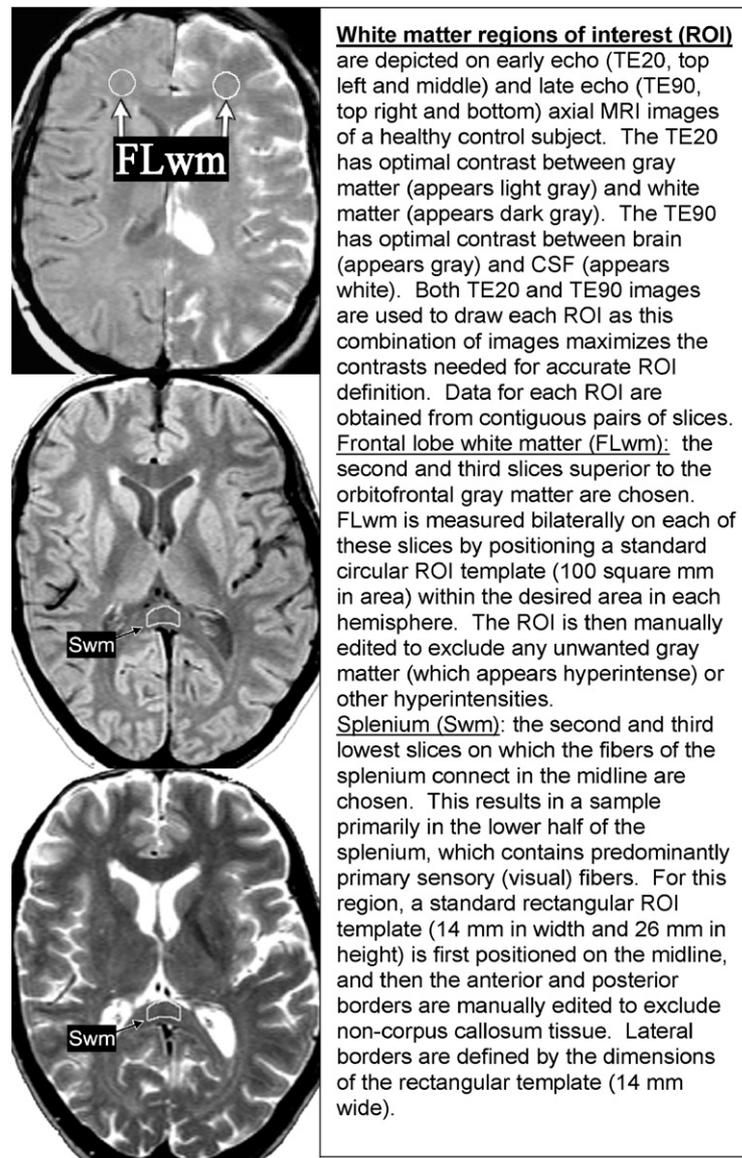


Fig. 1. White matter regions of interest (ROIs).

in order to sample primarily the lower half of the splenium that contains predominantly early-myelinating primary sensory (visual) fibers (Lamantia and Rakic, 1990; Pandya and Seltzer, 1986). For this structure, the rater manually positioned a rectangular ROI template centered along the midline of each region (Fig. 1).

Once the choice of slices and position of the ROI were completed, the rater excluded gray matter regions of the central sulcus,  $T_2$  hyperintensities, or other hyperintense structures such as periventricular halos [for further details please see (Bartzokis et al., 2003; Bartzokis et al., 2004)]. The ROIs thus contained normal appearing white matter free of  $T_2$  hyperintensities. The ROIs were then transferred onto the corresponding  $T_2$  maps. All voxels that had a  $T_2$  value above the right side inflection point of the histogram of the ROI were removed in order to assure that partial volume with CSF structures was eliminated (Bartzokis et al., 1994).

$T_2$  data for each ROI were obtained from contiguous pairs of slices. The relaxation rate ( $R_2$ ) was calculated as the reciprocal of  $T_2 \times 1000$ . The average  $R_2$  of the two slices from both hemispheres were the final measures used in the subsequent analyses. Reliability of the  $R_2$  measures was previously assessed using the intraclass correlation coefficient and was very good (frontal lobe white matter:  $R_{xx} = 0.91$ ,  $F = 21.3$ , d.f. = 1, 12,  $p < .0001$ ; splenium of the corpus callosum white matter:  $R_{xx} = 0.95$ ,  $F = 20.5$ , d.f. = 1, 11,  $p < .00001$ ) (Bartzokis et al., 2003, 2004).

## 2.5. Data/statistical analyses

Our interest was in comparing aging trajectories for tapping and FLwm  $R_2$ . The sample was comprised of 72 healthy males with valid tapping data (one outlier was excluded—his

right finger tapping was 3S.D. above the mean, but left was about .8S.D. above the mean).

The R and L hand tapping averages each had Chronbach's alpha of .96, and correlated with each other  $r = .78$ . To eliminate effects of handedness and hand used, tapping scores were standardized separately for left and right hand. Preliminary analyses using a mixed effects regression model confirmed that handedness did not need to be included in the repeated measures model after this standardization, and indicated that a quadratic model for age was required. Education was unrelated to tapping and was not considered further. The mixed effects regression model for tapping included fixed effects for age and age-squared, with left and right hand performance included separately as repeated measures with an unstructured covariance matrix. The regression model for FLwm  $R_2$  included linear and quadratic fixed effects for age. To make the regressions of tapping and  $R_2$  on age comparable, the  $R_2$  measure was also standardized with mean 0 and S.D. 1.

We attempted to obtain a more precise measure of maximum performance by avoiding spurious influences on performance such as unfamiliarity with the task in initial trials or finger fatigue in later trials. We therefore also analyzed the relationship by taking only the average of the highest two tapping scores (out of 5) from each hand as the *maximum* tapping performance for that hand.

### 3. Results

The estimated regression parameters from the mixed effects regression were used to graph the functions across the age range 23–80 and represent an average of right and

left hand tapping. Significant quadratic relationships with age were observed for FLwm  $R_2$  ( $t = 2.42$ , d.f. = 69,  $p = .018$ ) and for FTS ( $t = 2.46$ , d.f. = 69,  $p = .016$ ). The Swm did not exhibit a significant linear ( $r = -0.14$ , d.f. = 70,  $p = .25$ ) or quadratic ( $t = 0.32$ , d.f. = 69,  $p = .75$ ) association with age. The results are displayed in Fig. 2. The curves for FTS and FLwm  $R_2$  as a function of age are almost overlapping with maximums reached at 38.9 and 38.7 years of age, respectively.

In this sample, the FTS and FLwm  $R_2$  were significantly correlated  $r = 0.43$ , d.f. = 70,  $p = 0.0002$  while the correlation between FTS and splenium of corpus callosum white matter  $R_2$  was non-significant ( $p > .76$ ) (Fig. 3). However, the FTS and FLwm  $R_2$  relationship was no longer statistically significant after adjusting for the quadratic effects of age using partial correlation analysis ( $r = 0.19$ , d.f. = 68,  $p = 0.12$ ). The correlation coefficients for FLwm  $R_2$  and finger tapping was compared with that of Swm  $R_2$  and finger tapping using correlated coefficients and the difference was statistically significant ( $t = 3.02$ ,  $p = .004$ ) (Fig. 3).

Since we hypothesized that *maximum* performance requiring maximum action potential frequency would be most sensitive to the myelin health FLwm  $R_2$  biomarker we performed secondary analyses aimed at assessing this relationship with tapping measures that may more specifically reflect *maximum* possible FTS performance. The FTS and FLwm  $R_2$  analysis was repeated using the FTS score from the highest two tapping scores (out of 5) from each hand. Using these measures the FTS and FLwm  $R_2$  relationships improved. Thus, using the average of the 2 highest tapping scores for right hand, the relationship was  $r = .450$ , d.f. = 70,  $p < .0001$  (controlling for quadratic effects of age:  $r = .260$ , d.f. = 68,  $p = .030$ ). The average of the 2 highest tapping scores for the high-

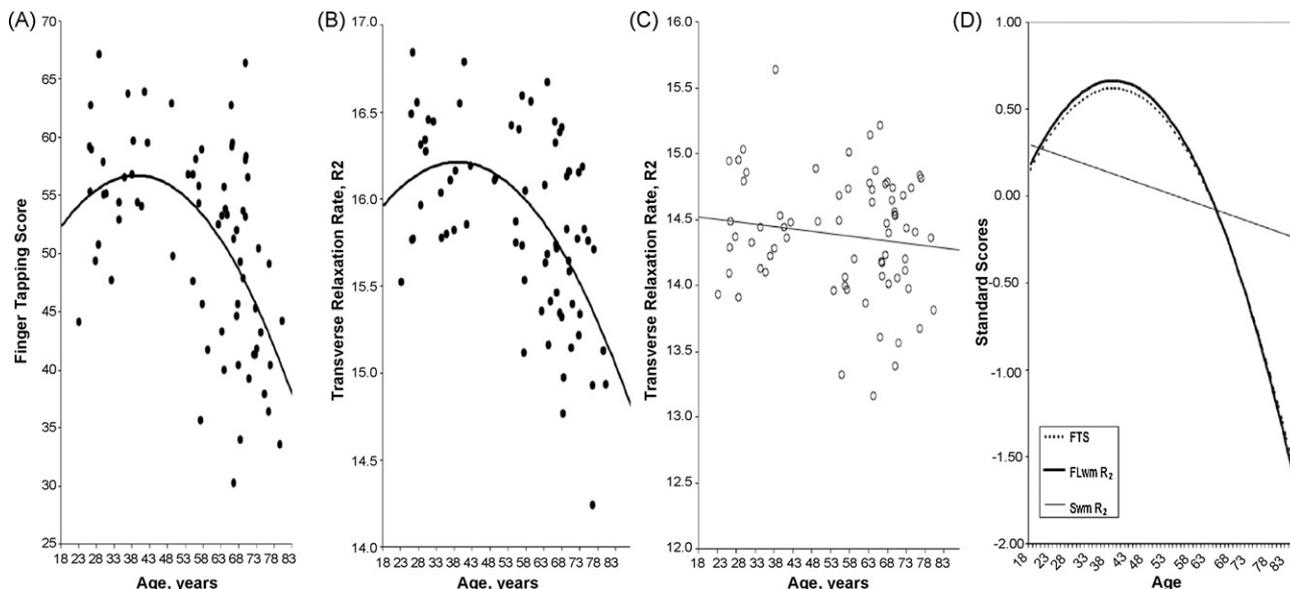


Fig. 2. (A–D) Age trajectories for finger tapping speed (FTS) and white matter transverse relaxation rate ( $R_2$ ) in frontal lobe (FLwm) and Splenium (Swm). Figures depict the relationships of finger tapping speed (FTS) performance (A), transverse relaxation rate in the frontal lobe white matter (FLwm  $R_2$ ) (B), and transverse relaxation rate in splenium of corpus callosum comparison region (Swm  $R_2$ ) (C) with age. (D) Depicts the trajectories of FTS, FLwm  $R_2$  and Swm  $R_2$  across the age range of 23–80 based on mixed effects regression models.

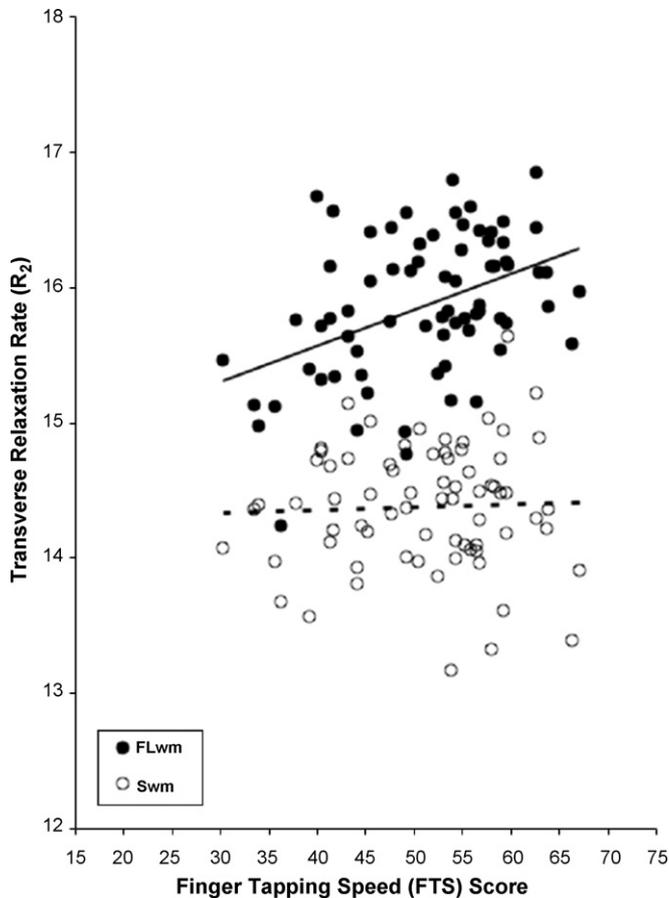


Fig. 3. Correlations between finger tapping speed (FTS) and white matter transverse relaxation rate ( $R_2$ ) in frontal lobe (FLwm) and splenium (Swm) regions.

est performing hand (either right or left) further improved the relationship ( $r = .470$ ,  $d.f. = 70$ ,  $p < .0001$ ; controlling for quadratic effects of age:  $r = .263$ ,  $d.f. = 68$ ,  $p = .028$ ).

Repeating the analyses described above after excluding the three subjects with treatment for chronic medical conditions did not meaningfully alter the results, with all relationships between the average and maximum tapping scores and  $R_2$  remaining similarly robust and statistically significant.

#### 4. Discussion

This is the first study to demonstrate that a functional performance measure (FTS) follows a quadratic lifespan trajectory that is virtually indistinguishable from the trajectory of a sensitive *in vivo* myelin integrity biomarker (Fig. 2) (Bartzokis et al., 2004). Furthermore, the data show a highly significant correlation between the functional (FTS) and biomarker (FLwm  $R_2$ ) measures that is specific to vulnerable late-myelinating FLwm and is not observed in the early-myelinating Swm contrast region (Fig. 3) that contains primarily large and more heavily myelinated axons of the visual system. The relationship between FTS and FLwm  $R_2$

was no longer statistically significant after controlling for the quadratic effects of age. This may be due to several factors including inadequate power and choice of region of interest (FLwm) that was based on its potential as a most sensitive biomarker of overall myelin health and not on its relationship to the motor system. Secondary analyses using a stricter measure of maximal FTS performance (average of two top trials out of five) further improved the relationship between FTS and FLwm  $R_2$ .

These observations are consistent with the hypothesis that in brain, maximum speeds are associated with higher frequency AP bursts (Ashe and Georgopoulos, 1994; Humphrey, 1972) that depend on the low refractory times made possible by myelin [(Felts et al., 1997; Sinha et al., 2006); reviewed in (Nashmi and Fehlings, 2001)], and that maximum performance therefore depends on myelin integrity of the neural networks involved in the task (Bartzokis, 2004a, b). We propose that beginning in middle age the process of age-related myelin breakdown slowly erodes the ability of myelin to support the *very highest* frequency AP bursts. At the time of functional testing, maximum performance speed will be determined by the peak AP frequency that can be supported by the entire network involved in the particular task assessed. The myelin segment(s) whose compromised integrity reduces its ability to support the higher frequencies supported by the other segments of the network will become “rate limiting” and determine the peak achievable AP frequency (Rasminsky and Sears, 1972).

Studies of myelin changes associated with aging are compatible with the hypothesis that myelin breakdown and repair is known to continually occur over the many myelin segments spanning neural networks (Bartzokis et al., 2004, 2006; Palop et al., 2006; Peters et al., 2001; Sloane et al., 2003). In older age, as the process of age-related myelin breakdown overtakes the repair process (Bartzokis et al., 2006; Peters et al., 2001; Sloane et al., 2003), the average performance of the networks will gradually and progressively decline at an accelerating rate (Bartzokis et al., 2003). On functional tests (such as FTS), this generalized age-related decline in myelin integrity should manifest as a similar gradual curvilinear degradation of maximal speed of performance observed in the aging population (Fig. 2). The striking, nearly identical quadratic trajectory across the lifespan for both measures of myelin integrity and fine motor speed further supports the postulation that myelin health is likely the biological process underlying this function. The myelin breakdown process should also reduce all other brain functions where performance speed is dependent on higher AP frequencies in similar quadratic-like trajectories over the lifespan. Indeed, although quadratic lifespan trajectories of neurocognitive measures (including episodic memory) have been repeatedly demonstrated (Hedden et al., 2005; Salthouse, 2000; Schaie et al., 2004), with the exception of myelin content and integrity (see Section 1), quadratic age-related changes in other aspects of brain biology that peak in mid-life have rarely been reported.

When only older age samples are examined a gradual decline would be observed. Such gradual age-related declines in performance are in fact observed in motor as well as sensory and cognitive functions (Era, 1988; Hedden and Gabrieli, 2004; Hoyer et al., 2004; Salthouse, 2000; Schaie et al., 2004), including fine motor speed such as finger tapping (Era, 1988; Fromm-Auch and Yeudall, 1983; Ruff and Parker, 1993; Yeudall et al., 1987). These generalized age-related declines in all these various functional domains support the notion that in brain, performance speed in general may be dependent on frequency of APs; however, the myelin breakdown may also interfere with the “pattern” of action potential activity (Rasminsky and Sears, 1972; Shrager, 1993) and thus also degrade fidelity of information transmission and processing. In this very healthy population alternative explanations are possible but are less likely. Peripheral causes are less likely since in healthy individuals, motor senescence is not related to synaptic delay or reduction in peripheral nerve conduction times (Koles and Rasminsky, 1972; Smith and Rosenheimer, 1984). Other age-related changes at key locations such as the nodes of Ranvier could impact refractory times and contribute to the age-related reduction in brain processing speed and FTS, however, myelin breakdown appears to precede such changes (Hinman et al., 2006).

Several limitations need to be considered before further interpretation of these data. First, the selection of healthy individuals may underestimate age-related decline in  $R_2$  and FTS if such declines are associated with motor and cognitive symptoms, debility, or mortality that caused potential subjects to be excluded (Bartzokis et al., 2004; Era, 1988; House et al., 2006; Ylikoski et al., 1999). Second, in cross-sectional studies, interpretation of age-related differences as “changes” or “cause and effect” must be made with caution (Kraemer et al., 2000; Schaie, 2005), and confirmatory prospective studies are needed (Schaie et al., 2004). Finally, measurement of specific neural networks connecting the different regions involved in specific cognitive tasks may reveal even more robust structure–function correlations (Thompson et al., 2005).

The relationship of these findings to human neuropsychiatric conditions and possible therapeutic interventions is worth considering in light of the findings in this healthy sample. Speed/time-dependent tests of motor, sensory, and cognitive functions are all good markers of brain aging (Era, 1988; Hedden et al., 2005; Hoyer et al., 2004; Salthouse, 2000, 2005; Schaie et al., 2004; Vanneste et al., 2001; Ylikoski et al., 1999) as is myelin breakdown (Bartzokis et al., 2004, 2006; Braak and Braak, 1996; Marner et al., 2003; Peters et al., 1996, 2001; Sloane et al., 2003). Other processes that are dependent on speed of transmission, precise timing, and high-frequency of APs such as high-frequency oscillations between regions [(Gonzalez et al., 2006; Kreiman et al., 2006; Lang and Rosenbluth, 2003); for review see (Buzsaki and Draguhn, 2004)] and LTP of synaptic transmission that underlies memory encoding [(Buhl and Buzsaki, 2005; Yun et al., 2002); for review see (Axmacher et al., 2006)] will also likely

be degraded by age-related myelin breakdown (Bartzokis, 2004b; Bartzokis et al., 2007). Age-related decline in processing speed underlies age-related declines in most cognitive functions (Hedden et al., 2005; Salthouse, 2000; Schaie et al., 2004). The data can thus be interpreted to support the hypothesis that by eroding maximal performance of most neural networks, myelin breakdown may underlie the trajectories of age-related decline of motor as well as cognitive functioning that eventually lead to pervasive motor slowing observed in old age as well as the cognitive declines that define MCI and AD (Bartzokis, 2004b; Bartzokis et al., 2007).

Since in healthy individuals brain myelin breakdown begins to occur in middle age, there is a decades-long period during which therapeutic interventions could alter the course of brain aging and possibly of degenerative brain disorders such as AD whose paramount risk factor is age (Bartzokis et al., 2001, 2004). Non-invasive, serial evaluations of myelin integrity could be used to monitor the effects of new treatments as well as currently available treatments that may impact the process of myelin breakdown as early as mid-life. Such treatments could potentially be useful in slowing brain aging and may have a wide spectrum of efficacy in delaying the emergence of degenerative brain disorders (Bartzokis, 2007; Bartzokis et al., 2006).

### Conflict of interest

The authors have no actual or potential conflicts of interest.

### Disclosure statement

All human 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.

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