Published in final edited form as:
Neurobiol Aging. 2010 September ; 31(9): 1554–1562. doi:10.1016/j.neurobiolaging.2008.08.015.

Lifespan trajectory of myelin integrity and maximum motor speed

George Bartzokis[a,b,c,*], **Po H. Lu**[d], **Kathleen Tingus**[d], **Mario F. Mendez**[c,d], **Aurore Richard**[a], **Douglas G. Peters**[a], **Bolanle Oluwadara**[a], **Katherine A. Barrall**[c], **J. Paul Finn**[e], **Pablo Villablanca**[e], **Paul M. Thompson**[b,d], and **Jim Mintz**[f]

[a]Department of Psychiatry and Biobehavioral Sciences, The David Geffen School of Medicine at UCLA, Los Angeles, CA 90024, United States

[b]Laboratory of Neuroimaging, Department of Neurology, Division of Brain Mapping, The David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, United States

[c]Greater Los Angeles VA Healthcare System, Department of Psychiatry, West Los Angeles, CA 90073, United States

[d]Department of Neurology, The David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, United States

[e]Department of Radiology, The David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, United States

[f]Department of Psychiatry, University of Texas Health Science Center San Antonio, San Antonio, TX 78229, United States

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

*Corresponding author at: 300 UCLA Medical Plaza, Suite 2200, Los Angeles, CA 90095-6968, United States. Tel.: +1 310 206 3207; fax: +1 310 268 3266. *E-mail address:* gbar@ucla.edu (G. Bartzokis).

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.

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.

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 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 vulner-ability 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 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 administered 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 × 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° 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 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 highest 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 curvilin-ear 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).

Acknowledgments

This work was supported in part by NIH grants (MH066029; AG027342; EB008281; P50 AG 16570; U54 RR021813); the RCS Alzheimer's Foundation, Sidell-Kagan Foundation; and the Department of Veterans Affairs.

References

Ashe J, Georgopoulos AP. Movement parameters and neural activity in motor cortex and area 5. Cereb. Cortex 1994;4:590–600. [PubMed: 7703686]

Axmacher N, Mormann F, Fernandez G, Elger CE, Fell J. Memory formation by neuronal synchronization. Brain Res. Brain Res. Rev 2006;52:170–182.

Bartzokis G. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol. Aging 2004a;25:5–18. [PubMed: 14675724]

Bartzokis G. Quadratic trajectories of brain myelin content: unifying construct for neuropsychiatric disorders. Neurobiol. Aging 2004b;25:49–62.

Bartzokis G. Acetylcholinesterase inhibitors may improve myelin integrity. Biol. Psychiatry 2007;62:294–301. [PubMed: 17070782]

Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J. Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. Arch. Gen. Psychiatry 2001;58:461–465. [PubMed: 11343525]

Bartzokis G, Cummings JL, Sultzer D, Henderson VW, Nuechterlein KH, Mintz J. White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study. Arch. Neurol 2003;60:393–398. [PubMed: 12633151]

Bartzokis G, Lu PH, Geschwind D, Tingus K, Huang D, Mendez MF, Edwards N, Mintz J. Apolipoprotein E affects both myelin breakdown and cognition: implications for age-related trajectories of decline into dementia. Biol. Psychiatry 2007;62:1380–1387. [PubMed: 17659264]

Bartzokis G, Lu PH, Geschwind DH, Edwards N, Mintz J, Cummings JL. Apolipoprotein E genotype and age-related myelin breakdown in healthy individuals: implications for cognitive decline and dementia. Arch. Gen. Psychiatry 2006;63:63–72. [PubMed: 16389198]

Bartzokis G, Mintz J, Sultzer D, Marx P, Herzberg JS, Phelan CK, Marder SR. In vivo MR evaluation of age-related increases in brain iron. AJNR Am. J. Neuroradiol 1994;15:1129–1138. [PubMed: 8073983]

Bartzokis G, Sultzer D, Lu PH, Nuechterlein KH, Mintz J, Cummings J. Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical "Disconnection" in aging and Alzheimer's disease. Neurobiol. Aging 2004;25:843–851. [PubMed: 15212838]

Benes FM, Turtle M, Khan Y, Farol P. Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. Arch. Gen. Psychiatry 1994;51:477–484. [PubMed: 8192550]

Berthoz A, Grantyn A, Droulez J. Some collicular efferent neurons code saccadic eye velocity. Neurosci. Lett 1986;72:289–294. [PubMed: 3822232]

Braak E, Braak H. Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. Acta Neuropathol 1996;92:197–201. [PubMed: 8841666]

Buhl DL, Buzsaki G. Developmental emergence of hippocampal fast-field "Ripple" oscillations in the behaving rat pups. Neuroscience 2005;134:1423–1430. [PubMed: 16039793]

Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. Science 2004;304:1926–1929. [PubMed: 15218136]

Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM, Knight RT. High gamma power is phase-locked to theta oscillations in human neocortex. Science 2006;313:1626–1628. [PubMed: 16973878]

Cohen JA, Fisher RS, Brigell MG, Peyster RG, Sze G. The potential for vigabatrin-induced intramyelinic edema in humans. Epilepsia 2000;41:148–157. [PubMed: 10691111]

Era P. Sensory, psychomotor, and motor functions in men of different ages. Scand. J. Soc. Med. Suppl 1988;39:1–77. [PubMed: 3162606]

Felts PA, Baker TA, Smith KJ. Conduction in segmentally demyelinated mammalian central axons. J. Neurosci 1997;17:7267–7277. [PubMed: 9295373]

Fromm-Auch D, Yeudall LT. Normative data for the halstead-reitan neuropsychological tests. J. Clin. Neuropsychol 1983;5:221–238. [PubMed: 6619304]

Fuster JM. Synopsis of function and dysfunction of the frontal lobe. Acta Psychiatry Scand. Suppl 1999;395:51–57.

Garvey MA, Ziemann U, Bartko JJ, Denckla MB, Barker CA, Wassermann EM. Cortical correlates of neuromotor development in healthy children. Clin. Neurophysiol 2003;114:1662–1670. [PubMed: 12948795]

Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, Kolson DL. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. AJNR Am. J. Neuroradiol 2002;23:1327–1333. [PubMed: 12223373]

Gomez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, Parisi JE, Hyman BT. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Ann. Neurol 1997;41:17–24. [PubMed: 9005861]

Gonzalez SL, Grave de Peralta R, Thut G, Millan@@del R, Morier P, Landis T. Very high frequency oscillations (vhfo) as a predictor of movement intentions. Neuroimage 2006;32:170–179. [PubMed: 16631386]

Grieve SM, Williams LM, Paul RH, Clark CR, Gordon E. Cognitive aging, executive function, and fractional anisotropy: a diffusion tensor MR imaging study. AJNR Am. J. Neuroradiol 2007;28:226–235. [PubMed: 17296985]

Hedden T, Gabrieli JD. Insights into the ageing mind: a view from cognitive neuroscience. Nat. Rev. Neurosci 2004;5:87–96. [PubMed: 14735112]

Hedden T, Lautenschlager G, Park DC. Contributions of processing ability and knowledge to verbal memory tasks across the adult life-span. Q. J. Exp. Psychol. A 2005;58:169–190. [PubMed: 15881297]

Hinman JD, Peters A, Cabral H, Rosene DL, Hollander W, Rasband MN, Abraham CR. Age-related molecular reorganization at the node of Ranvier. J. Comp. Neurol 2006;495:351–362. [PubMed: 16485288]

Homann CN, Quehenberger F, Petrovic K, Hartung HP, Ruzicka E, Homann B, Suppan K, Wenzel K, Ivanic G, Ott E. Influence of age, gender, education and dexterity on upper limb motor performance in Parkinsonian patients and healthy controls. J. Neural Transm 2003;110:885–897. [PubMed: 12898344]

House MJ, St Pierre TG, Foster JK, Martins RN, Clarnette R. Quantitative MR imaging R2 relaxometry in elderly participants reporting memory loss. AJNR Am. J. Neuroradiol 2006;27:430–439. [PubMed: 16484425]

Hoyer WJ, Stawski RS, Wasylyshyn C, Verhaeghen P. Adult age and digit symbol substitution performance: a meta-analysis. Psychol. Aging 2004;19:211–214. [PubMed: 15065945]

Humphrey DR. Relating motor cortex spike trains to measures of motor performance. Brain. Res 1972;40:7–18. [PubMed: 4624492]

Jackson GD, Williams SR, Weller RO, van Bruggen N, Preece NE, Williams SC, Butler WH, Duncan JS. Vigabatrin-induced lesions in the rat brain demonstrated by quantitative magnetic resonance imaging. Epilepsy Res 1994;18:57–66. [PubMed: 8088257]

Jancke L, Specht K, Mirzazade S, Loose R, Himmelbach M, Lutz K, Shah NJ. A parametric analysis of the 'rate effect' in the sensorimotor cortex: a functional magnetic resonance imaging analysis in human subjects. Neurosci. Lett 1998;252:37–40. [PubMed: 9756353]

Jernigan TL, Gamst AC. Changes in volume with age-consistency and interpretation of observed effects. Neurobiol. Aging 2005;26:1271–1274. [PubMed: 16006011]

Kauranen K, Vanharanta H. Influences of aging, gender, and handedness on motor performance of upper and lower extremities. Percept. Mot. Skills 1996;82:515–525. [PubMed: 8724924]

Kemper, T. Neuroanatomical and neuropathological changes during aging and dementia. In: Albert, M.; Knoefel, J., editors. Clinical Neurology of Aging. 2nd ed.. Oxford University Press; New York: 1994. p. 3-67.

Koles ZJ, Rasminsky M. A computer simulation of conduction in demyelinated nerve fibres. J. Physiol 1972;227:351–364. [PubMed: 4675037]

Kraemer HC, Yesavage JA, Taylor JL, Kupfer D. How can we learn about developmental processes from cross-sectional studies, or can we? Am. J. Psychiatry 2000;157:163–171. [PubMed: 10671382]

Krauzlis RJ. Neuronal activity in the rostral superior colliculus related to the initiation of pursuit and saccadic eye movements. J. Neurosci 2003;23:4333–4344. [PubMed: 12764122]

Kreiman G, Hung CP, Kraskov A, Quiroga RQ, Poggio T, DiCarlo JJ. Object selectivity of local field potentials and spikes in the macaque inferior temporal cortex. Neuron 2006;49:433–445. [PubMed: 16446146]

Lamantia AS, Rakic P. Cytological and quantitative characteristics of four cerebral commissures in the rhesus monkey. J. Comp. Neurol 1990;291:520–537. [PubMed: 2329189]

Lang EJ, Rosenbluth J. Role of myelination in the development of a uniform olivocerebellar conduction time. J. Neurophysiol 2003;89:2259–2270. [PubMed: 12611949]

Lutz K, Koeneke S, Wustenberg T, Jancke L. Asymmetry of cortical activation during maximum and convenient tapping speed. Neurosci. Lett 2005;373:61–66. [PubMed: 15555778]

Marner L, Nyengaard JR, Tang Y, Pakkenberg B. Marked loss of myelinated nerve fibers in the human brain with age. J. Comp. Neurol 2003;462:144–152. [PubMed: 12794739]

Mesulam M. Brain, mind, and the evolution of connectivity. Brain Cogn 2000;42:4–6. [PubMed: 10739582]

Miot-Noirault E, Barantin L, Akoka S, Le Pape A. T2 relaxation time as a marker of brain myelination: experimental MR study in two neonatal animal models. J. Neurosci. Methods 1997;72:5–14. [PubMed: 9128162]

Missal M, Coimbra A, Lefevre P, Olivier E. A quantitative analysis of the correlations between eye movements and neural activity in the pretectum. Exp. Brain Res 2002;143:373–382. [PubMed: 11889515]

Nashmi R, Fehlings MG. Mechanisms of axonal dysfunction after spinal cord injury: with an emphasis on the role of voltage-gated potassium channels. Brain Res. Brain Res. Rev 2001;38:165–191. [PubMed: 11750932]

Neema M, Stankiewicz J, Arora A, Dandamudi VS, Batt CE, Guss ZD, Al-Sabbagh A, Bakshi R. T1- and T2-based MRI measures of diffuse gray matter and white matter damage in patients with multiple sclerosis. J. Neuroimaging 2007;17(Suppl. 1):16S–21S. [PubMed: 17425729]

Oldendorf, WH.; Oldendorf, W, Jr.. Basics of Magnetic Resonance Imaging. Martinus Nijhof Publishing; Boston, MA: 1988. p. 159

Palop JJ, Chin J, Mucke L. A network dysfunction perspective on neurodegenerative diseases. Nature 2006;443:768–773. [PubMed: 17051202]

Pandya, DN.; Seltzer, B. The topography of commissural fibers. Two hemispheres-one brain: functions of the corpus callosum. Alan R. Liss, Inc; 1986. p. 47-73.

Peters A. Structural changes in the normally aging cerebral cortex of primates. Prog. Brain Res 2002;136:455–465. [PubMed: 12143402]

Peters A, Morrison JH, Rosene DL, Hyman BT. Are neurons lost from the primate cerebral cortex during normal aging? Cereb. Cortex 1998;8:295–300. [PubMed: 9651126]

Peters A, Rosene DL, Moss MB, Kemper TL, Abraham CR, Tigges J, Albert MS. Neurobiological bases of age-related cognitive decline in the rhesus monkey. J. Neuropathol. Exp. Neurol 1996;55:861–874. [PubMed: 8759775]

Peters A, Sethares C. Is there remyelination during aging of the primate central nervous system? J. Comp. Neurol 2003;460:238–254. [PubMed: 12687688]

Peters A, Sethares C. Oligodendrocytes, their progenitors and other neuroglial cells in the aging primate cerebral cortex. Cereb. Cortex 2004;14:995–1007. [PubMed: 15115733]

Peters A, Sethares C, Killiany RJ. Effects of age on the thickness of myelin sheaths in monkey primary visual cortex. J. Comp. Neurol 2001;435:241–248. [PubMed: 11391644]

Peyster RG, Sussman NM, Hershey BL, Heydorn WE, Meyerson LR, Yarrington JT, Gibson JP. Use of ex vivo magnetic resonance imaging to detect onset of vigabatrin-induced intramyelinic edema in canine brain. Epilepsia 1995;36:93–100. [PubMed: 8001516]

Qiao M, Malisza KL, Del Bigio MR, Kozlowski P, Seshia SS, Tuor UI. Effect of long-term vigabatrin administration on the immature rat brain. Epilepsia 2000;41:655–665. [PubMed: 10840396]

Rasminsky M, Sears TA. Internodal conduction in undissected demyelinated nerve fibres. J. Physiol 1972;227:323–350. [PubMed: 4647244]

Reed TE, Vernon PA, Johnson AM. Sex difference in brain nerve conduction velocity in normal humans. Neuropsychologia 2004;42:1709–1714. [PubMed: 15327938]

Ruff RM, Parker SB. Gender-and-age-specific changes in motor speed and eye-hand coordination in adults: normative values for the Finger Tapping and Grooved Pegboard Tests. Percept. Mot. Skills 1993;76:1219–1230. [PubMed: 8337069]

Salat DH, Tuch DS, Greve DN, van der Kouwe AJ, Hevelone ND, Zaleta AK, Rosen BR, Fischl B, Corkin S, Rosas HD, Dale AM. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. Neurobiol. Aging 2005;26:1215–1227. [PubMed: 15917106]

Salthouse TA. Aging and measures of processing speed. Biol. Psychol 2000;54:35–54. [PubMed: 11035219]

Salthouse TA. Relations between cognitive abilities and measures of executive functioning. Neuropsychology 2005;19:532–545. [PubMed: 16060828]

Schaie KW. What can we learn from longitudinal studies of adult development? Res. Hum. Dev 2005;2:133–158. [PubMed: 16467912]

Schaie KW, Willis SL, Caskie G. The seattle longitudinal study: relationship between personality and cognition. Aging Neuropsychol. Cog 2004;11:304–324.

Shrager P. Axonal coding of action potentials in demyelinated nerve fibers. Brain Res 1993;619:278–290. [PubMed: 8397054]

Sinha K, Karimi-Abdolrezaee S, Velumian AA, Fehlings MG. Functional changes in genetically dysmyelinated spinal cord axons of shiverer mice: role of juxtaparanodal kv1 family K^+ channels. J. Neurophysiol 2006;95:1683–1695. [PubMed: 16319208]

Sloane JA, Hinman JD, Lubonia M, Hollander W, Abraham CR. Age-dependent myelin degeneration and proteolysis of oligodendrocyte proteins is associated with the activation of calpain-1 in the rhesus monkey. J. Neurochem 2003;84:157–168. [PubMed: 12485412]

Smith DO, Rosenheimer JL. Factors governing speed of action potential conduction and neuromuscular transmission in aged rats. Exp. Neurol 1984;83:358–366. [PubMed: 6319172]

Srinivasan R. Spatial structure of the human alpha rhythm: global correlation in adults and local correlation in children. Clin. Neurophysiol 1999;1999:1351–1362. [PubMed: 10454270]

Sullivan EV, Rohlfing T, Pfefferbaum A. Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: relations to timed performance. Neurobiol. Aging. 2008 doi:10.1016/j.neurobiolaging.2008.04.007.

Takao M, Koto A, Tanahashi N, Fukuuchi Y, Takagi M, Morinaga S. Pathologic findings of silent hyperintense white matter lesions on MRI. J. Neuro. Sci 1999;167:127–131.

Tang Y, Nyengaard JR, Pakkenberg B, Gundersen HJ. Age-induced white matter changes in the human brain: a stereological investigation. Neurobiol. Aging 1997;18:609–615. [PubMed: 9461058]

Thompson PM, Sowell ER, Gogtay N, Giedd JN, Vidal CN, Hayashi KM, Leow A, Nicolson R, Rapoport JL, Toga AW. Glabus M. Structural MRI and brain development. Int. Rev. Neurosci. 2005

Vanneste S, Pouthas V, Wearden JH. Temporal control of rhythmic performance: a comparison between young and old adults. Exp. Aging Res 2001;27:83–102. [PubMed: 11205531]

Vermathen P, Robert-Tissot L, Pietz J, Lutz T, Boesch C, Kreis R. Characterization of white matter alterations in phenylketonuria by magnetic resonance relaxometry and diffusion tensor imaging. Magn. Reson. Med 2007;58:1145–1156. [PubMed: 18046700]

Walhovd KB, Fjell AM, Reinvang I, Lundervold A, Dale AM, Eilertsen DE, Quinn BT, Salat D, Makris N, Fischl B. Effects of age on volumes of cortex, white matter and subcortical structures. Neurobiol. Aging 2005;26:1261–1270. [PubMed: 16005549]

Waxman SG. Conduction in myelinated, unmyelinated, and demyelinated fibers. Arch. Neurol 1977;34:585–589. [PubMed: 907529]

Weiss KL, Schroeder CE, Kastin SJ, Gibson JP, Yarrington JT, Heydorn WE, McBride RG, Sussman NM, Arezzo JC. Mri monitoring of vigabatrin-induced intramyelinic edema in dogs. Neurology 1994;44:1944–1949. [PubMed: 7936252]

Yeudall LT, Reddon JR, Gill DM, Stefanyk WO. Normative data for the halstead-reitan neuropsychological tests stratified by age and sex. J. Clin. Psychol 1987;43:346–367. [PubMed: 3597789]

Ylikoski R, Ylikoski A, Keskivaara P, Tilvis R, Sulkava R, Erkinjuntti T. Heterogeneity of cognitive profiles in aging: successful aging, normal aging, and individuals at risk for cognitive decline. Eur. J. Neurol 1999;6:645–652. [PubMed: 10529751]

Yun SH, Mook-Jung I, Jung MW. Variation in effective stimulus patterns for induction of long-term potentiation across different layers of rat entorhinal cortex. J. Neurosci 2002;22:RC214:1–5. [PubMed: 11880535]

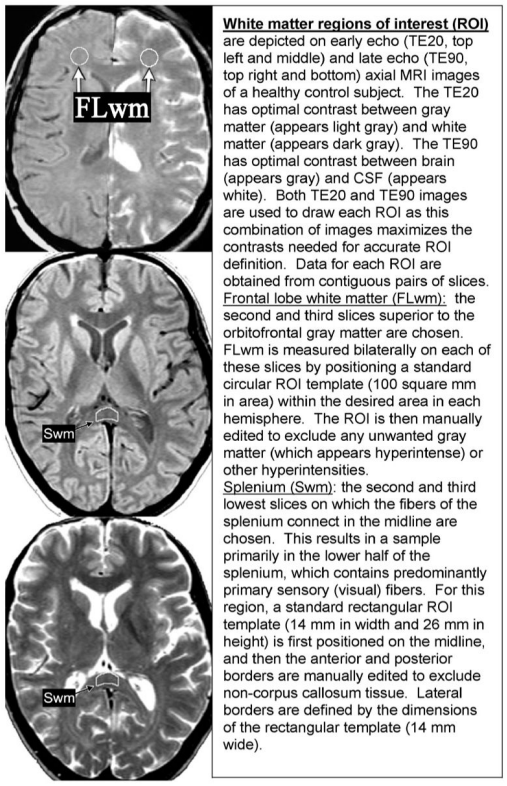

Fig. 1.
White matter regions of interest (ROIs).

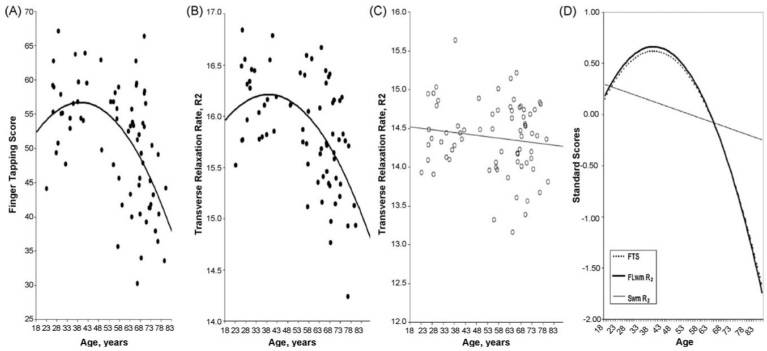

Fig. 2.

(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.

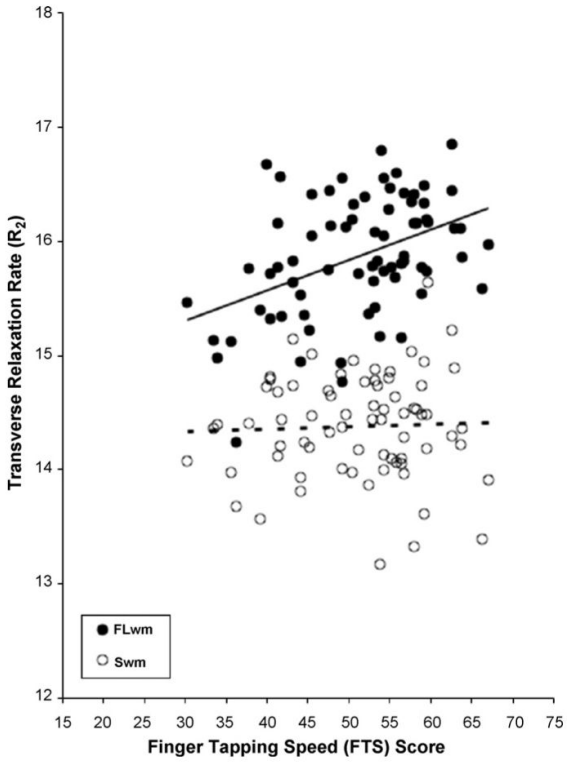

Fig. 3.
Correlations between finger tapping speed (FTS) and white matter transverse relaxation rate (R_2) in frontal lobe (FLwm) and splenium (Swm) regions.