



PAPER

White matter maturation supports the development of reasoning ability through its influence on processing speed

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Abstract

The structure of the human brain changes in several ways throughout childhood and adolescence. Perhaps the most salient of these changes is the strengthening of white matter tracts that enable distal brain regions to communicate with one another more quickly and efficiently. Here, we sought to understand whether and how white matter changes contribute to improved reasoning ability over development. In particular, we sought to understand whether previously reported relationships between white matter microstructure and reasoning are mediated by processing speed. To this end, we analyzed diffusion tensor imaging data as well as data from standard psychometric tests of cognitive abilities from 103 individuals between the ages of 6 and 18. We used structural equation modeling to investigate the network of relationships between brain and behavior variables. Our analyses provide support for the hypothesis that white matter maturation (as indexed either by microstructural organization or volume) supports improved processing speed, which, in turn, supports improved reasoning ability.

Introduction

The construct of ‘fluid’ reasoning represents flexibility of thought – the ability to solve problems and think logically even in new or unfamiliar settings (Cattell, 1987). For a growing child, the emergence of reasoning skills serves to scaffold the acquisition of new skills and knowledge (Blair, 2006; Cattell, 1971, 1987; Goswami, 1992). Indeed, prior research indicates that reasoning skills in childhood serve as a strong predictor of later academic achievement and even professional success (Gottfredson, 1997). This important facet of human cognition is often, as in the present study, assessed with standardized tests of visuospatial reasoning ability.

Existing work on the development of reasoning has focused on individual differences in its trajectory over time (McArdle, Ferrer-Caja, Hamagami & Woodcock, 2002) or on relations to other facets of cognitive ability

(Fry & Hale, 2000; Conway, Cowan, Bunting, Theriault & Minkoff, 2002; Salthouse, 1996; Salthouse, Babcock & Shaw, 1991). Still other work, involving functional magnetic resonance imaging (fMRI), has focused on the specific brain regions that are active while adults engage in tests of reasoning (for review, see Krawczyk, 2012), or differences in reasoning-related activation between children and adults (Crone, Wendelken, Donohue, van Leijenhorst & Bunge, 2006; Choi, Shamosh, Cho, DeYoung, Lee, Lee, Kim, Cho, Kim, Gray & Lee, 2008; Eslinger, Blair, Wang, Lipovsky, Realmuto, Baker, Thorne, Gamson, Zimmerman, Rohrer & Yang, 2009; Wright, Matlen, Baym, Ferrer & Bunge, 2009; Dumontheil, Houlton, Christoff & Blakemore, 2010; Wendelken, O’Hare, Whitaker, Ferrer & Bunge, 2011).

While informative in its own right, this fMRI research also serves as a road map for more extensive investigations into the relationships between changes in brain

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structure and reasoning ability over the course of development. The present study makes use of structural brain imaging data to explain why reasoning ability is subserved by a basic cognitive ability referred to as processing speed.

Development of reasoning ability

The capacity for reasoning begins to emerge in the first two or three years of life (Cattell, 1971, 1987), after the development of general perceptual, attentional, and motoric capabilities (Horn, 1991; Horn & Noll, 1997). The psychometric literature indicates that reasoning ability increases throughout childhood and adolescence, peaking in very early adulthood and declining subsequently (McArdle *et al.*, 2002). This pattern of growth and decline has been characterized by a double exponential function (McArdle *et al.*, 2002), with features similar to the patterns followed by other cognitive abilities such as processing speed up to adolescence (Kail, 1991; Kail & Ferrer, 2007; Kail & Park, 1992). According to this mathematical description, reasoning grows rapidly in early and middle childhood, continues to increase though at a slower rate in late childhood and early adolescence, and reaches asymptotic values in mid-adolescence, after which it begins to decline.

Although these mathematical functions are elegant and parsimonious in describing the changes of reasoning over development, the mechanisms underlying such changes are still unknown. Here, we sought to test whether a key aspect of brain development, white matter maturation, could account for changes in reasoning both directly and indirectly through effects on a more basic cognitive variable, namely the speed of cognitive processing.

Behavioral studies measuring concurrent relationships between cognitive abilities in children or adults have pointed to processing speed as a key mediator of reasoning. The speed and efficiency with which material can be processed, be it external stimuli or self-generated thoughts, strongly influences the recruitment of this information for complex cognition (Kail & Salthouse, 1994). Processing speed can be thought of as a bottleneck of reasoning development: the integration of multiple stimuli, which characterizes high-level cognitive processing, cannot occur until these stimuli can be individually understood. Processing speed not only correlates with performance on a broad range of cognitive tasks (Kail & Salthouse, 1994; Li, Lindenberger, Hommel, Aschersleben, Prinz & Baltes, 2004; Salthouse, 2005; Wechsler, 1999), but also with age-related changes throughout the life span (Kail, 1991; Salthouse, 1996).

Structural brain changes supporting the development of reasoning

Performance of even the most basic of tasks requires coordinated neural activity across distant brain regions. Thus, an individual's processing speed capacity must be related to the speed of neural signaling within and between brain regions in his or her brain. The long-range transmission of information across distributed brain networks is made possible by the presence in the brain of myelin, a fatty sheath that surrounds and insulates the long axons of neurons that project from one brain region to another. Myelin prevents signal degradation over the relatively long distances between distal cortical regions, and supports the high degree of temporal precision and fidelity of signaling that is critical for brain function.

The development of complex cognition relies heavily on the maturation of these structural connections. Both the thickness and degree of myelination of white matter fiber tracts affect action potential conduction speed (Gutiérrez, Boison, Heinemann & Stoffel, 1995; Tolhurst & Lewis, 1992; Waxman, 1980). Histological studies comparing *post mortem* brains from subjects of different ages have shown increases in myelin through childhood and adolescence, and even into the third decade of life (Yakovlev & Lecours, 1967). In addition, recent work using diffusion tensor imaging (DTI, explained in detail in the methods section) has provided an indirect measure of white matter maturation *in vivo* (Lebel, Walker, Leemans, Phillips & Beaulieu, 2008; Lebel & Beaulieu, 2011). DTI provides an index of the organization of white matter: i.e. the extent to which axons follow coherent pathways, as well as the degree to which these axons are myelinated (Beaulieu, 2002).

Individual differences in both processing speed and reasoning have been linked to *white matter organization* (WMO) throughout the brain. Significant correlations between processing speed and WMO have been reported for the parietal and temporal lobes as well as in the connections between these posterior brain regions and lateral prefrontal cortex (Turken, Whitfield-Gabrieli, Bammer, Baldo, Dronkers & Gabrieli, 2008). Likewise, correlations between reasoning and WMO have been reported for numerous white matter tracts (Chiang, Barysheva, Shattuck, Lee, Madsen, Avedissian, Klunder, Toga, McMahan, de Zubicaray, Wright, Srivastava, Balov & Thompson, 2009).

Our goal in this study was to investigate the mediating effect of cognitive processing speed between white matter organization and reasoning ability. Given the strong involvement of lateral prefrontal and parietal cortices in reasoning (for review see Krawczyk, 2012), we investigated WMO in bilateral white matter tracts connecting

these regions. However, because both processing speed and reasoning have been shown to correlate with WMO throughout the brain, we also sought to compare frontoparietal WMO with whole-brain WMO to determine which would better capture individual differences in processing speed and reasoning. Finally, we included a measure of white matter volume (in mm³) as a secondary index of white matter maturation.

Studies of brain development have shown that increased WMO over childhood is correlated with better cognitive performance (for review see Thomason & Thompson, 2011), and we predicted this pattern for reasoning ability as well. More specifically, however, we sought to test whether the relationship between white matter and reasoning is direct, or whether age-related changes in white matter are indirectly linked to changes in reasoning through their effects on processing speed.

To investigate these inter-related variables, all of which are increasing through this age range, we used structural equation modeling (SEM). We assumed a causal relationship from brain to behavior, with WMO affecting both reasoning and processing speed, and predicted a direct effect from processing speed to reasoning. SEM allowed us to construct a latent variable for reasoning from four separate neuropsychological tests (explained in detail in the methods section), and we were therefore able to generalize across four distinct instantiations of reasoning and minimize the effect of one specific task. We examined the extent of each relation, and investigated models using multiple measures of white matter maturation: (1) WMO in the fronto-parietal tract, which connects brain regions that have been implicated in reasoning, (2) WMO in the corticospinal tract and the body of the corpus callosum, control tracts that are believed to be relatively unimportant for reasoning, (3) whole-brain WMO, and (4) whole-brain white matter volume. We predicted that fronto-parietal WMO would have the strongest relationship with reasoning ability, reflecting increased speed and fidelity of communication between lateral PFC and parietal cortex, but that all of these measures of white matter maturation would be correlated with processing speed.

A recent paper by Salthouse (2011) called for more sophisticated statistical analyses when investigating the interrelated changes of brain, behavior, and age. Structural equation modeling accommodates the multivariate nature of this data set, which included latent factors and multiple manifest variables. It also facilitates the explicit test of hypotheses concerning the relation between brain structure and the behavioral data. Only a handful of studies have used SEM to model the relationship between DTI data and cognitive performance on a battery of tasks (Charlton, Landau, Schiavone, Barrick,

Clark, Markus & Morris, 2008; Chiang *et al.*, 2009; Voineskos, Rajji, Lobaugh, Miranda, Shenton, Kennedy, Pollock & Mulsant, 2010) and, to our knowledge, no prior study has used SEM to investigate the role of white matter maturation in cognitive development through childhood and adolescence.

Methods

Participants

Participants in this study were individuals from the *Neural Development of Reasoning Ability* (NORA) study, a project designed to examine the behavioral and neural factors that underlie reasoning. fMRI data from this cohort have previously been published in Wendelken *et al.* (2011). All participants were screened for neurological impairment, psychiatric illness, history of learning disability and developmental delay.

Parents completed the Child Behavioral Check List (Achenbach, 1991) on behalf of their child, and participants who scored in the clinical range for either externalizing or internalizing behaviors were excluded from further analyses. Of the 123 children and adolescents enrolled in the study who completed the necessary scans and scored in the normal range on the Child Behavior Check List, 20 were excluded due to data quality issues, and 103 (55 males) were included in the study. They ranged in age from 6.2 to 18.9 years (mean 11.6 ± 3.7). All participants and their parents gave their informed assent or consent to participate in the study, which was approved by the Committee for Protection of Human Subjects at the University of California at Berkeley.

Behavioral measures

The behavioral measures used in our longitudinal study were selected to have very high internal consistency and test-retest reliability, ranging from .94 to .95 (McArdle *et al.*, 2002; McGrew, Werder & Woodcock, 1991). For all five cognitive measures listed below, we used raw scores in our analyses. Processing speed was measured using the *Cross Out* subtest of the Woodcock-Johnson Tests of Achievement (Woodcock, Mather & McGrew, 2001). This test measures how rapidly and accurately one can identify, within an array of stimuli, a subset of geometric shapes that match a sample stimulus.

Visuospatial reasoning ability was assessed using a combination of measures, including the *Matrix Reasoning* and *Block Design* sub-tests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), and the *Analysis Synthesis* and *Concept Formation* sub-tests

of the Woodcock-Johnson Tests of Achievement (Woodcock *et al.*, 2001). *Matrix Reasoning*, modeled after a traditional test of ‘fluid’ or non-verbal reasoning, Raven’s Progressive Matrices (Raven, 1938), measures the ability to select the geometric visual stimulus that accurately completes an array of stimuli arranged according to one or more progression rules. *Block Design* measures the ability to arrange a set of red-and-white blocks in such a way as to reproduce a two-dimensional visual pattern shown on a set of cards. *Analysis Synthesis* measures the ability to analyze the components of an incomplete logic puzzle and to determine and name the missing components. *Concept Formation* measures the ability to identify and state the rules for concepts when shown illustrations of both instances and non-instances of the concept. Reasoning Ability factor scores were calculated from a factor analysis of these four tests.

Overview of DTI

DTI constitutes an indirect index of neuronal structure that measures the movement, or ‘diffusion’, of water in the brain with a diffusion-weighted MRI (DW-MRI) scan. DW-MRI detects the movement of protons, which are most commonly found in the brain as part of water molecules. Within the white matter of the brain, water molecules diffuse preferentially along axon bundles because the myelin sheath surrounding the axons impedes the diffusion of water molecules across it. Water molecules that have high directionality are said to exhibit *anisotropic* diffusion. Within gray matter and cerebrospinal fluid, water molecules can move freely in all directions and thus exhibit *isotropic* diffusion. Data from a DW-MRI scan can be fitted to a *tensor model* (see Figure 1A). The tensor is a multi-dimensional matrix that represents the amount of water diffusion in three orthogonal directions for every voxel in the brain.

Fractional anisotropy (FA) is a widely used measure of white matter microstructure. It is a scalar measure that quantifies how directional diffusion is within a voxel (see Figure 1B for equation). Voxels containing randomly oriented fibers will have a very small FA (close to 0, reflecting near-isotropic diffusion), while voxels containing coherently oriented fibers will have a large FA (close to 1, reflecting highly anisotropic diffusion). Measurement of these variables can provide clues regarding white matter tract development (see Figure 1C). When this index is large, the interpretation is that a single axis of movement is possible, with restriction of movement in the accompanying directions (Mori & Zhang, 2006). Increases in myelination around the neurons generally decrease movement perpendicular to the axis of greatest diffusion and thus increase FA. However, it is possible

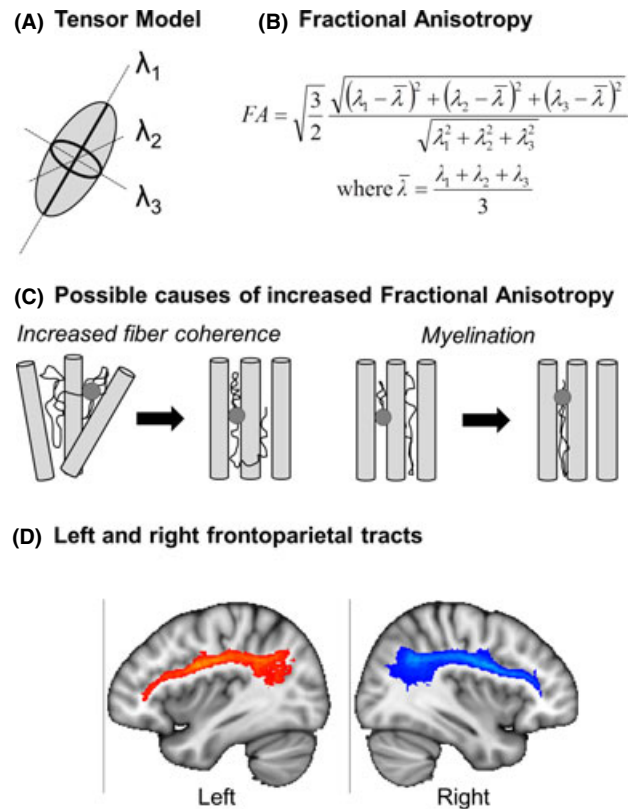


Figure 1 Illustration of tensor model and fractional anisotropy. A: Tensor model with eigenvectors along three orthogonal axes. B: Fractional anisotropy (FA) formula. C: Possible mechanisms for an increase in FA. Both increased fiber coherence – either from reorganization of existing axons (shown here) or pruning of axons running in different directions (not shown) – and myelination would result in an increased FA. D: Tracts connecting lateral frontal and parietal cortices in left and right hemispheres generated from this dataset with probabilistic tractography.

that an increase in FA could also be caused by an increase in the number of fibers along the primary axis, or a reduction in the number of crossing fibers. *In the context of healthy brain development*, increases in FA are thought to reflect increased white matter integrity.

Brain imaging data acquisition and analysis

Data acquisition

Brain imaging data were collected at UC Berkeley on a 3-T Siemens Trio TIM MR scanner using a 12-channel head coil with a maximum gradient strength of 40mT/m. Whole-brain DTI data were acquired using echo-planar imaging (EPI; TR = 7900 ms; TE = 102 ms; 2.2 mm³ isotropic voxels; 55 axial slices). Parallel acquisition (GRAPPA) was used with an acceleration factor of 2.

One non-diffusion-weighted direction and 64 diffusion-weighted directions were acquired with a b-value of 2000 s/mm^2 , uniformly distributed across 64 gradient directions. A T1-weighted image was also acquired in each participant for image registration and segmentation (MPRAGE; TR = 2300 ms; TE = 2.98 ms; 1 mm isotropic voxels).

Assessment of data quality

Both anatomical and DTI scans were assessed visually to determine scan quality, and subjects with obvious motion artifact were excluded. Specifically, six participants were excluded due to low-quality DTI data and eight were excluded due to low-quality anatomical data. In addition, six participants were excluded due to miscellaneous problems during scanning or testing. As is common in developmental MRI studies, younger participants were more likely to produce lower quality scans, and were thus excluded at a higher rate than older participants.

DTI data analysis

Analyses were performed using tools from FDT (for Functional MRI of the Brain (FMRIB) Diffusion Toolbox, part of FSL 4.1; Smith, 2002; Woolrich, Jbabdi, Patenaude, Chappell, Makni, Behrens, Beckmann, Jenkinson & Smith, 2009). Brain volumes were skull stripped using the Brain Extraction Tool (Smith, 2002) and a 12-parameter affine registration to the non-diffusion weighted volume was applied to correct for head motion and eddy current distortions introduced by the gradient coils, and the gradient directions were rotated accordingly. A diffusion tensor model was fitted to the data in a voxel-wise fashion to generate whole-brain maps of fractional anisotropy.

A white matter mask was created from each participant's high resolution T1-weighted scan, after brain extraction, using FAST (FMRIB's Automated Segmentation Tool; Zhang, Brady & Smith, 2001) which segments the brain into gray matter, white matter and cerebral spinal fluid. This mask was transformed into the subject's DTI space by applying the inverse of the affine registration of the non-diffusion-weighted volume to the high-resolution image. Both the registration and calculations of the inverse transform used FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson, Bannister, Brady & Smith, 2002). This mask is an independent definition of white matter voxels in the FA map created from the DTI acquisition.

We used probabilistic tractography to define tracts connecting anterior frontal and posterior parietal cortices within each hemisphere. The cortical regions

were defined from the Harvard-Oxford cortical atlas (Desikan, Ségonne, Fischl, Quinn, Dickerson, Blacker, Buckner, Dale, Maguire, Hyman, Albert & Killiany, 2006). The superior lateral occipital complex was used as the posterior parietal ROI and lateral frontal pole ($X > |14|$) as the lateral prefrontal cortex ROI. Voxel-wise estimates of the fiber orientation distribution, including the modeling of up to two fibers per voxel, were calculated using Bedpostx (Behrens, Berg, Jbabdi, Rushworth & Woolrich, 2007). Probabilistic fiber tracking was performed for each participant using the following settings: 5000 samples per voxel, maximum 2000 steps, curvature threshold of 0.2, 0.5 mm step length.

Left and right lateral fronto-parietal tracts were computed from anterior to posterior and posterior to anterior. 'Start' and 'stop' masks required tracts to pass through the two relevant cortical regions. Further, exclusion masks were used to restrict probabilistic streamlines to our *a priori* tracts. The exclusion mask for the fronto-parietal tracts prevented fibers that passed through the mid-sagittal plane, thalamus, basal ganglia, cingulum or insula from being included in our tract. All tractography was conducted in each participant's native DTI space, with masks transformed from standard space using FNIRT (FMRIB's Nonlinear Image Registration Tool; Andersson, Jenkinson & Smith, 2007a, 2007b).

Upon completion of tractography for each participant, tract images were thresholded to remove voxels through which fewer than 5% of the total number of generated tracts passed. Anterior-to-posterior and posterior-to-anterior tracts were added together and binarized. Individual tract images for all participants were then overlaid on one another in standard space (Figure 1D). These tract ROIs were transformed into subject space (using the non-linear warping described above) and WMO within each tract was defined as the average of every voxel in the FA map that fell both inside the tract ROI and the subject's white matter mask (WMOI-FPT).

Additional control tracts – left and right corticospinal tracts and the body of the corpus callosum – were obtained from the JHU white matter atlas (included with FSL). WMO in these tract ROIs ($\text{WMO}_{\text{L-CS}}$, $\text{WMO}_{\text{R-CS}}$ and WMO_{CC}) was calculated in the same manner as in the fronto-parietal tracts. Whole-brain WMO (WMO-global) was calculated for each subject as the average of every voxel in the FA map that fell within the subject's white matter mask.

Structural equation modeling

Our goal in this study was to investigate the network of relations among reasoning, processing speed, and WMO. All SEM analyses were carried out using SEM in Mplus

v6 (Muthén & Muthén, 2010). In our model, WMO was hypothesized to predict both processing speed and reasoning ability, whereas processing speed was hypothesized to predict reasoning ability. A Wald test was performed to assess the significance of removing the regression parameter from white matter on reasoning. This model tests the hypothesis that higher WMO leads to better cognitive processing speed, which in turn leads to increased reasoning ability. This model was fit for each of the white matter ROIS separately.

Results

As shown in Figure 2, we replicated previous findings that cognitive processing speed, reasoning ability, and fronto-parietal WMO all increase with age. Using an exponential model, age predicted 74% of the variance in cognitive speed ($p < .001$, Figure 2A), and 62% of the variance in reasoning ability ($p < .001$, Figure 2B). Similarly, age predicted 47% and 37% of the variance in FA in the right and left I-FPT ($p < .001$ for both, Figure 2C), and 42% of the variance in whole brain FA ($p < .001$, not shown). We also replicated previous findings that our neuropsychological tests of reasoning contribute strongly and equally to one latent variable (see results in Table 1).

We hypothesized that the effect of WMO on reasoning ability was mediated by processing speed. We first tested this hypothesis in our primary *regions of interest* (ROIs): left and right I-FPT. Statistical fit indices for this model are reported in Table 2. For both ROIs, the regression path from WMO to reasoning ability did not differ from zero (ps ranging from .235 to .685). Furthermore, a Wald test on this model parameter confirmed these results, indicating that removing this path did not significantly affect the overall model fit. The most parsimonious model, therefore, is one in which reasoning is regressed on processing speed and processing speed is regressed on WMO, with no direct link between reasoning and white matter (Figure 3). We conclude that the effect of white matter development on reasoning is mediated by processing speed.

Given that our initial analysis was limited to the lateral fronto-parietal white matter tracts, one reasonable question to examine is the extent to which our results are specific to those tracts or are really due to widespread changes in white matter organization. This question is especially important given the idea that fluid intelligence is related to parietal-frontal integration, which is strongly related to reasoning ability (Jung & Haier, 2007). To test the specificity of our results, we included other long

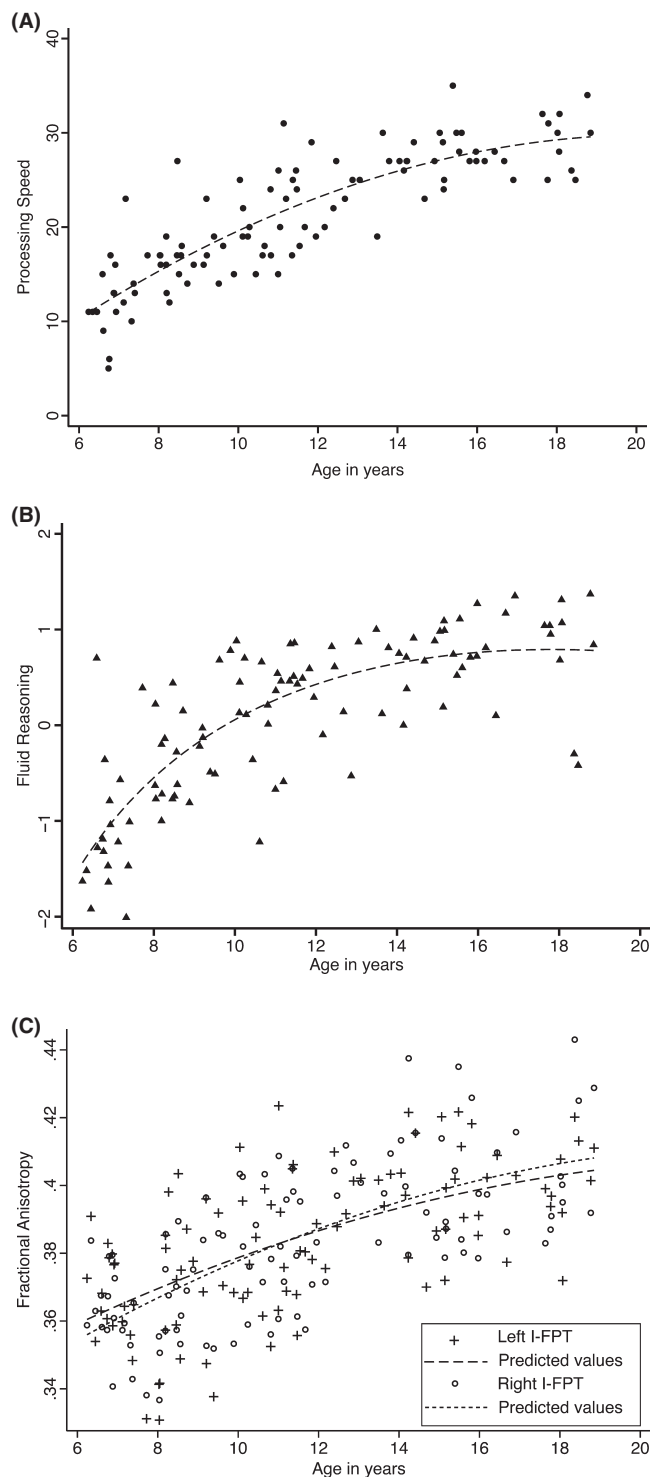


Figure 2 Age-related changes in (A) processing speed, (B) reasoning, and (C) WMO in left and right I-FPT. The model fit to the data was a Von Bertalanffy exponential growth model of the form $y = \beta_1 + \beta_2 e^{\frac{age}{p_3}}$

Table 1 Factor loadings for RA

Parameter	Estimate (SE)	Est/SE	p-value
Matrix reasoning	.863 (.032)	26.72	<.0001
Block design	.868 (.033)	26.37	<.0001
Concept formation	.817 (.049)	16.63	<.0001
Analysis synthesis	.821 (.039)	20.96	<.0001

Note: $N = 103$; All estimates are standardized values. Factor loadings for RA were equivalent across all DTI measures.

range tracts that do not overlap with lateral frontoparietal tracts. Specifically, we analyzed the same mediating model using corticospinal tracts (right and left) and the body of the corpus callosum. We also analyzed this model using whole-brain WMO. Across all of these measures, the results were consistent with the previous analyses, with no specific pathway departing from the overall results (see Table 2). Thus, the degree of white

matter maturation throughout the brain, rather than specifically in the frontoparietal tracts, influences reasoning ability through its influence on processing speed.

To examine the specificity of FA as a measure, in producing the pattern of results that we observed, we also analyzed our model using whole-brain white matter volume in place of WMO. Here again, we observed a similar pattern: the direct effect of white matter on reasoning ability was minimal, given the mediating effect of processing speed (see Table 2).

To rule out a spurious mediating effect from processing speed to reasoning ability, we examined an alternative model in which reasoning ability mediated the effect of whole-brain WMO on processing speed. The fit of this model was identical to the original specification, as both models used the same data and degrees of freedom. However, unlike the path from WMO to fluid reasoning in the original model, the path from WMO to processing speed in the new model was reliably different from zero

Table 2 Parameter estimates for the mediation model

Parameter	Estimate (SE)	Est/SE	p-value
Right lateral fronto-parietal tract WMO			
PS → RA	.784 (.065)	12.04	<.0001
Right l-FPT FA → PS	.585 (.065)	9.04	<.0001
Right l-FPT FA → RA	.034 (.083)	0.41	.685
Model fit	$\chi^2(8) = 35.3, p < .001$; CFI = .930; SRMR = .045; BIC = 2597.7		
Left lateral fronto-parietal tract WMO			
PS → RA	.757 (.061)	12.49	<.0001
Left l-FPT FA → PS	.515 (.072)	7.12	<.0001
Left l-FPT FA → RA	.092 (.039)	1.19	.235
Model fit	$\chi^2(8) = 29.9, p = .001$; CFI = .940; SRMR = .039; BIC = 2596.6		
Corpus Callosum Body (FA)			
PS → RA	.805 (.045)	18.01	<.0001
Corpus-Callosum FA → PS	.219 (.094)	2.33	<.002
Corpus-Callosum FA → RA	.008 (.069)	0.11	.910
Model fit	$\chi^2(8) = 29.3, p = .001$; CFI = .937; SRMR = .037; BIC = 3641.4		
Cortico-Spinal Tract Left (FA)			
PS → RA	.785 (.054)	14.43	<.0001
Cortico-Spinal Left FA → PS	.434 (.080)	5.43	<.0001
Cortico-Spinal Left FA → RA	.043 (.075)	0.58	.561
Model fit	$\chi^2(8) = 32.0, p < .001$; CFI = .933; SRMR = .041; BIC = 2781.7		
Cortico-Spinal Tract Right (FA)			
PS → RA	.786 (.050)	15.63	<.0001
Cortico-Spinal Right FA → PS	.340 (.087)	3.90	<.0001
Cortico-Spinal Right FA → RA	.051 (.071)	0.72	.470
Model fit	$\chi^2(8) = 29.8, p = .001$; CFI = .940; SRMR = .039; BIC = 2679.8		
Whole brain WMO			
PS → RA	.750 (.066)	11.30	<.0001
Whole brain FA → PS	.577 (.066)	8.79	<.0001
Whole brain FA → RA	.092 (.082)	1.13	.259
Model fit	$\chi^2(8) = 29.9, p = .001$; CFI = .940; SRMR = .039; BIC = 2596.6		
Whole-brain white matter volume (mm ³)			
PS → RA	.773 (.049)	15.86	<.0001
White matter volume → PS	.250 (.098)	2.55	<.011
White matter volume → RA	.120 (.072)	1.62	.100
Model fit	$\chi^2(8) = 28.9, p = .001$; CFI = .940; SRMR = .037; BIC = 4077.7		

Note: $N = 103$; RA = reasoning ability; PS = processing speed; FA = fractional anisotropy. MD = mean diffusivity. All estimates are standardized values. Factor loadings for RA were equivalent across all measures (as in Table 1).

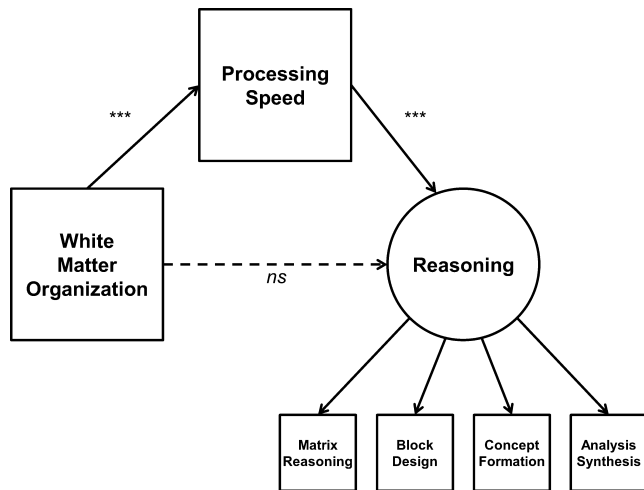


Figure 3 SEM for the mediation of the effect of whole-brain WMO on reasoning ability by processing speed. The pattern is the same for all white matter ROIs; see Table 1. This model indicates that the relationship between reasoning ability and white matter microstructure is mediated by processing speed. *** indicates $p < .0001$; ns indicates $p > .2$.

($p < .002$). Removing this path worsened the model fit significantly ($\chi^2(1) = 8.5, p < .01$), unlike the case in the original model ($\chi^2(1) = 1.2, p > .05$). This additional model supports the idea that processing speed mediates the relation between WMO and fluid reasoning.

In a final set of analyses, we examined whether WMI and processing speed are so highly linked that all other complex measures would appear to be mediated by processing speed, or is there something unique about the relationship between processing speed and reasoning ability (e.g. Deary, Penke & Johnson, 2010). Thus, we tested a model that included a measure of vocabulary (Woodcock-Johnson Revised 2001) instead of fluid reasoning. The results from this model indicated that vocabulary is directly related to WMO, in addition to being related to processing speed. Unlike with fluid reasoning, removing the path from WMO to vocabulary (that is, leaving only the relation through processing speed) worsens the fit of the model significantly ($\chi^2(1) = 5.2, p < .05$). This is also the case when vocabulary is added to the original model. Together, these analyses indicate that the mediating effects between WMO and fluid reasoning (through processing speed) do not generalize to another commonly used measure of cognitive aptitude.

Discussion

In this report we tested whether brain structural connectivity mediates the previously reported behavioral

relationship between processing speed and reasoning ability. Our analyses indicate that the structure of the relations among processing speed, reasoning, and whole-brain FA are best captured as unidirectional, with WMO predicting processing speed, and processing speed in turn predicting reasoning. The data analyzed in this study are consistent with a causal sequence in which white matter structural specialization is the leading indicator bringing about increases in processing speed, which in turn lead to increases in reasoning ability. However, these results are cross-sectional; longitudinal data analyses will be needed to elucidate the directionality of the relations among white matter organization, processing speed, and reasoning ability, and how these relations unfold over development (e.g. Lindenberger, von Oertzen, Ghisletta & Hertzog, 2011; Maxwell & Cole, 2007; Raz & Lindenberger, 2011).

The inclusion of age is warranted in any developmental study, though the specification of its influence is not always straightforward. We showed that all our measures were significantly increasing with age, but this does not elucidate the biological mechanisms that underlie the relationships. Practically speaking, age is a variable that summarizes changes in multiple factors that unfold together over an individual's lifespan, whether these factors are interrelated or not. Age is therefore not really an explanatory variable, in that it does not provide mechanistic insights, as its inclusion in the modeling may imply. However, we modeled multiple variables that all increase with age, and sought to understand how they relate to one another.

We found no differences in the pattern of results for the different white matter measures – WMO within the ROIs, whole-brain WMO, or whole-brain white matter volume. The global measures provide a more complete picture of the age-related changes in brain structure that support the development of processing speed and reasoning, both of which rely on distributed brain networks. Thus, we conclude that the mediation of the relationship between white matter maturation and reasoning by processing speed is an attribute of the whole brain, rather than specific regions of white matter. However, future research may uncover smaller areas of white matter, such as a portion of the I-FPT, that play a relatively more important role in reasoning than others.

In our model, white matter maturation leads to better reasoning. However, this unidirectional relationship could reasonably be questioned, given that brain structure is modified by neural activity (Barres & Raff, 1993). In fact, we have shown recently that three months of intensive reasoning can change frontal and parietal WMO in adults (Mackey, Whitaker & Bunge, 2012). Future longitudinal research will be required to further

untangle the complex reciprocal relationships between brain structure, brain function, and cognition.

Important new research reveals that chronological age can be predicted with 92% accuracy on the basis of approximately 250 variables derived from region of interest analyses of DTI and structural MRI data (Brown, Kuperman, Chung, Erhart, McCabe, Hagler, Venkatraman, Akshoomoff, Amaral, Bloss, Casey, Chang, Ernst, Frazier, Gruen, Kaufmann, Kenet, Kennedy, Murray, Sowell, Jernigan & Dale, 2012). In cases where the prediction error is large, an individual's biological maturity ('brain age') either lags behind or leads his or her chronological age by several years (see Bunge & Whitaker, 2012). In light of this new work, it is worth taking seriously the claim that indices of brain maturation serve as a more precise and relevant explanatory variable than age in research on the dynamic relationships between cognitive abilities over development.

Conclusion

In sum, the present study contributes to our understanding of how structural brain changes support the emergence of critical cognitive abilities during childhood and adolescence. Our findings show that processing speed is tightly linked to whole-brain WMO, and further that the strong relationship between reasoning and white matter microstructure is mediated by processing speed. More generally, many cognitive and brain measurements change together over development, and so it is a challenge to determine which brain changes directly contribute to which cognitive changes. We show here how SEM can be applied to neuroscientific data to elucidate the mechanisms of cognitive development.

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References

Achenbach, T.M. (1991). *Integrative guide for the 1991 CBCL/4-18, YSR and TRF profiles*. Burlington, VT: University of Vermont, Department of Psychiatry.

- Andersson, J.L.R., Jenkinson, M., & Smith, S.M. (2007a). Non-linear optimisation FMRIB Technical Report TR07JA1 (June).
- Andersson, J.L.R., Jenkinson, M., & Smith, S.M. (2007b). Non-linear registration aka Spatial normalisation FMRIB Technical Report TR07JA2 (June).
- Barres, B.A., & Raff, M.C. (1993). Proliferation of oligodendrocyte precursor cells depends on electrical activity in axons. *Nature*, **361** (6409), 258–260.
- Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR Biomed*, **15** (7–8), 435–455.
- Behrens, T.E.J., Berg, H.J., Jbabdi, S., Rushworth, M.F.S., & Woolrich, M.W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? *NeuroImage*, **34** (1), 144–155.
- Blair, C. (2006). How similar are fluid cognition and general intelligence? A developmental neuroscience perspective on fluid cognition as an aspect of human cognitive ability. *Behavioral and Brain Sciences*, **29** (2), 109–125; discussion 125–160.
- Brown, T.T., Kuperman, J.M., Chung, Y., Erhart, M., McCabe, C., Hagler, D.J. Jr., Venkatraman, V.K., Akshoomoff, N., Amaral, D.G., Bloss, C.S., Casey, B.J., Chang, L., Ernst, T.M., Frazier, J.A., Gruen, J.R., Kaufmann, W.E., Kenet, T., Kennedy, D.N., Murray, S.S., Sowell, E.R., Jernigan, T.L., & Dale, A.M. (2012). Neuroanatomical assessment of biological maturity. *Current Biology*, **22** (18), 1693–1698.
- Bunge, S.A., & Whitaker, K.J. (2012). Brain imaging: your brain scan doesn't lie about your age. *Current Biology*, **22** (18), R800–R801.
- Cattell, R.B. (1971). *Abilities: Their structure, growth and action*. Boston MA: Houghton-Mifflin.
- Cattell, R.B. (1987). *Intelligence: Its structure, growth and action*. New York: Elsevier.
- Charlton, R.A., Landau, S., Schiavone, F., Barrick, T.R., Clark, C.A., Markus, H.S., & Morris, R.G. (2008). A structural equation modeling investigation of age-related variance in executive function and DTI measured white matter damage. *Neurobiology of Aging*, **29** (10), 1547–1555.
- Chiang, M.-C., Barysheva, M., Shattuck, D.W., Lee, A.D., Madsen, S.K., Avedissian, C., Klunder, A.D., Toga, A.W., McMahon, K.L., de Zubicaray, G.I., Wright, M.J., Srivastava, A., Balov, N., & Thompson, P.M. (2009). Genetics of brain fiber architecture and intellectual performance. *Journal of Neuroscience*, **29** (7), 2212–2224.
- Choi, Y.Y., Shamosh, N.A., Cho, S.H., DeYoung, C.G., Lee, M.J., Lee, J.-M., Kim, S.I., Cho, Z.-H., Kim, K., Gray, J.R., & Lee, K.H. (2008). Multiple bases of human intelligence revealed by cortical thickness and neural activation. *Journal of Neuroscience*, **28** (41), 10323–10329.
- Conway, A.R.A., Cowan, N., Bunting, M.F., Theriault, D.J., & Minkoff, S.R.B. (2002). A latent variable analysis of working memory capacity, short-term memory capacity, processing speed, and general fluid intelligence. *Intelligence*, **30** (2), 163–183.
- Crone, E.A., Wendelken, C., Donohue, S., van Leijenhorst, L., & Bunge, S.A. (2006). Neurocognitive development of the

- ability to manipulate information in working memory. *Proceedings of the National Academy of Sciences of the United States of America*, **103** (24), 9315–9320.
- Deary, I.J., Penke, L., & Johnson, W. (2010). The neuroscience of human intelligence differences. *Nature Reviews Neuroscience*, **11** (3), 201–211.
- Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., & Killiany, R.J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, **31** (3), 968–980.
- Dumontheil, I., Houlton, R., Christoff, K., & Blakemore, S.-J. (2010). Development of relational reasoning during adolescence. *Developmental Science*, **13** (6), F15–F24.
- Eslinger, P.J., Blair, C., Wang, J., Lipovsky, B., Realmuto, J., Baker, D., Thorne, S., Gamson, D., Zimmerman, E., Rohrer, L., & Yang, Q.X. (2009). Developmental shifts in fMRI activations during visuospatial relational reasoning. *Brain and Cognition*, **69** (1), 1–10.
- Fry, A.F., & Hale, S. (2000). Relationships among processing speed, working memory, and fluid intelligence in children. *Biological Psychology*, **54** (1–3), 1–34.
- Goswami, U. (1992). *Analogical reasoning in children*. Hillsdale, NJ: Laurence Erlbaum.
- Gottfredson, L.S. (1997). Why g matters: the complexity of everyday life. *Intelligence*, **24** (1), 79–132. doi: 10.1016/S0160-2896(97)90014-3
- Gutiérrez, R., Boison, D., Heinemann, U., & Stoffel, W. (1995). Decomposition of CNS myelin leads to a reduction of the conduction velocity of action potentials in optic nerve. *Neuroscience Letters*, **195** (2), 93–96.
- Horn, J.L. (1991). Measurement of intellectual capabilities: a review of theory. In K.S. McGrew, J.K. Werder & R.W. Woodcock (Eds.), *Woodcock-Johnson Technical Manual*. Allen, TX: DLM Teaching Resources.
- Horn, J.L., & Noll, J. (1997). Human cognitive capabilities: Gf-Gc theory. In D.P. Flanagan, J.L. Genshaft & P.L. Harrison (Eds.), *Contemporary intellectual assessment: Theories, tests, and issues* (pp. 53–91). New York: Guilford Press.
- Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, **17** (2), 825–841. doi: 10.1006/nimg.2002.1132
- Jung, R.E., & Haier, R.J. (2007). The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. *Behavioral and Brain Sciences*, **30** (2), 135–154; discussion 154–187.
- Kail, R. (1991). Developmental change in speed of processing during childhood and adolescence. *Psychological Bulletin*, **109** (3), 490–501.
- Kail, R.V., & Ferrer, E. (2007). Processing speed in childhood and adolescence: longitudinal models for examining developmental change. *Child Development*, **78** (6), 1760–1770.
- Kail, R., & Park, Y. (1992). Global developmental change in processing time. *Merrill-Palmer Quarterly*, **38**, 525–541.
- Kail, R., & Salthouse, T.A. (1994). Processing speed as a mental capacity. *Acta Psychologica*, **86** (2–3), 199–225.
- Krawczyk, D.C. (2012). The cognition and neuroscience of relational reasoning. *Brain Research*, **1428**, 13–23.
- Lebel, C., & Beaulieu, C. (2011). Longitudinal development of human brain wiring continues from childhood into adulthood. *Journal of Neuroscience*, **31** (30), 10937–10947.
- Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *NeuroImage*, **40** (3), 1044–1055. doi: 10.1016/j.neuroimage.2007.12.053
- Li, S.-C., Lindenberger, U., Hommel, B., Aschersleben, G., Prinz, W., & Baltes, P.B. (2004). Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span. *Psychological Science*, **15** (3), 155–163.
- Lindenberger, U., von Oertzen, T., Ghisletta, P., & Hertzog, C. (2011). Cross-sectional age variance extraction: what's change got to do with it? *Psychology and Aging*, **26**, 34–47.
- McArdle, J.J., Ferrer-Caja, E., Hamagami, F., & Woodcock, R.W. (2002). Comparative longitudinal structural analyses of the growth and decline of multiple intellectual abilities over the life span. *Developmental Psychology*, **38** (1), 115–142.
- McGrew, K.S., Werder, J.K., & Woodcock, R.W. (1991). *WJ-R technical manual*. Itasca, IL: Riverside Publishing.
- Mackey, A.P., Whitaker, K.J., & Bunge, S.A. (2012). Experience-dependent plasticity in white matter microstructure: reasoning training alters structural connectivity. *Frontiers in Neuroanatomy*, **6**, 32.
- Maxwell, S.E., & Cole, D.A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychological Methods*, **12**, 23–44.
- Mori, S., & Zhang, J. (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron*, **51** (5), 527–539.
- Muthén, L.K., & Muthén, B.O. (2010). *Mplus user's guide* (6th edn.). [Computer software and manual]. Los Angeles, CA: Muthén & Muthén.
- Raven, J.C. (1938). Standardization of progressive matrices. *British Journal of Medical Psychology*, **19** (1), 137–150.
- Raz, N., & Lindenberger, U. (2011). Only time will tell: cross-sectional studies offer no solution to the age–brain–cognition triangle: Comment on Salthouse (2011). *Psychological Bulletin*, **137**, 790–795.
- Salthouse, T.A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, **103** (3), 403–428.
- Salthouse, T.A. (2005). Relations between cognitive abilities and measures of executive functioning. *Neuropsychology*, **19** (4), 532–545.
- Salthouse, T.A. (2011). Neuroanatomical substrates of age-related cognitive decline. *Psychological Bulletin*, **137** (5), 753–784.
- Salthouse, T.A., Babcock, R.L., & Shaw, R.J. (1991). Effects of adult age on structural and operational capacities in working memory. *Psychology and Aging*, **6** (1), 118–127.

- Smith, S.M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, **17** (3), 143–155.
- Thomason, M.E., & Thompson, P.M. (2011). Diffusion imaging, white matter, and psychopathology. *Annual Review of Clinical Psychology*, **7**, 63–85.
- Tolhurst, D.J., & Lewis, P.R. (1992). Effect of myelination on the conduction velocity of optic nerve fibres. *Ophthalmic & Physiological Optics*, **12** (2), 241–243.
- Turken, A.U., Whitfield-Gabrieli, S., Bammer, R., Baldo, J.V., Dronkers, N.F., & Gabrieli, J.D.E. (2008). Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. *NeuroImage*, **42** (2), 1032–1044.
- Voineskos, A.N., Rajji, T.K., Lobaugh, N.J., Miranda, D., Shenton, M.E., Kennedy, J.L., Pollock, B.G., & Mulsant, B.H. (2010). Age-related decline in white matter tract integrity and cognitive performance: a DTI tractography and structural equation modeling study. *Neurobiology of Aging*, **33** (1), 21–34. doi: 10.1016/j.neurobiolaging.2010.02.009
- Waxman, S.G. (1980). Determinants of conduction velocity in myelinated nerve fibers. *Muscle & Nerve*, **3** (2), 141–150.
- Wechsler, D. (1999). *The Wechsler Abbreviated Scale of Intelligence*. San Antonio TX: The Psychological Corporation.
- Wendelken, C., O'Hare, E.D., Whitaker, K.J., Ferrer, E., & Bunge, S.A. (2011). Increased functional selectivity over development in rostralateral prefrontal cortex. *Journal of Neuroscience*, **31** (47), 17260–17268.
- Woodcock, R.W., Mather, N., & McGrew, K.S. (2001). *Woodcock-Johnson III*. Itasca, IL: Riverside Publishing.
- Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T.E.J., Beckmann, C.F., Jenkinson, M., & Smith, S.M. (2009). Bayesian analysis of neuroimaging data in FSL. *NeuroImage*, **45**, S173–S186.
- Wright, S.B., Matlen, B.J., Baym, C.L., Ferrer, E., & Bunge, S.A. (2007). Neural correlates of fluid reasoning in children and adults. *Frontiers in Human Neuroscience*, **1**, 8.
- Yakovlev, P., & Lecours, A. (1967). The myelogenetic cycles of regional maturation of the brain. In A. Minkowski (Ed.), *Regional development of the brain in early life* (pp. 3–70). Oxford: Blackwell Scientific.
- Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, **20** (1), 45–57.

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