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ORIGINAL ARTICLE

Timing of White Matter Development Determines Cognitive Abilities at School Entry but Not in Late Adolescence

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Abstract

The primary aim of this study was to investigate to what degree the age-related white matter development, here called "brain age", is associated with working memory (WM) and numeric abilities in 6-year-old children. We measured white matter development using diffusion tensor imaging to calculate fractional anisotropy (FA). A "brain age" model was created using multivariate statistics, which described association between FA and age in a sample of 6- to 20-year-old children. This age model was then applied to predict "brain age" in a second sample of 6-year-old children. The predicted brain age correlated with WM performance and numerical ability (NA) ($P < 0.01$, $P < 0.05$) in the 6-year-old children. More than 50% of the stable variance in WM performance was explained. We found that in children older than 13 years of age, this association between brain age and WM was no longer significant ($P > 0.5$). The results bear theoretical implications as they suggest that the variability in individual developmental timing strongly affects WM and NA at school start but badly predicts adolescent cognitive functioning. Furthermore, it bears practical implications as one may differentiate maturation lags from persistent low cognitive abilities in school children, complementing cognitive tests.

Key words: development, DTI, working memory

Introduction

The rise in cognitive abilities during childhood can be attributed both to age-dependent maturation of the brain and environmental influences, which leads to an increase in cognitive performance (Johnson et al. 2001; Karmiloff-Smith et al. 2009; Jolles et al. 2012). Just as early developmental milestones of language, motor function, and pubertal onset differs between individuals, there may be variability in the timing of cognitive development. The variability in infant cognitive measures badly predict later IQ, which successively stabilizes during childhood (McCall et al. 1993; Fagan et al. 2007). Timing of cognitive development in childhood may be early or late but the relationship to cognitive capacity later in life is thus unclear. The concept of variability in timing of development is well illustrated in a study of cognitive development in 9000 children and adolescents (Roalf et al. 2014). In this study, the variability over a broad range of cognitive tests decreased steadily from 8 to 13 years of age followed by a slow increase until 21 years of age. The initial decrease in variability was interpreted as due to differences in timing of development, whereas the later increase was interpreted as experience-dependent development. According to this theory, the variance in cognitive abilities may be partly separated into an initial timing-dependent and a later experience-dependent part. The theory goes well in line with discussions in the developmental cognitive science literature describing environmentally independent maturation as an earlier process than later environmental stimulation-dependent development (Klingberg 2014). A prediction that can be derived from these theories is

that a proportion of the of the variance in cognitive functions in children should be due to transient developmental lags that may decrease or disappear with time as the maturation process finishes for the late developing children.

The clinical significance of developmental lags can be illustrated by studies showing that being born late in an academic year carries a higher risk of receiving neuropsychiatric diagnoses and in turn receiving stimulant medication compared with being born early (Goodman et al. 2003; Zoega et al. 2012), which indicates that maturational differences can be misinterpreted as neuropsychiatric disorders (Pottegård et al. 2014).

Here, we focused on answering these questions by studying Working Memory (WM) development. WM has numerous times been found to be predictive of concurrent as well as future school performance (Gathercole et al. 2003; Bull et al. 2008). The relationship between WM and neurodevelopmental disorders such as attention-deficit hyperactivity disorder (ADHD) and autism is well known (Kasper et al. 2012; Barendse et al. 2013) making the measure clinically relevant. Furthermore, the development of WM follows a protracted development with a steep increase in early childhood (Klingberg 2006). These features makes it suitable for studying variability in timing of development in children at the age of starting school. Numerical ability (NA) was used as a measure more closely related to activities in performed in the early school years and has been shown to predict school performance (Passolunghi et al. 2007; Gilmore et al. 2010).

Given the possible variability in timing of cognitive development, individual maturity would hypothetically be more accurately evaluated using a combination of biological measures, such as MRI, and cognitive tests. The biological level of development could be evaluated together with cognitive tests to differentiate developmental lags from persistent low cognitive functioning. With the increased pressure put upon children in school and the observed rise in neurodevelopmental diagnoses of school children (Castle et al. 2007; McCarthy et al. 2009), a better understanding of the causes of cognitive deficits is highly warranted.

In this study, we explored to what degree WM and NA in 6 year olds, the age of school entry, is determined by the variability in maturity of white matter development. Furthermore, we aim to explore how the relationship between variability in developmental maturity and cognitive functions changes during childhood and adolescence. Given previous studies, we hypothesized that individual developmental level would explain a larger amount of variance in cognitive abilities in children at school entry compared with adolescence due to a developmental lag. This developmental lag would get less pronounced with age, weakening the relationship between developmental maturity and cognitive functions. We used diffusion tensor imaging (DTI) data from a sample of developing children to construct a multivariate model representing "brain age." This model was then applied to the 6 year olds in order to test if the variability in "brain age" was associated with WM and numeric abilities. This is an extension of our previous work showing that multivariate models based on functional magnetic resonance imaging (MRI) and DTI can be used to predict WM development (Ullman et al. 2014).

Materials and Methods

The general strategy with the analysis was to first construct a DTI-based multivariate model to use as a biomarker for chronological brain development, here called Brain Age. This model was subsequently used to predict Brain Age from DTI data and correlate it with WM and NA. The study was approved by the Ethical Committee of Karolinska Institutet. Written informed consent was obtained from all subjects, or parents, when appropriate.

Subjects

Two samples of healthy children were recruited to this study. The first sample, called the developmental sample, included 82 children randomly selected from the county of Nynäshamn, Sweden. This sample has been used in the previous studies (Söderqvist et al. 2010; Darki and Klingberg 2014; Ullman et al. 2014). The subjects went through cognitive testing as well as MRI scanning. The age range of the sample was 6–20 years of age, with an average age of 13.0 years. The distribution was close to uniformly distributed in the age range.

The second sample, called the 6-year-old sample, consisted of 31 typically developing children in the younger range of the larger sample. Their mean age was 6.8 years and standard deviation was 0.30. This sample was used to measure how variability in white matter development correlated with cognitive abilities at the time of school entry. Half of the sample was selected on the basis on lower scores on a screening test measuring NA, the other half was a random selection from a public school.

Cognitive Data

Cognitive tests measuring WM and NA was used in this study. WM was measured in the developmental sample using the block repetition from the Automated Working Memory Assessment battery (Alloway et al. 2008). This test measures visuospatial WM by asking subjects to remember a sequence of positions on a grid. In the 6-year-old sample, WM was calculated as a latent variable using 3 scales of WM, 1) a block repetition task similar to the above described, 2) a backwards block repetition task where the subjects had to report the sequence backwards, and 3) a computerized visuospatial grid task where the subjects had to remember a sequence of stimuli on at grid. The latent variable was calculated by averaging the Z-scores for the 3 tests.

NA was measured in the 6-year-old sample as an average Z-score of the 3 tests: 1) verbal arithmetic ability from the WISC-IV, 2) a computerized arithmetic addition test, and 3) a computerized arithmetic subtraction test.

MRI Data

For both of the groups, diffusion weighted imaging (DWI) was acquired. The developmental sample was scanned in a Siemens 1.5 Tesla over a period of 6 years. Subjects were scanned multiple times with 2-year interval during this period; however, only the first acquisition for each subject was included in the study. No longitudinal analysis was performed on the developmental sample as the objective of the analysis was to make a comparison with the 6-year-old sample, for which no developmental follow-up was available. The DWI consisted of a sequence with field of view 230 × 230 mm, a voxel size of 1.8 × 1.8 × 6.5 mm and 20 gradient directions.

The 6-year-old sample was scanned in a GE 3 Tesla machine. The DWI consisted of a sequence with field of view of

220 × 220 mm and an isotropic voxel size of 2.3 mm and 32 gradient directions.

Analysis

In the first step of the study, we created a multivariate model of the developing brain using the DTI data from the developmental sample. The main goal with the analysis was to maximize the predictive ability of the model. For this purpose, we chose to employ multivariate techniques that have been shown to be excellent for this purpose in neuroimaging data (Norman et al. 2006). Multivariate analysis also produce a single prediction for each subject, which makes it suitable when the prediction of a second data set is obtained as no correction for multiple comparisons is needed.

The diffusion properties of white matter was represented as fractional anisotropy (FA). FA represents the microstructure of the white matter and has been shown to be tightly linked with brain development (Barnea-Goraly et al. 2005).

After eddy current correction, a linear realignment was done between the b0 and T1 Montreal Neurological Institute (MNI) template. A tensor model was fitted to the diffusion data, and FA volumes were created. After this, a nonlinear normalization to the standard MNI space was performed based on the FA volumes and MNI FA template.

The FA maps were smoothened with an 8-mm Gaussian kernel and then used to fit a multivariate model representing developmental Brain Age. An inclusive brain mask was first used to remove extra cerebral structures. Subsequently, a support vector regression (SVR) model was fitted using chronological age as the dependent variable. All cerebral voxels was used when fitting the model without further feature reduction. To reduce complexity of the model in order to avoid overfitting, only linear kernels were used. Parameters for the SVR model was set using a cross-validated grid search. In order to first appreciate the generalization of the model, an internal leave-one-out cross validation was carried out. This resulted in an unbiased prediction of chronological age from the data. Subsequently, a model was trained using the full developmental sample. This model was used for determining Brain Age in the 6-year-old sample.

The 6-year-old sample was preprocessed in the same way as the developmental sample. In a final step, the data were resampled to the voxel size of the developmental sample in order to apply the Brain Age model from the developmental sample. The Brain Age model was subsequently applied to obtain a predicted Brain Age of each individual in the 6-year-old sample. The Brain Age for the 6-year-old sample was then correlated with cognitive scales.

We used SVR in this study. This is a regression adaptation of the Support Vector Machine, a statistical model that has been well used within neuroimaging due to its high performance with noisy data and limited sample sizes (Bray et al. 2009). The model makes use of a kernel function to transform the input features to a higher dimensional space in which the model is fitted. Another key feature of the model is that the models only use a subset of the data points, called support vectors, to model the data. This feature makes the model fitting resistant to outliers.

Statistical analyses were conducted in the Python programing language (www.python.org) using Scikit-Learn machine learning library (Abraham et al. 2014). MRI preprocessing used the FSL software library as well as ANTS (Avants et al. 2011).

Results

The first step was to create an SVR model predicting age from the FA values in subjects from the developmental sample (age 6–20). The predicted age is called Brain Age. All intracerebral voxels were used as the features for fitting this multivariate regression model. The model was then trained using this data to predict the age of the children. For evaluating the model performance, we used leave-one-out cross-validated predictions. The cross-validated predicted Brain Age was significantly correlated with the real chronological age ($r = 0.81$, $P < 0.001$). The Brain Age could thus capture the variance in microstructural changes that occur during development to a high degree and was a good measure of individual brain development (Fig. 1).

In the second step, the Brain Age based on the FA values from the 6-year-old sample was calculated using the model in step 1. The data from the 6-year-old sample was fed to the model trained on the developmental sample, and a predicted Brain Age was obtained. This Brain Age of the 6-year-old sample was then correlated with concurrent WM and NA. The Brain Age correlated positively with both the latent WM variable $r = 0.50$, $P < 0.01$ (Fig. 2*a*) and with the latent NA variable $r = 0.41$, $P < 0.05$. This showed that the variability in Brain Age as measured with DTI correlated with the cognitive ability of children at school entry. The real chronological age was not correlated with either WM or NA ($r = 0.56$, $P = 0.52$). Akaike Information Criterion was calculated for the models in order to statistically compare the difference in the explained variance. The DTI-derived Brain Age was a significantly better predictor of WM at school entry than chronological age ($P < 0.05$), while this significance was not retained for NA ($P = 0.11$). This indicated that WM abilities at school entry are better correlated with the DTI developmental level than actual chronological age. However, due to the narrow range in chronological age, the absence of correlation between cognitive abilities and chronological age was expected. It does not show that Brain Age in general is more strongly correlated with cognitive abilities than age as the correlation strengths of the 2 measures depends highly on the amount of variability in age. The absence of correlation rather shows that the relationship between Brain Age and cognitive abilities are not confounded by chronological age in this study.

To explore confounding of movement in the scanner, a compound movement variable was calculated by combining the average movement between each diffusion direction volume in the raw DWI series. To standardize the scale, each movement

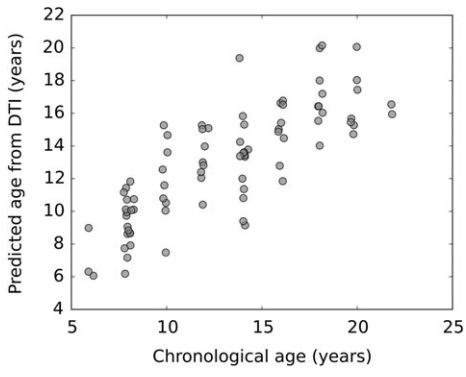

Figure 1. Scatter plot of predicted chronological age from DTI versus measured chronological age. Pearson $r = 0.81$, $P < 0.001$, $n = 82$.

parameter was subtracted by its median value then divided by its interquartile range. This variable did not correlate with neither the DTI Brain Age ($P = 0.19$) nor the cognitive variables ($r = 0.99$, $P = 0.29$). Thus, movement in the MRI scanner was not a confounding variable in this study.

The SVR analysis showed that the pattern of chronological brain developmental level determined cognitive abilities at school entry. To also illustrate that chronological age and WM overlap spatially in their univariate correlations, voxelwise correlation maps were calculated between FA and chronological age in the developmental sample and between FA and WM in the 6-year-old sample. The maps illustrating voxels with significant positive correlations are shown in Figure 3*a*, illustrating similar patterns of positive correlation widespread over the major white matter pathways. As the univariate significance in the 6-year-old sample was lower, presumably due to a smaller sample size, voxels were not corrected for multiple comparisons for illustration of the pattern. Statistical evaluation of the univariate overlap was instead carried out by calculating the percentage of overlap at different statistical thresholds. Area under the curve for the statistical thresholds was calculated and tested using a permutation test. WM ability was permuted in the 6-year-old group, and univariate correlation maps was calculated in each permutation. The area under the curve for these permutations served as a null distribution. In total, 10 000 permutations were carried out. This resulted in a significant overlap of the WM correlates in the 6-year-old sample, and the chronological age correlates in the developmental sample ($P < 0.05$, Fig. 3*b*).

If the variance in cognitive abilities at school entry explained by Brain Age corresponds to a developmental lag, the correlation would be expected to decrease with age as the later developing children catch up. To further explore this hypothesis, correlations between the SVR results and WM, after removing age-related variability, were calculated in the developmental sample that had a broader age range. The sample was split into 2 groups based on the median age. This resulted in one group aged between 6 and 13 years and the other group aged between 13 and 20 years. The results of the correlations within the 3 groups are illustrated in Figure 4. While 52% ($P < 0.01$) of the stable variance in WM was explained in the 6-year-old sample, 16% ($P < 0.1$) was explained in the younger developmental sample and merely 8% ($P > 0.5$) in the older developmental sample. There was thus a subsequently lower part of the variance in WM explained by the developmental model as children aged. Only the youngest group showing a significant portion of variance explained. As a result of developmental lags explaining cognitive variance in younger children more than adolescents, Brain Age in adolescents could be hypothesized to have a higher correlation with future development. This is summarized in Figure 5. When developmental lags are overcome, children would be expected to continue development along their developmental curve. Individual

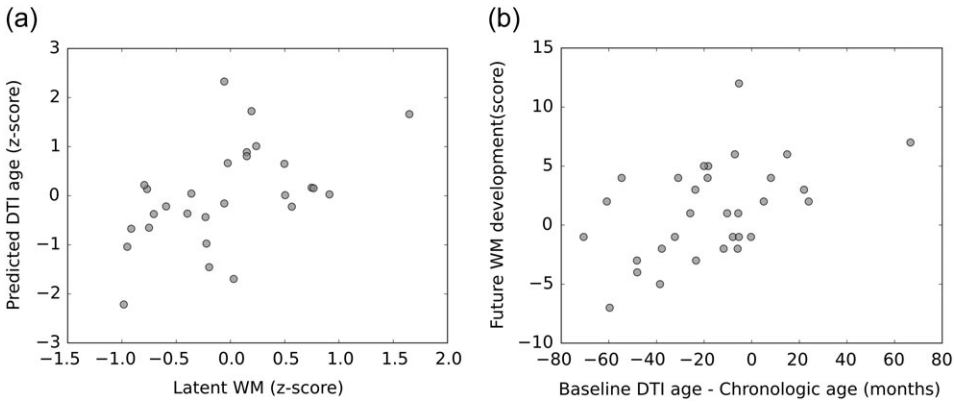

Figure 2. Scatter plots of the predicted age from the DTI models and WM. (*a*) Scatter plot of predicted chronological age from the DTI versus WM capacity in the 6-year-old group. Pearson $r = 0.50$, $P < 0.01$, $n = 26$. (*b*) Scatter plot of predicted future WM development from baseline difference between DTI age and real age. Pearson $r = 0.48$, $P < 0.01$, $n = 31$.

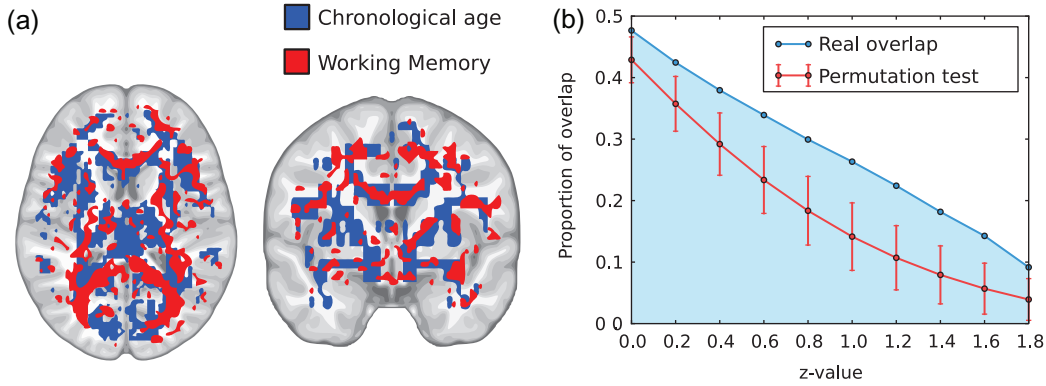

Figure 3. Illustrations of the similarity between the correlates of white matter maturation and the correlates of WM. (*a*) Overlay of univariate correlation maps for chronological age versus FA and WM and FA. (*b*) Proportion of overlap at various statistical thresholds, compared with a permutation test. Error bars indicate standard deviation.

variations in Brain Age are thus more likely to reflect previous developmental speed and would be expected to predict future change, regardless of genetic or environmental origin . We tested this hypothesis by correlating age-standardized Brain Age with the rise in WM performance in the developmental sample 2 years after scanning as compared with the baseline WM. In the younger half of the sample, Brain Age did not correlate with the subsequent rise in WM ($r = 0.13$, $P > 0.4$), but it did so in the older sample ($r = 0.48$, $P < 0.01$) (Fig. 2*b*). This shows that as developmental lags are overcome, Brain Age is a strong predictor of future cognitive development.

Since the 6-year-old sample and the developmental sample did not complete the same WM tests, we had to exclude the possibility of a lower test–retest reliability in the developmental sample as a confounding factor. Both groups repeated their tests at a later time point. The gap was 10–12 weeks for the 6-year-old sample and 2 years for the developmental sample. Test–retest for the developmental sample was $r = 0.69$ and $r = 0.72$ for the 6-year-old sample. This excluded the possible confounding occurring if the 6-year-old sample had a less reliable testing score.

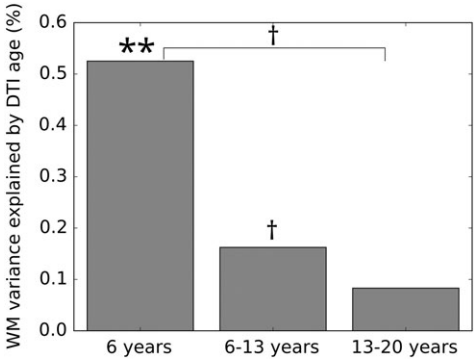

Figure 4. Proportion of stable WM variance explained by the variability in developmental patterns at different ages. **P < 0.01; †P < 0.1.

Discussion

On an individual level, most developmental processes show variability in timing. This is evident for early milestones in motor and cognitive development as well as later physical development and pubertal onset. The biological development of the brain is not exempt from this variability. However, it has not been clear to what extent this variability in anatomical development bear relevance for healthy cognitive development and performance in school. In this study, we capture the developmental level by training a DTI-derived multivariate model on a developmental sample of children and then apply it to a sample of children at school entry. The results show that the brain developmental level correlated with both WM and NA at the age of school entry. This was in contrast to chronological age that did not correlate to these cognitive abilities. This lack of correlation is explained by the low variability of age in this sample relative to the sample size and is expected. We rather used the low variability of age in the sample to exclude the variability in cognitive function related to age without having to correct for confounding effects. As the correlation between age and WM depends to a large degree on the age range, the results may not be generalized outside the range studied here. The variability in chronological DTI pattern explained 25% of the variability in WM capacity. This number can be seen in relation to the 48% explained variance when the WM test is readministered after 10–12 weeks. Our results thus indicate that 52% of the stable variance in WM in 6 year olds is explained by individual variability in developmental level. Furthermore, this effect of developmental timing appears to decrease up until adolescence, as would be expected when children get closer to the asymptote of their developmental curves. It is in line with the decrease in variability during childhood seen in behavioral studies (Roalf et al. 2014).

To illustrate that the correlates of chronological development and WM function were similar, we analyzed the spatial overlap of univariate correlation maps at various thresholds (Fig. 3). This

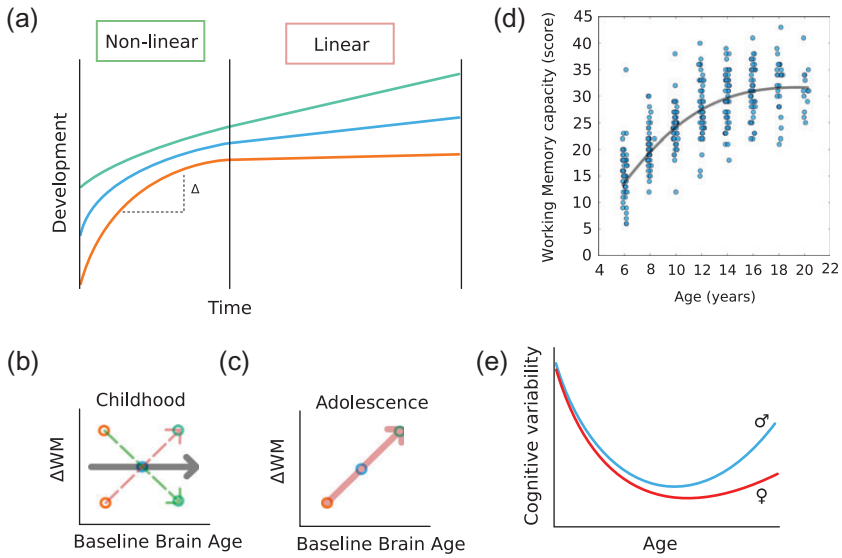

Figure 5. Illustration of the interpretation of the results. (*a*) Nonlinear and linear models of WM development will lead to correlations in opposite directions when predicting future WM change from concurrent WM. (*b*) A nonlinear model where some children are delayed in their development will results in an inverse correlation. (*c*) A linear model where subjects are diverging due to cumulative environmental stimuli will result in a positive correlation. (*d*) Scatter plot of the development of WM, $n = 323$ from a normal sample (see Söderqvist et al.). In early development, these 2 models will be mixed, thus canceling each other out. In later development when the nonlinear development largely has leveled of linear change leads to predictability of future change from current brain age. (*e*) This linear change is also illustrated by an increased cognitive variability in later development (adapted from Roalfs et al. 2014).

strategy was chosen due to the ease of interpretation of the results. The results showed a significant anatomical overlap, confirming the results from the multivariate analysis.

White matter development measured with DTI has been intensively studied in relationship with cognitive development (Olesen et al. 2003; Schmithorst et al. 2005). This study offers an important link between this knowledge base and the pattern of cognitive development seen in large pediatric studies. The results support the hypothesis that variability of cognitive function can be divided into a brain-maturation related and unrelated part. While the maturation-related variance is proportionally large in the early childhood, the variability in the adolescent population is however less related to the degree of chronological development. FA, used in the study, measures the white matter microstructure. This includes but is not limited to myelination (Beaulieu 2009; Sepehrband et al. 2015). Given the protracted course of myelination of the human brain, it is plausible that the observed effects can be attributed to myelination. However, other axonal changes cannot be excluded.

The finding that white matter brain development correlates stronger with WM at school entry than chronological age bears relevance from a societal point of view. School entry is for the largest part based on chronological age. However, if biomarkers of brain development correlates stronger than chronological age with core cognitive abilities such as WM and mathematics, this may offer a possible utility for school readiness assessment, supporting cognitive testing. The study is particularly interesting in connection with the studies showing higher risk of ADHD diagnosis and stimulant medication for children youngest in class at school entry (Goodman et al. 2003; Zoega et al. 2012). A report from the Swedish Social Insurance Agency has also recently shown that individuals born late in the year consume a higher amount of social insurance money and have an increased risk of early retirement due to behavioral disorders debuting in childhood (Goine et al. 2016). This shows that starting school too early may lead behavioral problems that persist long after the maturational lags would have disappeared. We hypothesize that the DTI Brain Age from this study would correlate even stronger than chronological age with the risk of school problems and neurodevelopmental diagnoses as it taps on the individual variability in biological development.

Recently, there has been an increased interest in using neuroimaging for predictive purposes (Dumontheil et al. 2012; Gaser et al. 2013; Ullman et al. 2014; Gabrieli et al. 2015). The current results may also help providing predictions by grouping low-performing children based on their MRI-derived biological developmental level. Children with a low performance due to a developmental lag would have a good prognosis if they are allowed to catch up with their peers, possibly through a delayed school start. However, children where low performance is accompanied by a normal level of MRI development would be predicted to have a higher risk of persistent low performance in adolescence as the low performance is not due to a lag in development. In this study, this prediction was not significant. This is probably due to the high correlation between the Brain Age and future cognitive development that works in the opposite direction and thus cancels this effect out (Fig. 5*b*). Further studies must aim to separate the developmental lag from the slope of the individual developmental curves.

A limitation of this study is the anatomical specificity of development. Due to our aim of quantifying the degree of general white matter development, we reduced all different white matter regions to only one dependent variable in our multivariate model. The developmental curves for different regions may differ so that individuals may have a developmental lag in specific white matter tracts subserving anatomically localized functions. Thus, for applying this study on delays in regionally defined cognitive modalities such as language, one should consider more anatomically restricted models. Furthermore, within developmental cognitive neuroscience, longitudinal analysis may reveal relationships between neuroimaging and cognition that may otherwise be hard to find (Shaw et al. 2006; Yeatman et al. 2012). In this study, however we could only use longitudinal data when predicting the cognitive development based on brain age as no longitudinal neuroimaging data was available for the 6-year-old sample.

In summary, this study shows that a significant and practically important portion of WM and NAs in children at the age of school entry was explained by a pattern of white matter immaturity. This immaturity effect decreased with age and was not significant in adolescents. These results illustrates that children with cognitive difficulties at school entry should be viewed as a diverse group, and that their difficulties may or may not be caused by a late but normal brain development.

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Notes

Conflict of Interest: None declared.

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