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Quantitative *in vivo* evidence for broad regional gradients in the timing of white matter maturation during adolescence

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Abstract

A fundamental tenet in the field of developmental neuroscience is that brain maturation generally proceeds from posterior/inferior to anterior/superior. This pattern is thought to underlie the similar timing of cognitive development in related domains, with the dorsal frontal cortices – important for decision making and cognitive control – the last to fully mature. While this caudal to rostral wave of structural development was first qualitatively described for white matter in classical postmortem studies, and has been discussed frequently in the developmental neuroimaging literature and in the popular press, it has *never* been formally demonstrated continuously and quantitatively across the whole brain with magnetic resonance imaging (MRI). Here we use diffusion imaging to map developmental changes in the white matter in 32 typically-developing individuals age 5-28 years. We then employ a novel meta-statistic that is sensitive to the timing of this developmental trajectory, and use this integrated strategy to both confirm these long-postulated broad regional gradients in the timing of white matter maturation *in vivo*, and demonstrate a surprisingly smooth transition in the timing of white matter maturational peaks along a caudal-rostral arc in this cross-sectional sample. These results provide further support for the notion of continued plasticity in these regions well into adulthood, and may provide a new approach for the investigation of neurodevelopmental disorders that could alter the timing of this typical developmental sequence.

Keywords

White matter; myelin; diffusion; DTI; development; gradient

1. Introduction

Much of the current understanding of white matter development has evolved from the seminal work of the pioneering neuroanatomists who first mapped the regional histology of the brain in postmortem samples. Influential observations during the 1960s demonstrated that myelination, while beginning in the second trimester of pregnancy, continues prominently into

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adulthood through the second and third decades of life – and perhaps beyond (Yakovlev and Lecours, 1967). Moreover, these data extended much earlier observations of regional variations in myelination (Kemper, 1994) and contributed to the wider maxim that brain development generally proceeds along a caudal-rostral arc. Thus, it would appear that myelination within the white matter proceeds in tune with the development of overlying gray matter (Giedd et al., 1999; Gogtay et al., 2004; Huttenlocher, 1990) and the overall emergence of brain function (Spear, 2000) – with more posterior/inferior areas underlying earlier-emerging sensory functions myelinating earlier, and more anterior/superior areas mediating later-emerging higher order executive processes myelinating later.

More recently, MRI has allowed these phenomena to be investigated *in vivo*. In particular, diffusion tensor imaging (DTI) enables measurement of the diffusion properties of water within the brain, which are affected by constraints placed by the neuronal microenvironment (Le Bihan, 2003; Mori and Zhang, 2006). Fractional anisotropy (FA), a measure of diffusion directionality summarizing individual diffusion components along the axial and radial directions (AD and RD, respectively), has been shown to be sensitive to myelination, and so has received significant attention as 1) a metric to track the developmental maturation of white matter (Lebel et al., 2008), 2) a means of mapping normal white matter connectivity (Behrens et al., 2003), 3) a possible imaging biomarker in disease (Sowell et al., 2008; Versace et al., 2008), and 4) a way to investigate the relationship between white matter structure and cognitive function (Bengtsson et al., 2005; Scholz et al., 2009; Tuch et al., 2005). The developmental trajectory of white matter, in general, has been shown to be a complex temporally and regionally dynamic function of age (Hsu et al., 2010; Lebel et al., 2008; Mukherjee et al., 2001). Extended postnatal myelination contributes to a period of increasing FA through greater insulation of the intracellular environment, a more restricted extracellular milieu, and overall reduced diffusion. As the period of rapid developmental maturation plateaus during adulthood, so too does FA. Accordingly, this nonlinear trajectory has been modeled as an exponential rise (Lebel et al., 2008; Mukherjee et al., 2001), but has also been approximated through young adulthood by polynomial models that integrate well with established whole-brain general linear modeling (GLM) packages (Hsu et al., 2010) (Fig. 1).

Previous developmental DTI reports that have binned different age groups (*i.e.* child, adolescent, adult) have shown that changes in diffusion parameters are generally concentrated in more posterior occipital regions during the transition between earlier age groups, and in more frontal regions later in development (Asato et al., 2010; Nomura et al., 1994). Similarly, when developmental changes in diffusion parameters have been analyzed with age as a continuous variable, frontal regions-of-interest (ROIs) generally show later timing than other brain regions (Lebel et al., 2008; Mukherjee et al., 2001; Tamnes et al., 2010). Nevertheless, these previous observations of patterns in developmental timing have generally been qualitative in nature – either noted through visual inspection of voxelwise or surface-based statistical maps, or individual pairwise comparisons between binned tract or volume ROIs. Despite the nuanced details about white matter development that have emerged using these strategies, the simplest classical hypothesis – that maturation proceeds in a posterior-to-anterior and inferior-to-superior fashion – remains largely untested in this context.

In the present article, we demonstrate this broad pattern of white matter maturation, as indexed by FA, in the most general sense in a continuous and *quantitative* fashion across the whole brain. To do so, we introduce a novel “developmental timing quotient” that is sensitive to the nonlinear timing of white matter development and fits within a simple GLM framework. While all areas of the brain will eventually reach some sort of developmental peak or plateau, perhaps the majority of regions even within our age window, we reasoned that one could harness the assumed finite power to detect this plateau – usually a limitation of standard analyses – in a useful metric that is sensitive to developmental timing. By doing so, we were able to observe

broad gradients in developmental timing within the white matter along posterior-to-anterior and inferior-to-superior axes, and quantify these gradients in a continuous fashion across the brain.

2. Material and Methods

2.1. Participants

32 healthy participants (age 5-28 years, mean 14.4 ± 7.2 years (standard deviation, SD), 16 females, 16 males) were recruited in response to advertisements and word-of-mouth. Exclusion criteria included: 1) Known exposure to alcohol or drugs of abuse; 2) age younger than 5 years; 3) IQ less than 70; 4) head injury with loss of consciousness over 20 minutes; 5) physical (e.g. hemiparesis), psychiatric illness, or developmental disability (e.g. autism) that would preclude participation; 6) other potential known causes of mental deficiency (e.g. chromosomal disorders); 7) significant maternal illness with increased risk for fetal hypoxia (e.g. sickle cell disease); and 8) presence of implanted metal in the body. After a thorough discussion of the study protocol, participant consent (or for age < 18, parent/guardian consent and participant assent) was obtained in accordance with procedures approved by the UCLA Institutional Review Board.

2.2. DTI acquisition and processing

Whole-brain diffusion-weighted imaging data were acquired on a 1.5 Tesla Siemens Sonata MRI scanner. Three sets of whole-brain data were acquired for each subject, with each set including diffusion weighted volumes (6 directions, $b=1000$ s/mm², 50 axial slices, $3 \times 3 \times 3$ mm³ isotropic voxels) and one non-diffusion-weighted volume ($b=0$ s/mm²). Brain volumes were skull stripped with the Brain Extraction Tool (BET) (Smith, 2002) and a 12 parameter affine registration to the first $b=0$ volume was applied to correct for minor head motion and eddy current distortions introduced by the gradient coils. A diffusion tensor model was fitted to the data in a voxelwise fashion to generate whole-brain maps of fractional anisotropy (FA; the directionality of the diffusion). DTI preprocessing was performed using the FMRIB Software Library (FSL) 4.1.0 analysis suite (<http://www.fmrib.ox.ac.uk/fsl>) (Smith et al., 2004; Woolrich et al., 2009), and automated within the UCLA LONI Pipeline 4.2.1 processing environment (<http://pipeline.loni.ucla.edu>) (Rex et al., 2003).

Tract-based Spatial Statistics (TBSS; <http://fsl.fmrib.ox.ac.uk/fsl/tbss>) was then used to investigate the regional dynamics of age-related maturational changes in this white matter parameter (Smith et al., 2006). First, B-spline based nonlinear registration was performed between all subjects' FA maps and the FMRIB58 58-subject average FA template using the FSL Nonlinear Image Registration Tool (FNIRT). In turn, this FA template was registered to the ICBM152 1mm standard T1-weighted template using an affine transformation, and all study subjects were brought through this concatenated spatial normalization and up-sampling interpolation process into MNI152 standard space. A study-specific mean FA image was generated in standard space, and skeletonised into a tract-based template at an FA threshold of 0.2. Each subject's registered FA map was then projected onto this skeleton for voxelwise statistical inference.

2.3. Statistical analysis

White matter maturation was first modeled as a curvilinear trajectory along this tract-based skeleton template using standard voxelwise GLM tools. Age-related changes in FA were determined in FSL by including age and age² as predictors in a whole-brain GLM. One-way *t*-statistic maps (testing for direct and inverse relationships with the age and age² terms) were generated for the strengths of the corresponding regression coefficients, and threshold-free cluster enhancement (TFCE) was performed to up-weight cluster-like features in the data by

incorporating neighborhood information around each voxel (Smith and Nichols, 2009). Nonparametric permutation testing was used to empirically determine the null distribution of the maximum test statistic across space (*i.e.* across the entire TBSS tract skeleton), control the family-wise error (FWE) rate, and generate empiric *p*-values fully corrected for multiple comparisons (Nichols and Holmes, 2002).

A novel, yet simple, “developmental timing quotient” was then introduced using these whole-skeleton *p*-value maps of the significance of the regression coefficients: For a given arbitrary region-of-interest (in the present case, a single axial or coronal slice through the tract skeleton) this metric is equal to the fraction of voxels that have a significant ($p < 0.05$, corrected) linear (*i.e.* age) regression coefficient that *additionally* have a significant quadratic (*i.e.* age²) regression coefficient. This quotient was calculated for each axial slice along the inferior-superior (IS) axis, and each coronal slice along the posterior-anterior (PA) axis. Using the slice views in Fig. 2a,b as an example (see also Supplemental Movie online), this would be the number of red/yellow voxels divided by the number of underlying blue voxels in each slice. Intuitively, this can be thought of as similar to “the fraction of the volume that is still showing any age-related increase in FA in our age window, which is nearing its developmental plateau in the neighborhood of our age window.” For areas that are developing earlier, a greater proportion of the voxels will exhibit this nonlinear component (*i.e.* will have a significant age² term) as they near their developmental plateau, and this timing quotient will be closer to unity. Conversely, areas that are developing later will have a timing quotient closer to zero, as white matter development continues beyond the age range studied and fewer voxels exhibit a significant bending towards a plateau. As such, this metric is sensitive to the nonlinear timing parameter of interest, and yet fits easily within a simpler linear modeling framework. Importantly, this method assumes that, on average, we have less power to detect nonlinear changes (*i.e.* a significant age² term) in regions that plateau later. We therefore expect fewer significant voxels for the quadratic model term that accounts for this effect in the regions of the brain that plateau later, and ultimately a lower developmental timing quotient. The extreme aspects of the tract skeleton were cropped to only include slices with 100 or more skeleton voxels, as the timing quotient becomes unstable near the extreme edges of the brain where the denominator approaches zero. Finally, weighted least squares linear regression was used to investigate how the developmental timing quotient is related to position in the brain along the IS and PA axes, with the number of voxels in each slice (which is inversely related to the expected variance in the timing quotient) used as the weighting function.

3. Results

As predicted, voxelwise modeling along the tract-based skeleton demonstrated widespread age-related increases in FA in our 32 subject cross-sectional sample ($p < 0.05$, corrected). Further, many of these regions where the age regressor was significant also demonstrated a significant negative age² term ($p < 0.05$), indicating a quadratic-type nonlinear relationship in these regions over our age range. No voxels were observed with a significant inverse relationship between age and FA or a significant positive age² term. See slice views in Fig. 2a,b and also the Supplemental Movie online for a full collection of these raw first-level statistical maps.

When the individual diffusion components along the axial and radial directions were analyzed (AD and RD), which together contribute to the FA measure, widespread significant decreases in RD were observed with similar regional and inverse temporal dynamics compared to FA (*i.e.* a significant negative age term and a significant positive age² term were observed; $p < 0.05$, corrected) (See Fig. 3a,b). No voxels were observed with significant increases in RD or changes in AD.

By implementing the developmental timing quotient meta-statistic in a slice-wise fashion, we were able to collapse whole-brain three-dimensional statistical maps down into one-dimensional high-level summary views along the inferior-to-superior (Fig. 4a) and posterior-to-anterior axes (Fig. 4b). As long-expected, prominent gradients in the developmental timing of white matter maturation, as measured by FA, were observed and quantified in both the inferior-to-superior ($R^2=0.74$, $b=-0.00614$, $t=-18.36$, $p=1.61e-36$, $n=121$ axial slices) and posterior-to-anterior directions ($R^2=0.54$, $b=-0.00456$, $t=-13.35$, $p=2.69e-27$, $n=152$ coronal slices). Our results show a dramatic reduction in the volume of voxels that reach their developmental peak in the most anterior and superior regions of the brain, compared to the more posterior and inferior regions, suggesting continued white matter maturation beyond the age range studied here in dorsal frontal brain regions. This general pattern remained unchanged during a *post hoc* analysis that excluded the cerebellum.

4. Discussion

The observed trends in the developmental timing quotient across the brain provide strong support to the long-held hypothesis that white matter maturation proceeds in an inferior-to-superior and posterior-to-anterior manner, and provide a straightforward confirmation of this fundamental phenomenon in developmental neuroscience. In particular, the results agree with the classical postmortem literature (Kemper, 1994; Yakovlev and Lecours, 1967), while also providing a validation of other neuroimaging studies examining more nuanced details of brain development (Tzarouchi et al., 2009) or aging (Davis et al., 2009) in the context of this often-cited global developmental pattern – one that has not been previously demonstrated in a continuous and quantitative fashion. Importantly, this picture suggesting prolonged myelination in frontal regions also is consistent with the protracted trajectory of cognitive development in executive functioning domains, which similarly continues through adolescence and is known to involve processing in the frontal lobe (Luna et al., 2004, 2010; Romine and Reynolds, 2005). Previous observations have linked both DTI-measured connectivity (Liston et al., 2006; Madsen et al., 2010) and fMRI-measured activation patterns (Bunge et al., 2002; Casey et al., 1995, 2005; Luna et al., 2001) with performance on cognitive control tasks across this age range, strongly implicating these systems as part of the neural basis for real-world changes seen during adolescence in areas like risk/reward processing (Chau et al., 2004; Olson et al., 2009; Spear, 2000), and also as a potential contributing factor to neurodevelopmental disorders like ADHD (Casey et al., 2007) and neuropsychiatric illnesses that often begin to emerge during adolescence (Reichenberg et al., 2010; Versace et al., 2008). The implications of this new approach are particularly valuable as they relate to the period of adolescent brain development. Because this technique extracts regional developmental timing information in a *continuous* manner and *across* an age window, it may prove useful to investigators as an attractive means of probing developmental delays and other clinical phenomena that appear during adolescence. For instance, the slope of the developmental timing gradient across an entire region and the entire age window could be compared between groups, as a complementary method to traditional examination of a series of regions-of-interest between several binned age groups in a pairwise manner. In particular, processing speed is an attractive target for further study, as it shares an intuitive foundation in connectivity, and has been shown to exhibit some of the strongest advances during adolescence (Anderson et al., 2001). This may be related, in part, to concomitant prolonged myelination in the white matter through an advancing structural network and increasing transmission efficiency. Further, recent evidence demonstrating *slower* advances in processing speed in children preceding adult schizophrenia makes the quantified regional timing of white matter development discussed in this report a particularly attractive metric that may also be slowed in these individuals (Reichenberg et al., 2010). These core developmental gradients could also be investigated more closely as quantifiable imaging biomarkers in the context of typical development. It is possible that, like similar unexpected findings in gray matter (Shaw et al., 2006), a higher-order timing parameter

like the one described may explain individual variance in performance better than the raw diffusion imaging parameters at any one point in time.

Although not the primary focus of the present investigation, first-level voxelwise results are in general agreement with the published literature documenting broadly distributed increases in FA during development (Fig. 2, Fig. 3a) (Lebel et al., 2008; Mukherjee et al., 2001; Qiu et al., 2008; Snook et al., 2005). Analysis of the underlying axial and radial diffusion components suggests that decreasing RD is the dominant contributor to the observed changes in FA (Fig. 3b), although subthreshold contributions by changes in axial diffusivity are also likely. A similar pattern of decreasing diffusivity, driven predominantly by decreasing RD, is reported in the majority of developmental DTI studies (Schmithorst and Yuan, 2010).

One of the most interesting aspects of the quantified gradients demonstrated here is the smoothness with which the developmental timing of white matter maturation changes across the brain – particularly along the inferior-to-superior axis (Fig. 4a). The similarity of the developmental timing gradients between the inferior-to-superior and posterior-to-anterior axes is also compelling. While not totally unexpected, since the trajectories along the PA and IS axes will naturally be somewhat correlated because more inferior regions of the brain also contain more posterior voxels, this coordination is also consistent with the notion of a continuous caudal-rostral wave in the timing of white matter maturation. For both trajectories, the timing quotient begins near 0.8 and then decreases robustly, but smoothly and with similar slope, to below 0.4. In fact, the only regional locus that may not warrant inclusion in this continuum model is the occipital lobe (Fig. 4b), which exhibits an unexpected drop in the timing quotient. This could be due, in part, to the unstable nature of the timing quotient as one moves to the extreme edges of the brain and the number of skeleton voxels approaches zero. To accommodate this behavior in the statistical analysis, we chose to apply a weighted least-squares fit to the data, which down-weights these unstable slices with very few voxels. However, upon closer inspection, some of these slices through the occipital lobe actually have enough voxels that we would expect the timing quotient estimates to be reliable (*i.e.* they are above the *ad hoc* 100 voxel threshold, below which the timing quotient can oscillate unstably). Accordingly, this area in particular warrants future examination to determine to what extent this effect is real.

While this is the first time that these broad gradients in developmental timing have been quantified continuously across the white matter, these results are in agreement with the strong tradition of qualitative DTI observations that have previously been made on this topic – particularly concerning the more focused notion that frontal lobe white matter connectivity tends to have the longest course of development, relative to other regions (See Schmithorst and Yuan, 2010 for an excellent review of this developmental DTI literature). When diffusion parameters have been compared between two (or several) binned age groups, the magnitude of the change in these metrics between age groups tends to be greater in frontal regions, especially when using contrasts that span older age ranges – suggesting that frontal regions are undergoing a larger portion of their maturation at later ages, as compared to more posterior regions (Nomura et al., 1994; Qiu et al., 2008; Snook et al., 2005). Similarly, when the timing parameters of exponential models have been compared across ages within binned regional ROIs, frontal regions tend to have a slower rise (*i.e.* a later time-to-plateau) than more posterior regions (Lebel et al., 2008; Schneider et al., 2004). Our results reported here provide further evidence in support of the presence of a particularly extended developmental trajectory in the frontal lobe, and additionally help extend this notion to suggest a relatively smooth gradient transition in timing from more posterior/inferior regions.

Another key aspect of the present report is the introduction of the simple developmental timing quotient meta-statistic that was used to demonstrate these findings. This metric can be readily

computed from the statistical maps generated by standard GLM analyses, and gives insight into the timing of the developmental trajectory in a given ROI (in this case, a specific slice). Previously, in order for timing phenomena to be investigated, a time constant parameter would need to be modeled directly, which requires a nonlinear model – like the exponential function described in Fig. 1 – to be fitted in a voxelwise fashion. This comes at a considerable computational cost, and additionally introduces the practical challenge of being incompatible with the major voxelwise modeling packages in the neuroimaging community. These difficulties perhaps explain why the important fundamental notion of a broad caudal-rostral wave of brain maturation, which has been qualitatively and anecdotally referenced quite often, has until now never been directly demonstrated and quantified with MRI. Importantly, however, one must remain aware that the design presented here offers an *indirect* window into the timing properties of this system. As one consequence, the ability to demonstrate these timing gradients could be affected, for example, if the power to detect individual voxelwise relationships in the first-level GLM analysis was increased to the point that a significant quadratic age² term could be demonstrated *everywhere* in the brain. In this case, the timing quotient would saturate and the gradients would be obscured, or perhaps only observable with different first-level significant thresholds. Likewise, if the age window were altered to be older, then the number of regions showing any developmental increases in FA would start to decrease as they complete their plateau. Therefore it is important that the study sample and significance thresholds are tuned to the question of interest.

Although it might be assumed that close to all of the voxels in the brain are exhibiting some form of real neurobiological development over the age range from childhood to adulthood, we were only able to demonstrate significant FA-indexed “development” in a subset of these voxels (those with a significant age term, displayed as the extent of underlying blue voxels in Fig. 2). There are several explanations for this, any or all of which could be contributing, including: 1) The voxels have already “matured” in terms of their developmental changes in FA, 2) The voxels are maturing slowly enough that they not only fail to show a significant quadratic age² term, but additionally fail to show a significant linear age term, 3) There is finite power to detect developmental changes (e.g. due to acquisition SNR, intersubject variation, misregistration, etc.), even for structures that *are* developing over our age range, 4) Methodological issues are involved – for instance, those associated with the tensor model of diffusion like partial volume averaging within voxels that contain multiple fiber populations, and 5) Although we failed to demonstrate this anywhere in the brain, some voxels may actually exhibit *decreasing* FA during development (Schmithorst et al., 2008). Other methodological limitations should also be considered when interpreting these results. Although data interpolation is a standard component of the TBSS processing pipeline, it can affect the apparent resolution when visually interpreting the resulting statistical maps. In the present case, this means that the effective resolution across the developmental gradients is likely to be much coarser than the 1mm thick slices on which the data were processed. Additionally, while the observed trends in developmental timing quotient are expected to be relatively robust to intersubject variation in raw diffusion MRI parameters – as the developmental timing quotient effectively averages out some of this variation – it should be noted that this sample is relatively sparse during the age range of late adolescence. Increasing the number of subjects studied, especially during this period, should increase power to detect both voxelwise and timing quotient changes, and improve confidence in the shape of the underlying developmental trajectory.

5. Conclusions

In summary, we have employed a simple quantitative approach using diffusion imaging data in a developmental sample which 1) provides confirmation, in a continuous and quantitative manner across the whole brain, that broad regional gradients are present in the developmental

timing of white matter maturation, 2) introduces a novel meta-statistic that is sensitive to the developmental timing of white matter maturation in our study population and fits within the established GLM framework of whole-brain mapping strategies, and 3) presents a new opportunity for the investigation of the structural basis of advances in executive function during adolescence and their relationship to the emergence of neuropsychiatric disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

White matter developmental trajectory example: White matter development, as indexed by FA, deviates from linearity (black line) during adolescence and young adulthood. This has been approximated as a quadratic relationship over this age range (red, dashed), although an exponential fit may be more biologically appropriate because of its stable plateau (blue, dotted). Displayed FA values are taken as the subjects' means from a representative example region in the left corticospinal tract.

Figure 2.

TBSS voxelwise results: Statistical maps of the significance of the age (blue-aqua, $p < 0.05$, corrected) and age² (red-yellow, $p < 0.05$, corrected) regressors, from the first-level tract-based spatial statistics (TBSS) analysis of age-related changes in fractional anisotropy (FA), are overlaid on the white matter tract skeleton (green) and the study-specific mean FA template volume. Axial (a) and coronal (b) slices are displayed in 10 mm increments. The complete collection of slices is available as a Supplemental Movie online.

Figure 3.

FA, AD, and RD changes by region: (a) Developmental trajectory curves for FA are shown from a representative “inferior” ROI in the corticospinal tract that was classified as quadratic (colored red to match the red/yellow quadratic voxels in Fig. 2), and a “superior” ROI in the cingulum that was still increasing linearly (colored blue to match the blue linear voxels in Fig. 2). (b) The axial diffusivity (AD) and radial diffusivity (RD) components are displayed for the same regions, demonstrating the general pattern that the observed FA changes are predominantly due to changes in RD. Trendlines are selectively added according to which terms of the model (age or age+age²) are significant ($p<0.05$, corrected) in the FA, RD, and AD voxelwise analyses.

Figure 4.

Gradients in white matter developmental timing: White matter development takes place along inferior-to-superior (a) and posterior-to-anterior (b) gradients. The developmental timing quotient is plotted against slice index (mm), and the weighted least squares linear regression line ($\pm 95\%$ pointwise confidence interval) is overlaid. The number of white matter tract voxels in each slice was used as the weighting function, and is plotted on the right y-axis. Slice overlays show representative examples of the statistical maps used to calculate the timing quotient (blue-aqua, age term ($p < 0.05$); red-yellow, age² term ($p < 0.05$); green, white matter tract skeleton). I, inferior; S, superior; P, posterior; A, anterior; PC, posterior commissure; AC, anterior commissure.