Development of Superficial White Matter and Its Structural Interplay With Cortical Gray Matter in Children and Adolescents

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Abstract: Healthy human brain undergoes significant changes during development. The developmental trajectory of superficial white matter (SWM) is less understood relative to cortical gray matter (GM) and deep white matter. In this study, a multimodal imaging strategy was applied to vertexwise map SWM microstructure and cortical thickness to characterize their developmental pattern and elucidate SWM-GM associations in children and adolescents. Microscopic changes in SWM were evaluated with water diffusion parameters including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in 133 healthy subjects aged 10–18 years. Results demonstrated distinct maturational patterns in SWM and GM. SWM showed increasing FA and decreasing MD and RD underneath bilateral motor sensory cortices and superior temporal auditory cortex, suggesting increasing myelination. A second developmental pattern in SWM was increasing FA and AD in bilateral orbitofrontal regions and insula, suggesting improved axonal coherence. These SWM patterns diverge from the more widespread GM maturation, suggesting that cortical thickness changes in adolescence are not explained by the encroachment of SWM myelin into the GM-WM boundary. Interestingly, age-independent intrinsic association between SWM and cortical GM seems to follow functional organization of polymodal and unimodal brain regions. Unimodal sensory areas showed positive correlation between GM thickness and FA whereas polymodal regions showed negative correlation. Axonal coherence and differences in interstitial neuron composition between unimodal and polymodal regions may account for these SWM-GM association patterns. Intrinsic SWM-GM relationships unveiled by neuroimaging in vivo can be useful for examining psychiatric disorders with known WM/GM disturbances. *Hum Brain Mapp* 35:2806–2816, 2014. © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

Superficial white matter (SWM) consists of primarily short cortical association fibers, referred to as u-fibers of Meynert [1872], which connect adjacent gyri and make up the majority of corticocortical white matter (WM) [Schuz and Braitenberg, 2002]. Despite the significant role of corticocortical connections in supporting information processing and integration, there is limited knowledge regarding the normal developmental trajectory of SWM. While brain organization is more adaptable in earlier years, it is also more vulnerable to insults. Understanding the developmental deviations of SWM could inform origins and bases of neuropsychiatric disorders that potentially surface in childhood and adolescence [Phillips et al., 2011]. Most of previous neuroimaging studies focused on the maturation of gray matter (GM) and deep WM, while only a few studies have explored the maturation of SWM microstructure from childhood to young adulthood [Lebel et al., 2008b; Snook et al., 2005; Tamnes et al., 2010]. Therefore, the development of SWM microstructure in children and adolescents is less characterized, and the complex interplay between cortical GM and SWM is particularly poorly understood and needs systematic investigation.

Previous neuroimaging studies have provided valuable insights into the development of GM and WM in children and adolescents. In particular, cortical GM volume shows regionally specific inverted U-shaped developmental trajectories, with an initial increase in early childhood followed by post-adolescent decrease [Giedd, 2004; Giedd et al., 1999; Gogtay et al., 2004; Lenroot and Giedd, 2006]. Cortical thickness shows a linear or nonlinear decline with age [Muftuler et al., 2011; O'Donnell et al., 2005; Ostby et al., 2009; Shaw et al., 2006] and its development aligns closely with established architectonic maps [Gogtay et al., 2004; Shaw et al., 2008]. WM volume and density show generally linear increase with age during childhood and adolescence [Giedd et al., 1999; Lebel and Beaulieu, 2011; Lenroot and Giedd, 2006; Paus et al., 1999; Sowell et al., 2002]. With the advent of diffusion tensor imaging (DTI), it is possible to noninvasively probe the integrity of WM at a microscopic level. Using DTI, the microstructures of deep WM tracts appear to follow a linear maturation pattern from childhood to adolescence (6–17 years) [Eluvathingal et al., 2007] and during adolescence (13.5–21 years) [Giorgio et al., 2008]. These tracts likely show nonlinear changes when extended to adulthood with a broader age range (5–30 years) [Lebel and Beaulieu, 2011; Lebel et al., 2008b] or through entire life span [Kochunov et al., 2011].

DTI methods such as tract based spatial statistics [Smith et al., 2006] and tractography-based methods [Jiang et al., 2006; Wang et al., 2007; Yendiki et al., 2011] are appropriate for examining deep WM tracts, but are not suitable to study SWM due to lack of major tracts and greater inter-subject variations in SWM. Therefore region of interest (ROI) based method using manual tracing [Lebel et al., 2008b; Snook et al., 2005] or automated parcellation [Fjell

et al., 2008; Oishi et al., 2008; Salat et al., 2009; Walimuni and Hasan, 2011] were developed to examine regional SWM. During childhood and adolescence, the left and right SWM show increased average fractional anisotropy (FA), which continues into adulthood [Ben Bashat et al., 2005]. Using a manual tracing method, the microstructural development of five SWM regions—right superior frontal gyrus, right supramarginal gyrus, right middle occipital gyrus, left superior temporal gyrus, and left postcentral gyrus—showed nonlinear increase in FA and decrease in mean diffusivity (MD) with age (5–30 years) [Lebel et al., 2008b]. The same five SWM regions showed linear changes when examined in narrower age ranges in children (8–12 years) and in young adults (21–27 years) respectively [Snook et al., 2005]. Tamnes and colleagues used an automated WM parcellation approach to divide SWM into 33 different gyral-based areas covering the entire cortical mantle. Both linear and quadratic effects of age on SWM diffusion parameters were observed, but with significant regional variations during the age range of 8–30 years [Tamnes et al., 2010]. Furthermore, they reported regional correlations between cortical thickness and WM DTI measures across the brain from childhood to adulthood. Whole-brain FA and GM thickness were also linearly correlated through life span [Kochunov et al., 2011]. Although providing valuable insights into SWM maturation, the ROI-based methods have limitations such as lack of fine spatial details in subregions of large ROIs. Additionally, manual tracing of ROI is labor intensive and is subject to operator errors.

In this study, we applied a novel multi-modal imaging approach, vertex-based surface statistics (VBSS), to map automatically individual SWM DTI measures into a common surface space. With the coregistration of T1-weighted (T1w) image and DTI data, SWM DTI measures are sampled from the WM immediately below the cortex, averaged and projected onto the T1w WM surface, which are further mapped onto a common surface for across-subject comparison, via cortical transformation of the T1w images with a cortical folding pattern matching algorithm [Dale et al., 1999; Fischl et al., 1999a,b]. Compared with ROI-based approaches, VBSS can detect subtle SWM changes at finer spatial scale and avoid operator bias. Using VBSS, we mapped the development of SWM in children and adolescents from 10 to 18 years of age and compared SWM and cortical GM maturation patterns in the same sample to explore the complex interplay between SWM and cortical GM in children and adolescents.

In contrast to GM maturation, WM shows protracted maturation through the life span. Particularly, SWM fibers are the slowest fibers to myelinate within the nervous system and myelination may extend into the fourth decade of life [Barkovich, 2000; Maricich et al., 2007; Reiser et al., 2008]. Therefore we hypothesize that during childhood and adolescence, SWM maturation will be observable and substantially differ from the maturation pattern of GM. Meanwhile, with GM generating neural signal and WM enabling neural

communication, GM and WM collaborate to support smooth information processing with functional specialization and integration. Therefore, we hypothesize that there will be intrinsic relationship between cortical GM and SWM structural properties, and that different patterns of GM-SWM relationship may reflect divergent brain functional demands.

MATERIALS AND METHODS

Subjects

The sample consisted of 133 healthy children and adolescents with a mean age of 14.29 ± 2.24 years, of whom 79 were females, and 124 were right-handed [Annett, 1970]. The sample had a mean intelligence quotient (IQ) of 112.3 ± 14.07 [Wechsler, 1999], mean Tanner's stage at 3.67 ± 0.99 [Tanner, 1962], and mean childhood socioeconomic status (SES) at 2.91 ± 1.29 . Exclusionary criteria included: history of head trauma, neurological, or psychiatric disorders, currently medicated, or history of psychiatric illness in first-degree relatives. There was no significant difference in age between male and female participants ($p = 0.49$). There was no significant correlation between age and IQ ($p = 0.41$) or between age and SES ($p = 0.52$). The study was approved by the University of Illinois at Chicago (UIC)'s Institutional Review Board. Written informed consent was obtained from at least one parent/guardian of participants, and assent was obtained from all participants.

MR Data Acquisition

Imaging data were acquired on a 3.0 Tesla GE Signa HDx scanner (General Electric Health Care, Waukesha,

Wisconsin) using an 8-channel head coil. Participants were instructed to fixate on a central crosshair and to stay awake during image acquisition. Subject alertness and head motion were monitored in real-time using a custom-made infrared camera focusing on the eyes of the subject. Anatomic T1w images were acquired in the axial plane using a 3D FSGPR BRAVO sequence with the following parameters: TR = 11.58 ms, TE = 4.96 ms, TI = 450 ms, flip angle = 13° , FOV = 240×240 mm², matrix = 384×256 , 120 slices, slice thickness/gap = 1.5/0 mm. DTI images were acquired in the axial plane using a single-shot spin-echo echo planar imaging sequence with customized eddy current compensation capability [Zhou et al., 1999]. The sequence parameters were: TR = 5400 ms, TE = 75.3 ms, FOV = 200×200 mm², matrix = 256×256 , 20 slices, slice thickness/gap = 4/1 mm, NEX = 2, 27 noncollinear diffusion gradient directions with $b = 750$ s/mm² and one nondiffusion-weighted scan (b_0 : $b = 0$ s/mm²) [Poonawalla and Zhou, 2004].

Cortical Thickness Analysis

All MR images were processed and analyzed at the Pediatric Brain Research and Intervention (BRAIN) Center, UIC. The analysis pipeline of T1w and DTI images is summarized in Figure 1. For each subject, FreeSurfer (version 5.1.6, <https://surfer.nmr.mgh.harvard.edu/>) was used for automated cortical surface reconstruction and cortical thickness estimation on the T1w image. Additional customized manual interventions were applied to improve the surface reconstruction, when the automated processing stream failed. Individual T1w image was first linearly registered to the Talairach space [Collins et al., 1994; Talairach

Figure 1.

A summary of the analysis pipeline for T1-weighted and diffusion-weighted images. L: left; R: right.

and Tournoux, 1988]. This transformation result was visually checked and was manually reoriented and/or scaled using tkmedit (FreeSurfer) when necessary. Next, the intensity variation of WM was used to estimate the bias field from B1 inhomogeneity, and was then used for bias correction on the T1w image. Skull stripping was performed to remove the nonbrain tissue using a deformable model, and WM was segmented based on intensity and neighbor constraints. The brain mask was also visually inspected and input parameters were adjusted to fix a poor skull strip. Control points were manually added within the WM boundary to avoid erroneous WM segmentation. Next, the white surface (gray-white boundary) was generated by tiling the outside of the WM and refined by following the intensity gradient between GM and WM. The pial surface was estimated by nudging the WM surface to follow the intensity gradients between GM and CSF. Cortical thickness was calculated as the distance between the white surface and corresponding pial surface vertices. Finally, the pial surface was inflated and morphed into a sphere, and registered to an average spherical atlas based on cortical folding pattern [Dale et al., 1999; Fischl et al., 1999a,b].

SWM Analysis

DTI data were visually inspected to ensure image quality and brain coverage except for cerebellum and brainstem. Data with substantial artifacts or missing top slices were excluded from the study. During the data acquisition, a real-time motion monitoring system aided the scanner operators to alert the subject about head motion and re-scanned the protocol if necessary. Eddy current compensation was incorporated in the DTI protocol to minimize the distortion induced by eddy currents [Zhou et al., 1999]. Any residual motion effects and image distortion in the DTI images were corrected through an affine registration to the nondiffusion-weighted (b_0 : $b = 0$ s/mm²) volume. The motion parameters—translation and rotation—were extracted for each participant, which were used for further quantitative quality control. Participants with average translation > 2.5 mm or average rotation > 2° were excluded. In total, this excluded 14 participants and yielded a sample of 133 participants (translation, mean/standard deviation (SD): 1.49/0.49 mm, rotation, mean/SD: 0.48°/0.35°). The rotation parameters were applied to the gradient table (b-matrix) to correct for subject motion [Lee-mans and Jones, 2009]. Next, diffusion tensor fitting with least-squares tensor estimation was performed and eigenvalues ($\lambda_1 \geq \lambda_2 \geq \lambda_3$) were estimated. Diffusion-tensor (DT)-derived scalar measures including FA, MD, axial diffusivity (AD), and radial diffusivity (RD) were calculated for each voxel. These parameters provide complementary characterization of WM microstructural properties, and can inform myelination, axon packing density, and/or axonal coherence [Beaulieu, 2002; Song et al., 2002, 2003,

2005]. FA reflects the degree of diffusion anisotropy of the water molecules and MD represents the average water diffusion along the three eigenvector directions [Pierpaoli and Basser, 1997]. A large FA value is associated with highly organized fibrous structures, increasing axon density and/or myelination [Beaulieu, 2002] and is often used as a quantitative biomarker of WM integrity. To pinpoint the nature of FA changes, additional DTI parameters such as AD and RD were also investigated. While AD reflects parallel diffusivity along the fiber bundles, RD reflects average diffusivity in the plane perpendicular to the fiber bundles and has been associated with myelination [Song et al., 2002, 2005].

For each subject, the nondiffusion-weighted (b_0) volume in the DTI data was registered to the T1w anatomical image using a cross-modal registration with a 6-parameter rigid body transformation and a boundary-based cost function in FreeSurfer. The coregistration of the b_0 image and the T1w image was visually inspected and manually tweaked to improve poor alignment. Then, the DT-derived measures (e.g., FA) of the SWM were averaged along the WM surface normal (every 1 mm, to 5 mm distance to the WM surface) and projected onto the template WM surface via the rigid transformation ($b_0 \rightarrow$ T1w) and the cortical pattern matching information (individual T1w surface $\rightarrow$ template surface). Finally, surface-based smoothing with 10 mm FWHM Gaussian kernel was applied on the DTI scalar and cortical thickness measures.

Statistical Analysis

General linear model (GLM) analyses (mri_glmfit tool of the FreeSurfer package) were performed vertexwise to test for effect of age (controlling for gender) on cortical thickness and SWM DT-derived measures respectively. Cluster-based correction for multiple comparisons was performed using mri_glm-sim with 10000 iterations in FreeSurfer.

RESULTS

Age Effects in SWM

Fractional anisotropy

The age effects on DT-derived measures (FA, MD, AD, and RD) are shown in Figure 2. Significant increase in FA with age (adjusted for gender, Fig. 2a) was seen in the following SWM regions: frontal lobe [bilateral precentral, orbitofrontal cortex (OFC), and insula], limbic lobe (bilateral posterior cingulate), temporal lobe (bilateral superior temporal), parietal lobe (bilateral postcentral, posterior parietal), and occipital lobe (left lingual).

Mean diffusivity

As expected, the age effect on MD generally showed the opposite pattern as FA (see Fig. 2b). MD decreased significantly with age in the following SWM regions: frontal lobe

Figure 2.

Linear age effects on SWM DT-derived measures (controlled for gender). Red color reflects increase in DTI measures with age, and blue color reflects decrease in DTI measures with age. L: left hemisphere; R: right hemisphere. The gold-edge clusters survived a corrected $p < 0.01$. Two developmental patterns of

SWM microstructure were observed: (1) increasing FA and decreasing MD and RD in bilateral precentral, superior temporal, isthmus of cingulate, and precuneus areas and (2) increasing FA and AD in bilateral OFC and insula.

(bilateral precentral and superior frontal), temporal lobe (right superior temporal), parietal lobe (bilateral postcentral and right precuneus), and occipital lobe (bilateral lingual, right lateral occipital, and right cuneus). Meanwhile, significantly increased MD with age was found in left orbitofrontal SWM. To further explore, the physiological process underlying the SWM changes, AD- and RD-age maps were also generated and are shown in Figure 2c,d.

Patterns between FA and other DTI measures

Two general developmental patterns of SWM microstructure were observed. First, increasing FA and decreasing MD were accompanied by decreasing RD in bilateral precentral, superior temporal, isthmus of cingulate, and precuneus areas. Second, increasing FA was accompanied by increasing AD in bilateral OFC and insula. These two different patterns of microstructural change may correspond to varied neurophysiological substrates occurring in SWM, as discussed below. There were also regions where there was no clear correspondence between FA and other DTI measures. For example, significantly increased FA was observed in posterior parietal regions without significant changes in MD, AD, or RD.

The two patterns of SWM microstructural change were explored further via scatterplots in Figure 3. Linear correlations between DT-derived measures (FA, MD, AD, and

RD) and age (after controlling for gender) are shown in two vertices corresponding to SWM of left precentral gyrus and insula (as marked in Fig. 2a), which depict two distinct patterns of change. In left precentral SWM (Fig. 3a), there was significant increase in FA (at $b = 0.005/\text{year}$), decrease in MD (at $b = -6.84\text{E}-6 \text{ mm}^2/\text{s}/\text{year}$) and RD (at $b = -8.49\text{E}-6 \text{ mm}^2/\text{s}/\text{year}$) with age ($R^2 \geq 0.10$, $p < 0.001$), while in left insular SWM (Fig. 3b) there was significant increase in FA (at $b = 0.005/\text{year}$) and AD (at $b = 8.79\text{E}-6 \text{ mm}^2/\text{s}/\text{year}$) with age ($R^2 \geq 0.14$, $p < 0.001$).

Age Effects in Cortical Thickness

To examine the pattern of cortical GM change with age, vertexwise GLM analysis was used to study the age effect on cortical thickness after controlling for gender (Fig. 4a,b). A comprehensive view of ongoing cortical changes with age is illustrated with an uncorrected p map in Figure 4a, and with the gold-edged clusters outlining areas that survived the corrected $p < 0.001$. Significant negative correlation between cortical thickness and age was observed in distinct regions across all lobes: frontal lobe [bilateral OFC, ventrolateral prefrontal cortex, dorsolateral prefrontal cortex (DLPFC), and superior frontal regions], limbic lobe (bilateral posterior cingulate and left pregenual cingulate), temporal lobe (bilateral middle and inferior

Figure 3.

Scatterplots of DT-derived measures (FA, MD, AD, and RD) and age (controlled for gender) in two SWM regions (as marked in Fig. 2a) with distinct patterns of changes: (a) Increasing FA and decreasing MD and RD in SWM underlying the left precentral gyrus. (b) Increasing FA and AD in SWM underlying the left insula.

temporal gyri, fusiform gyri), parietal lobe (bilateral superior and inferior parietal lobules, precuneus), and occipital lobe (bilateral cuneus, lateral occipital cortices). In contrast, cortical regions associated with basic sensory and motor functions, such as primary motor cortex (precentral gyrus), somatosensory cortex (postcentral gyrus), auditory (superior temporal) and visual (pericalcarine) cortices, did not show significant change in thickness during the adolescent period. Scatterplots for the linear correlation between cortical thickness and age after controlling for gender are shown in Figure 4b, in four vertices corresponding to orbitofrontal, inferior parietal, precuneus and fusiform areas, where the local maximum occurred on the statistical map. These scatterplots show that there was significant negative correlation between age and cortical thickness in these regions ($R^2 \geq 0.19$, $p < 0.001$) and cortical thickness linearly declined with age at variable rates (-0.05 to -0.08 mm/year).

Interplay Between SWM and Cortical Thickness Independent of Age

SWM FA and cortical thickness

Pearson's partial correlation maps between cortical thickness and SWM DTI-derived measures (FA and MD), controlled for age and gender, and are shown in Figure 5. Cortical thickness correlated positively with underlying SWM FA in primary cortices such as somatosensory and motor (bilateral precentral and postcentral gyri), auditory

(superior temporal), and visual areas (pericalcarine and lingual) and some secondary areas such as supplementary motor area, superior parietal, posterior cingulate, fusiform, and parahippocampal regions. Conversely, cortical thickness was found to be negatively correlated with FA in higher-level prefrontal and parietal regions: bilateral DLPFC, anterior cingulate, inferior parietal lobules, and precuneus, where lower cortical thickness is accompanied by higher FA in the SWM directly underneath the corresponding cortex.

SWM MD and cortical thickness

Compared with FA, Pearson's partial correlation of cortical thickness and SWM MD revealed a generally opposite pattern, as expected. For most cortical regions, where FA was positively correlated with thickness, we observed negative correlation between MD and thickness (bilateral postcentral, superior temporal, pericalcarine, cuneus, lingual, fusiform, and parahippocampal regions). Alternatively, where thickness was negatively correlated with FA, we observed positive correlation between MD and thickness (bilateral DLPFC, anterior cingulate, middle temporal, and inferior parietal lobules).

DISCUSSION

To the best of our knowledge, this is the first vertex-based study characterizing the maturational pattern of

Figure 4.

Linear age effect on cortical thickness. (a) Significant cortical thinning (blue) with age (controlled for gender). L: left hemisphere; R: right hemisphere. The gold-edged clusters survived the corrected $p < 0.001$. (b) Scatterplots of cortical thickness and age in left lateral orbitofrontal area, precuneus, and right inferior parietal and fusiform areas (as marked in a). The cortical thickness values were already adjusted for gender.

SWM and its association with GM in children and adolescents. There are three main findings. First, two distinct patterns of SWM maturation were found in the 10–18 year age range: Increased FA and decreased RD were observed in sensorimotor and temporoparietal regions, which may reflect increasing myelination in these regions. Increased FA and AD were observed in the OFC and insula, possibly suggesting improved axon coherence and density. Second, there is no substantial overlap between SWM and cortical thickness changes with age. This lack of overlap does not support the notion that cortical thinning can be explained by expansion of myelin into the GM/WM boundary [Shaw

et al., 2008; Sowell et al., 2004]. Third, the intrinsic relationship between SWM and GM follows a pattern consistent with hierarchical processing, with SWM FA and cortical thickness being positively correlated in unimodal brain regions that process primary sensory information and negatively correlated in polymodal association areas that integrate information across multiple sensory modalities.

SWM Maturation with Age

Our study showed two patterns of age-related microstructural change in SWM. First, an overall increase in FA and decrease in MD were observed in motor and perceptual processing regions (Fig. 2), which was accompanied by a decrease in RD. This pattern indicates that the increased FA was predominantly caused by reduction in RD. This finding is consistent with observations in humans from childhood to young adulthood [Tamnes et al., 2010] and in rhesus monkeys from late infancy to early adulthood [Shi et al., 2013]. Decreasing RD has been associated with increasing myelination [Song et al., 2003, 2005]. SWM changes in motor and temporal-parietal areas likely reflect increasing myelination during the 10–18 years of age range. Increasing FA and decreasing RD are observed in a portion of the precuneus in our study, but not in the previous ROI-based human study [Tamnes et al., 2010]. This may be because our vertex-based method is more sensitive to subtle SWM changes in subregions when compared to ROI-based approaches.

A second pattern was observed in bilateral OFC and insula, where increasing FA was accompanied by increasing AD. This pattern was also observed in rhesus monkeys [Shi et al., 2013], but variable results were found in human subjects [Tamnes et al., 2010]. Tamnes and colleagues did not examine insular SWM, and they reported increasing FA and decreasing RD with age in the OFC. Their upper age range extended up to 30 years, older than the 18 years in our study. Tamnes et al. may have captured the later stages of SWM development, while we identified the earlier developmental change in the OFC. Both adolescent human and monkey data [Shi et al., 2012] suggest that increasing FA in the OFC and insular SWM may be explained by increasing AD, which has been associated with improved axon coherence, axonal density or axonal integrity [Beaulieu, 2002; Dubois et al., 2009; Paus, 2010; Song et al., 2002, 2003]. SWM change in OFC and insula during adolescence may reflect improved WM integrity between frontal and limbic regions, which may correspond with improvement in emotional regulation capabilities during the adolescent age range [Casey et al., 2008; Davidson et al., 2000; Steinberg, 2005].

Cortical Thickness Change with Age

During 10–18 years, cortical thickness (Fig. 4a) stayed relatively stable in the primary cortices (e.g., precentral

Figure 5.

Intrinsic association between SWM and cortical GM. Partial correlation coefficient maps between (a) cortical thickness and SWM FA and (b) cortical thickness and SWM MD (controlled for age and gender). L: left hemisphere; R: right hemisphere. The gold-edged clusters survived the corrected $p < 0.05$. Red-yellow indicates significant positive correlation while blue-cyan

indicates significant negative correlation. The intrinsic association between SWM and cortical GM generally follows brain functional organization: positive correlation between cortical thickness and SWM FA in unimodal sensory areas, and negative correlation between cortical thickness and SWM FA in polymodal brain regions.

and postcentral gyri), suggesting that these regions have reached maturation by age 10. Different brain regions showed varied temporal patterns of cortical thickness changes, which are consistent with previous reports and likely related to different functional specialization [Gogtay et al., 2004].

Association Between SWM and Cortical Thickness

Age-related developmental associations

Cortical thinning during the adolescent period has been attributed to synaptic pruning (decreased synaptic density) [Huttenlocher, 1979; Huttenlocher et al., 1982], increased myelination along the GM/WM boundary [Yakovlev and Lecours, 1967], or a combination of both effects [Lebel et al., 2008a; Sowell et al., 2004]. Increased myelination along the GM-WM border may change its T1w signal, possibly leading to the misclassification of GM and WM, which can be interpreted incorrectly as cortical thinning. Meanwhile, if the myelination along the GM-WM border is significant enough to change its T1w signal to the degree of causing GM/WM misclassification, this increase in myelination should also cause microstructural changes in the SWM and lead to changes in DTI signals as well. Therefore, we assume myelination-driven T1w signal change will be accompanied by SWM changes, which can be detected by highly sensitive DTI methods. Under this assumption, a tight correspondence between SWM and GM maturational maps would suggest that cortical thin-

ning is accompanied by underlying SWM microstructural changes, and would support that, in addition to synaptic pruning, myelination may explain cortical thinning. In contrast, the lack of a tight coupling of cortical thinning and SWM maturation patterns would support that cortical thinning is not primarily attributable to SWM myelination.

Visual comparison of the age-related changes in cortical thickness (Fig. 4a) and SWM (Fig. 2) suggests that the maturation patterns of GM and SWM diverge substantially. During childhood and adolescence, there is no obvious overlap in cortical and SWM developmental changes in the brain except for the OFC and posterior cingulate cortex. These findings of varied temporal-spatial maturation patterns between GM and SWM are consistent with those reported by Tamnes et al. [2010]. These findings provide indirect neuroimaging evidence and converge to support that myelination-driven T1w signal change is not a substantial contributor to cortical thinning, which instead may be due to other factors, such as synaptic pruning and/or glial cell density change in cortical regions.

An exception was observed in the OFC, where parallel age-related cortical thickness and underlying SWM changes were present. As discussed above, increasing FA and AD in the OFC suggest improved axonal coherence or increased axonal density during the age range of 10–18 years [Beaulieu, 2002; Song et al., 2002, 2003, 2005]. Lack of change in RD suggests that SWM change in the OFC is not associated with myelination. Thus, cortical thinning in the OFC is likely not driven by increasing myelination, but is more likely to be due to other factors such as elaboration of dendritic arborization.

Age-independent intrinsic association

The varied patterns of intrinsic SWM-GM relationships observed (Fig. 5) are consistent with known functional organization of the brain. Cortical thickness is positively correlated with SWM FA in unimodal regions (e.g., primary sensory and motor regions), but negatively correlated in polymodal association regions (e.g., DLPFC). Unimodal regions, relative to polymodal regions, have more homogenous neuronal connectivity. For example, the primary visual cortex (Brodmann's areas 17, BA 17) receives highly organized input from the lateral geniculate nucleus (LGN), which retains retinotopic mapping, and projects to relatively restricted regions including visual association areas (e.g., BA 18, 19) and LGN [Bear et al., 2007]. Such systematic and coherent organization is also observed in the primary auditory cortex as tonotopic map and in primary somatosensory and motor cortices as homunculus maps [Bear et al., 2007]. Highly coherent fibers in the underlying SWM are presumed to contribute to such organization. In contrast, in polymodal regions such as BA 46/9 (DLPFC), afferent association and commissural fibers originate from varied regions such as parietal, temporal, and other frontal cortices, and efferent fibers project to diverse cortical and subcortical regions [Kolb and Whishaw, 2009]. Relative to unimodal regions, axons in polymodal SWM are likely to be less coherent and have more crossing fibers. Thus one possible explanation of the divergent SWM-GM intrinsic relationships is the coherence of axonal fibers. In unimodal regions, where SWM contains highly coherent axonal fibers, thicker cortex may lead to greater axonal packing density with high coherence, as reflected by increasing FA. In contrast, in polymodal regions, thicker cortex may lead to greater axonal packing density in the SWM with less coherence, as reflected by decreasing FA.

Alternatively, unimodal and polymodal regions have different compositions of interstitial neurons in their SWM that may partially contribute to the observed intrinsic relationships [Defelipe et al., 2010]. Post mortem studies showed that interstitial neurons in primate SWM are sparse in the visual cortex but abundant in prefrontal SWM [Suarez-Sola et al., 2009]. The function of interstitial neurons is hypothesized to be related to blood flow regulation and precise establishment of complex corticocortical connections. Specifically, polymodal brain regions such as the prefrontal cortex may need interstitial neurons to guide axons to correct cortical layers/locations and establish effective connectivity among complex projection terminals. Increased presence of SWM interstitial neurons in polymodal regions may contribute to lower FA in these regions. Thus divergent patterns of intrinsic SWM-GM relationships observed may also be related to different concentrations of interstitial neurons between polymodal and unimodal regions. The convergence of in vivo neuroimaging and postmortem findings suggests that neuroimaging may be a fruitful methodology to inform basic neurophysiological questions using in vivo tissue.

In summary, the intrinsic SWM-GM relationships appear to be consistent with hierarchical processing, although current findings are not able to address whether the underlying physiological explanation lies in coherence of axon fibers, presence of interstitial neurons, or a combination of both factors. Our study provides a novel way to examine the intrinsic SWM-GM coupling, and may potentially extend the evaluation of structural integrity in psychiatric disorders.

Several limitations of this study should be considered. We examined the linear, instead of nonlinear, growth of cortical GM and SWM. Previous literature has suggested age-related linear change in cortical thickness and SWM in narrow age spans [Snook et al., 2005]. Whole-brain FA and cortical thickness are linearly correlated, even though each undergoes continuous nonlinear change over the life span [Kochunov et al., 2011]. Therefore, given the narrow age span of our participant population (10–18 years), we think it is reasonable to examine the linear growth of cortical GM and SWM and the linear relationship between them. We also examined brain development using a cross-sectional instead of longitudinal design, which is more vulnerable to intersubject variance and cohort effects. However, large sample size in our study offered good statistical power and high confidence that the developmental patterns observed are reliable, although confirmation with longitudinal data would be valuable. The data collection for this study began several years ago, and used a DTI protocol with 4-mm slice thickness, 1-mm gap, and a, b-value of 750 s/mm². This DTI protocol may not be optimal for brain development of children and adolescents by current standards, but was maintained during this study for data acquisition consistency and a large sample size. An updated DTI protocol with an isotropic voxel size (2 × 2 × 2 mm), b-value of 1000 s/mm² and 55 noncollinear diffusion gradient directions has been incorporated in our current imaging protocols. Similarly, the anatomic T1w images used in this study were axially acquired with nonisotropic voxel size (FOV = 240 × 240 mm², matrix = 384 × 256, slice thickness/gap = 1.5/0 mm). Axial slice thickness of 1.5 mm may be too coarse to resolve the cortical ribbon in brain areas with high complexity. We have updated the T1w 3D BRAVO protocol in our current imaging protocols as well. Like all DTI-based studies, this study is unable to determine the exact neurobiological causes underlying the DTI findings. The neurobiological underpinnings for changes in DTI measures are known primarily from animal studies. While biophysiological alterations that contribute to DT-derived measures are assumed to be similar across humans and animal species, there is a possibility that findings from animal studies may not completely translate to humans. Finally, our stance against the encroachment of myelin into the GM-WM boundary as an explanation for cortical thinning rests on the assumption that tissue alterations that lead to T1w signal change will also affect DTI signals. However, there is the possibility,

though unlikely, that myelination can affect T1w signal without affecting DT-derived measures.

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