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Age-related changes in prefrontal white matter volume across adolescence

Bonnie J. Nagel^{a,c,e}, Krista Lisdahl Medina^{a,c}, June Yoshii^a, Alecia D. Schweinsburg^{b,c}, Ida Moadab^b, and Susan F. Tapert^{a,c,d}

a Department of Psychiatry, University of California, San Diego

b Department of Psychology, University of California, San Diego

c Department of Veterans Medical Research Foundation, University of California, San Diego

d VA San Diego Healthcare System, San Diego, California

e Department of Psychiatry, Oregon Health and Science University, Portland, Oregon, USA

Abstract

Past research has suggested that white matter volume increases from childhood to adulthood; however, during adolescence, there is somewhat limited data to support this finding. In the present study, 65 typically developing adolescents underwent structural magnetic resonance imaging. Using magnetic resonance imaging, prefrontal white matter volumes were examined in relation to adolescent age and sex. Surprisingly, results suggested that prefrontal white matter volume decreased during late adolescence, particularly among the female sex. These findings are inconsistent with past research and suggest that perhaps some developmental processes in late adolescence are not yet fully explained. Possible methodological contributions and implications for the current findings are discussed

Keywords

adolescent development; frontal lobes; magnetic resonance imaging; segmentation; white matter

Introduction

Neuroimaging has greatly increased scientific understanding of adolescent brain development. As the field progresses, themes are drawn from the growing preponderance of converging evidence. Several studies have examined both gross morphological and microstructural indices of brain development, revealing that, along with decreasing cortical gray matter volumes [1, 2], increases in cerebral white matter volumes [2–6] as well as increasing density, organization, and integrity of white matter pathways [7–9] appear across adolescence. These white matter changes are likely a function of increased myelination and axon organization, which ultimately result in more efficient transport of neural signals, permitting greater capacity for higher-level cognition during adolescence (for a review, see [10]).

Although these findings appear well established, it is important to systemically examine the substantiating studies before drawing firm conclusions regarding adolescent white matter development. Our first indication of progressive white matter change during adolescence came

from Yakovlev and Lecours [11], in which post-mortem myelin staining suggested protracted increases in the density of myelinated fibers in cortical association areas into the third decade of life. Since then, investigators have examined *in vivo*, white matter change across adolescence using structural magnetic resonance imaging. In a landmark quasi-longitudinal study (each participant received ≥ 2 exams), Giedd and colleagues [2] demonstrated a linear increase of 12% in global white matter volume among children, adolescents, and young adults, aged 4–21 years, with a steeper rate of increase for those of the male sex than those of the female sex. While the data fit a linear model, it is difficult to determine whether analysis of regional white matter in the adolescent age range of the sample (e.g. ages 12–18 years) suggests a similar developmental trajectory, and whether regional development is similar in members of the male and female sexes. One study examining overall white matter volume across 88 individuals ranging in age from 3 months to 30 years demonstrated increases in overall white matter volumes until approximately the age of 20 years when volumes leveled off [4]. In several additional cross-sectional studies, white matter volumes were measured across childhood to adolescence, suggesting linear patterns of overall [6] and prefrontal white matter [3] volume increases. Sowell and colleagues [5], however, found that among children and adolescents aged 7–16 years, frontal white matter volumes were not significantly correlated with age. Thus, the positive association between age and white matter volume has only been demonstrated in samples ranging from early school age to adolescence or young adulthood, and has not consistently been found with regard to regional (e.g. prefrontal) white matter. Thus, critical consideration of the data on which we base our conclusions about white matter changes during adolescence suggests that extant findings are somewhat equivocal.

The purpose of the current study was to carefully examine the relationship between age and prefrontal white matter volume in a relatively large cross-sectional sample of typically developing adolescents. On the basis of the research to date, we hypothesized that, with our adolescent-only sample, we would replicate previous findings of a positive relationship between prefrontal white matter volume and age.

Methods

Participants

Sixty-five healthy adolescents (31 girls, 34 boys; ages 12–18 years; mean $\pm$ SD 14.95 $\pm$ 1.92 years) underwent structural magnetic resonance imaging. Adolescents were studied as part of ongoing adolescent brain imaging studies. Written consent and assent were obtained from teens and their parent/legal guardians in accordance with the University of California San Diego Institutional Review Board. On the basis of comprehensive structured screening measures administered to teens and guardians, all teens were free from use of psychotropic medications; histories of head injury with loss of consciousness for more than 2 min, neurological or medical illness; learning disabilities or mental retardation, and DSM-IV [12] axis I disorders; significant maternal drinking during pregnancy (≥ 4 or ≥ 7 drinks/week); parental history of bipolar I, psychotic disorders or substance use disorders; left handedness; and magnetic resonance imaging contraindications.

The mean grade point average (GPA) for the sample was 3.49 (± 0.50), and the mean family income was 113.42 thousand dollars/year (± 50.08). All teens were administered a version of the Wechsler Vocabulary subtest (e.g., see [13]), and scores were converted to standardized *t*-scores (mean $\pm$ SD=56.78 $\pm$ 8.28). Male and female participants did not differ on these variables, nor were GPA, family income (an estimate of socioeconomic status), or Vocabulary *t*-score related to overall or prefrontal white matter volume. The mean volume of white matter for all participants was 509.69 cm³ (± 45.70), and the mean volume of prefrontal white matter volume was 109.09 cm³ (± 13.36). Gross brain volumes (uncorrected for intracranial volume, ICV)

were significantly greater in male participants than in female participants, and were analyzed accordingly (see Results section).

Magnetic resonance imaging protocol and structural processing

Imaging data were acquired on a 1.5-T General Electric Signa LX system (General Electric, Milwaukee, Wisconsin, USA) using a sagittally acquired inversion recovery prepared T1-weighted three-dimensional spiral fast spin echo sequence (TR=2000 ms, TE=16 ms, FOV=240 mm, voxels $0.9375 \times 0.9375 \times 1.328$ mm, 128 continuous slices, acquisition time=8.36) [14].

From all teens' anatomical imaging, skull stripping was performed, overall cerebral volumes were calculated, white matter was segmented, the prefrontal region was delineated, and white matter volumes were calculated. Skull stripping was achieved using a combination of a hybrid watershed and deformable surface semi-automated skull-stripping program [15] and manual editing. Fully skull-stripped T1 images were processed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's automated segmentation tool (FAST) [16]. Using a hidden Markov random field model and an associated expectation-maximization algorithm, this automated program segmented white matter from other brain tissues, while correcting for spatial intensity variations. The FAST algorithm has been shown to be superior to other automated and semiautomated segmentation programs for segmenting white matter [17]. White matter volumes were analyzed as a ratio to overall ICV to control for individual and sex variability in brain size.

The prefrontal region of interest included all cortical white matter anterior to the anterior commissure and was manually delineated on images in the coronal orientation (perpendicular to the anterior commissure–posterior commissure plane). This tracing excluded the corpus callosum, subcortical (internal capsule) and insular white matter. Boundaries were selected to stereotactically demarcate prefrontal cortical regions to increase tracing reliability across study participants. Tracing continued to the most anterior slice on which the cortex was still visible. The corpus callosum was manually removed from each region of interest using AFNI's [18] *edge detection* feature in the sagittal orientation, and was excluded from the mid-sagittal slice and right and left lateral slices until the edge could no longer be detected (across an average of 18 1-mm sagittal slices). The prefrontal region of interest was applied to the segmented white matter map, resulting in a voxel count for overall prefrontal white matter (see Fig. 1 [16]). Manual editing and region of interest drawing was performed independently in AFNI by three highly trained individuals (B.N., I.M., and J.Y.) blind to participant characteristics. For all manual methods, high levels of inter-rater and intra-rater reliability were attained (intra-class correlation coefficients >0.90) before data collection.

Statistical analysis

Data were examined for statistical assumptions and potential covariates. Using standard entry multiple regression, age, sex, and the age–sex interaction were examined in relation to the dependent measures of overall white matter volume and prefrontal white matter volume (both represented as a ratio to ICV). For significant predictors, goodness of fit was examined to investigate nonlinear relationships. All statistics were interpreted using $\alpha < 0.05$.

Results

Overall white matter volume

With age and sex in the model, age was not significantly related to overall white matter volume (examined as a ratio to ICV) [$F(62) = 6.09$, $P < 0.01$; $\beta = -0.12$, NS]. Sex, however, significantly accounted for overall white matter ($\beta = 0.39$, $P < 0.01$), with male participants having a greater

proportion of white matter to overall brain volume. No age–sex interaction was found [$F(61)=4.27$, $P < 0.01$; $\beta = 0.13$, NS]. The regression equation including age and sex accounted for 16% of the variance in whole brain white matter.

Prefrontal white matter volume

With both age and sex in the model, adolescent age had a significant negative effect on prefrontal white matter volume (also examined as a ratio to ICV) [$F(63)=7.16$, $P < 0.01$; $\beta = 0.34$, $P < 0.01$]. As with overall white matter volume, there was a significant effect of sex ($\beta = 0.28$, $P < 0.05$), with male participants having a greater proportion of prefrontal white matter volume to overall brain volume. No significant age–sex interaction [$F(62)=5.54$; $\beta=0.22$, NS] was observed; however, examination of the data (see Fig. 2) suggests that the negative relationship between age and prefrontal white matter volume was stronger for adolescent female participants. The regression model including age and sex accounted for 19% of the variance in prefrontal white matter volume. Goodness of fit analyses suggested that the relationship between age and prefrontal white matter volume was best fit by a quadratic model ($n=65$, $r^2=17\%$, $P < 0.01$), particularly for female participants ($n=31$, $r^2=37\%$, $P < 0.01$).

Discussion

This study examined the relationship between prefrontal white matter volume and age in a relatively large ($n=65$) cross-sectional sample of typically developing adolescents. Given past research suggesting continued frontal lobe development and increasing white matter volume between childhood and adulthood (for a review, see [19]), we hypothesized that increased adolescent age would be associated with greater prefrontal white matter volume. Consistent with past studies of young adults, our data suggested that those of the male sex have greater overall brain volume and a greater ratio of white matter to overall brain volume [20]. Surprisingly, however, our findings suggested a negative relationship between prefrontal white matter volume and age, particularly among adolescent female participants. The data were best fit by a nonlinear model and indicate that at approximately 15 years of age, prefrontal white matter volume appeared to decline. These findings are in stark contrast to the existing studies of white matter from childhood to adulthood that suggest, although the slope of change from childhood to adulthood is smaller for females than males, white matter volumes increase across this age range [2–6]. Still, careful examination of the existing literature suggests some discrepancies in the conclusions regarding neuromaturational patterns from childhood to adulthood, and little attention has been given to this circumscribed period of development.

Given that the results of this study diverge from the existing literature on adolescent white matter development, it is important to consider other possible explanations for and limitations of our findings. First, despite a reasonably powered and well-characterized sample, and utilization of careful and well-validated methods, one possible contributing factor pertains to the reliability of white matter segmentation across development. Although the current methods used for delineating white matter have been shown superior to other automated segmentation programs in adults [17], changes in T1 signal and tissue biochemistry may affect sensitivity to gray/white matter boundaries across development [19,21]. To our knowledge, no study has systematically examined the appropriateness of using adult-based segmentation algorithms across the adolescent age range, so we cannot rule out the possibility of age-related variation in our methods. Further, methods widely differ across developmental studies and while age-related changes in tissue dynamics potentially confound all segmentation methods, there is no available data to suggest whether different algorithms handle this variation in a consistent manner.

Second, diffusion tensor imaging research examining microstructural prefrontal white matter changes across adolescence provides indirect evidence that prefrontal white matter pathways

become better myelinated, organized, and parallel aligned across adolescent development [9]. In young adults, however, no significant relationship between this microstructural development and prefrontal white matter volume was demonstrated [22]. Thus, it is possible that these microstructural changes in white matter lead to more compact, organized fiber tracts that may result in smaller measurable volumes, particularly in regions with high parallel axonal alignment (e.g. internal capsule). Although the current study used stereotactic boundaries to parcel out prefrontal white matter, we may be able to learn more about the nature of the relationship between white matter microstructure and morphometry from future studies that include refined neuroanatomical delineations.

Another potential explanation for the difference between the current findings and past research is that studies examining a wide age range from childhood through adulthood may not capture potential developmental nuances inherent to the adolescent years. For example, in a study examining white matter volume in individuals 11–76 years of age, the overall relationship was described as a linear negative correlation [23]. As, on the basis of current research and knowledge, there should have been at least a nonlinear relationship between age and white matter volume across this age range (inverted U-shaped curve), perhaps studies examining larger age ranges have had insufficient sample sizes within a given developmental stage to detect subtle, nonlinear relationships.

Finally, this study is limited by its cross-sectional design, which could lead to results being simply due to sampling artifact. While the current sample is relatively large and very carefully screened, examination of demographic characteristics suggests that in general these teens come from families of relatively high socioeconomic status (mean family income $\approx$ \$113 000/year), perform quite well academically (mean GPA $\approx$ 3.5), and are above average intellectually (mean Vocabulary *t*-score $\approx$ 57). None of these variables were related to sex, age, or overall or prefrontal white matter volumes. While we are unable to examine the relationship between overall intelligence and white matter in this study, recent research suggests that individual differences in intellectual ability influence rates and patterns of cortical development [24]. Thus, while we found no sample-specific confounds, participant characteristics may contribute to these white matter findings.

Conclusion

The results of this study point to the possibility that, while contrary to existing evidence, white matter volumes may actually decrease during late adolescence, particularly among those of the female sex. We cautiously present these findings and are not attempting to refute existing data on the trajectory of white matter development across adolescence. We are, however, suggesting that this period of dynamic development needs to be explored more carefully, and that large, longitudinal samples should be used to allow for individual and sex differences to be taken into account. Despite the possible methodological contributions to our findings, these data hold important implications for examining the relationship between white matter structure and function across healthy adolescent development, and are particularly important for studying adolescent populations in which white matter pathology may be implicated.

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Fig. 1. Representative segmentation of prefrontal white matter (denoted in black) using functional magnetic resonance imaging of the brain's automated segmentation tool [16]. Includes all cortical white matter anterior to the anterior commissure.

Fig. 2.

Graphical representation of best fit models for the relationship between age and prefrontal white matter volume [expressed as a ratio to overall intracranial volume (ICV)] within the whole sample ($n=65$, $r^2=17\%$, $P < 0.01$), males only ($n=34$, $r^2=3\%$, NS), and females only ($n=31$, $r^2=37\%$, $P < 0.01$).