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MAPPING AGE EFFECTS ALONG FIBER TRACTS IN YOUNG ADULTS

Emily L. Dennis^{1,2}, Faisal Rashid¹, Josh Faskowitz¹, Yan Jin¹, Katie L. McMahon³, Greig I. de Zubicaray⁴, Nicholas G. Martin⁵, Ian B. Hickie⁶, Margaret J. Wright^{3,7}, Neda Jahanshad¹, and Paul M. Thompson^{1,2,8}

¹Imaging Genetics Center, USC Keck School of Medicine, Marina del Rey, CA, USA

²Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, UCLA, Los Angeles, CA, USA

³Center for Advanced Imaging, Univ. of Queensland, Brisbane, Australia

⁴School of Psychology, University of Queensland, Brisbane, Australia

⁵Queensland Institute of Medical Research, Brisbane, Australia

⁶Brain and Mind Centre, University of Sydney, Australia

⁷Queensland Brain Institute, University of Queensland, Brisbane, Australia

⁸Departments of Neurology, Pediatrics, Psychiatry, Radiology, Engineering, and Ophthalmology, USC, Los Angeles, CA

Abstract

Brain development is a protracted and dynamic process. Many studies have charted the trajectory of white matter development, but here we sought to map these effects in greater detail, based on a large set of fiber tracts automatically extracted from HARDI (high angular resolution diffusion imaging) at 4 tesla. We used autoMATE (automated multi-atlas tract extraction) to extract diffusivity measures along 18 of the brain's major fiber bundles in 667 young adults, aged 18–30. We examined linear and non-linear age effects on diffusivity measures, pointwise along tracts. All diffusivity measures showed both linear and non-linear age effects. Tracts with the most pronounced age effects were those that connected the temporal lobe to the rest of the brain. Nonlinear age effects were picked up strongly in the anterior *corpus callosum* and right temporo-parietal tracts.

Index Terms

tractography; development; diffusion weighted imaging; structural connectivity

1. INTRODUCTION

Brain structural development continues into the 3rd decade of life (1) and supports the development of higher cognitive functions. Gray matter volume decreases during adolescence (2), but white matter (WM) volume increases, as myelination continues. Many studies have detailed the structural development of the brain (reviewed in (3)). Defining

healthy norms for development, and mapping the profile of brain changes, can further our understanding of mechanisms of brain development. Such data also provides normative statistics to help identify alterations associated with developmental disorders or brain injury.

Diffusion-weighted MRI (dMRI) can be used to assess the geometry, connectivity, and microstructural properties of WM tracts in the brain. In diffusion tensor imaging, which models local diffusion of water in the brain as a 3D Gaussian process, commonly accepted indices include fractional anisotropy (FA – the degree to which diffusion is constrained in a preferred direction). Other commonly studied measures include MD (mean diffusivity – an average measure of diffusivity along all three eigenvectors), RD (radial diffusivity – the average diffusivity along the two non-primary eigenvectors), and AD (axial diffusivity – diffusivity along the primary eigenvector direction). AutoMATE (automated multi-atlas tract extraction) is a method we developed to parcellate the whole-brain tractography into component tracts of interest, enabling the mapping of statistical effects on common tract indices across subjects in group analyses (4). AutoMATE was developed using the dataset we study here, but on a smaller sample ($N=198$), and focusing on heritability, a measure of the genetic contribution to the observed variations in a population. Prior studies have used DTI tractography to investigate brain development as well (5). Lebel et al. (2008) mapped developmental trends across ages 5–30 using measures averaged along tracts (6). Johnson et al. (2014) used point-wise measures to map age effects along tracts in a sample of young children (7). Here we expanded this, using a large sample ($N=667$) of young adult Australian twins.

2. METHODS

2.1 Subjects and Image Acquisition

Participants were recruited as part of a 5-year research project scanning healthy young adult Australian twins with structural brain MRI and DTI (8). We analyzed scans from 667 right-handed subjects (414 women/253 men, average age=22.7, SD=2.8). This population included 260 monozygotic (MZ) twins, 342 dizygotic (DZ) twins, and 65 non-twin siblings, from 415 families. The age range was 18–30 years. Whole-brain anatomical MRI and high angular resolution diffusion images (HARDI) were collected with a 4T Bruker Medspec MRI scanner. T1-weighted anatomical images were acquired with an inversion recovery rapid gradient echo sequence, with TI/TR/TE = 700/1500/3.35ms; flip angle = 8 degrees; slice thickness = 0.9mm, and a $256 \times 256 \times 256$ acquisition matrix. Diffusion-weighted images (DWI) were also acquired using single-shot echo planar imaging with a twice-refocused spin echo sequence to reduce eddy-current induced distortions. Imaging parameters were: 23cm FOV, TR/TE 6090/91.7ms, with a 128×128 acquisition matrix. Each 3D volume consisted of 55 2-mm thick axial slices with no gap and $1.79 \times 1.79 \text{ mm}^2$ in-plane resolution. 105 images were acquired per subject: 11 with no diffusion sensitization (i.e., T2-weighted b_0 images) and 94 diffusion-weighted (DW) images ($b = 1159 \text{ s/mm}^2$) with gradient directions evenly distributed on the hemisphere. The HARDI scan took 14.2 min to collect.

2.2 AutoMATE

AutoMATE (automated multi-atlas tract extraction), developed by our lab, is described fully in prior papers (4, 9, 10). Diffusion images were corrected for eddy-current induced distortions using the FSL tool “eddy_correct” (<http://fsl.fmrib.ox.ac.uk/fsl/>). DWI scans were skull-stripped using “BET”. FA and MD maps were computed using “dtifit”. Whole-brain tractography was performed with Camino (<http://cmic.cs.ucl.ac.uk/camino/>). Tracing stopped when fractional anisotropy (FA) dropped below 0.2, as is standard in the field.

As part of autoMATE, five WM tract “atlases” were reconstructed from healthy young adults’ (20–30 years old) DWI data, as detailed previously (4, 9, 10). The atlas, based on the “Eve” brain atlas (11), which is based on a 32-year old female, includes 18 major WM tracts: the anterior thalamic radiation (left and right – atr_l and atr_r), corticospinal tract (left and right – cst_l and cst_r), cingulum (left and right – cgc_l and cgc_r), inferior fronto-occipital fasciculus (left and right – ifo_l and ifo_r), inferior longitudinal fasciculus (left and right – ilf_l and ilf_r), arcuate fasciculus (left only), fornix, and corpus callosum tracts divided into 6 segments – frontal, precentral gyrus, postcentral gyrus, parietal, temporal, and occipital. The Eve atlas was registered, linearly and then non-linearly, to each subject’s FA map using ANTs (Advanced Normalization Tools (12)) and its ROIs were correspondingly warped to extract 18 tracts of interest for each subject based on a look-up table (11). Each subject’s FA map was then registered non-linearly to each of the 5 manually constructed atlases. Registrations were visually inspected for quality. We refined each tract’s fiber extractions based on the distance between the corresponding tract of each atlas and the subject’s fiber candidates from the ROI extraction. Individual results from the 5 atlases were fused. We visually inspected the resulting fiber bundles. For each of the 18 WM tracts, we selected one example subject to display results of group analyses. We then densely sampled the tracts to extract FA, MD, RD, and AD along consistent indices across subjects.

2.3 Age Regression

Age effects on tract-wise FA, MD, RD, and AD were estimated using several general linear mixed effects models:

$$dMRI \sim A + \beta_{age}Age + \beta_{sex}Sex + \alpha \quad (\text{Model 1})$$

$$dMRI \sim A + \beta_{age}Age + \beta_{sex}Sex + \beta_{age-sq}Age^2 + \alpha \quad (\text{Model 2})$$

$$dMRI \sim A + \beta_{age}Age + \beta_{sex}Sex + \beta_{agensex}AgexSex + \alpha \quad (\text{Model 3})$$

Here “dMRI” is FA, MD, RD, or AD along tract, input as 18496×15 matrices each. A is a constant for each regression model, the β s are the covariate regression coefficients, and α is a coefficient that accounts for random effects. Random effects were used to account for

family relatedness. We modeled the other variables (age, sex, age²) as fixed effects. We hypothesized that frontal and temporal tracts would show the most pronounced age effects.

3. RESULTS

3.1 Linear Age Effects

The results of Model 1 are shown in Figure 1. All measures showed significant results, but only FA is displayed. We found widespread positive associations with tract-wise FA, as expected. MD and RD decreased with age, and AD increased. Which measure showed the strongest age effect differed across models, but between FA, MD, RD, and AD the effects were approximately equivalent. Knowing which measures are most sensitive is important for future GWAS. The most extensive results were in the long anterior-posterior tracts connecting the temporal lobe with the rest of the brain. Age effects also appeared more pronounced in the left hemisphere.

3.2 Non-linear Age Effects

The nonlinear age effects from Model 2 are shown in Figure 2. Associations between age² and FA, after fitting other effects, were similarly extensive. Results were more extensive in the anterior projections and mid-body of the *corpus callosum*, as well as the temporo-parietal projections in the right hemisphere. The regression coefficients for age² were negative, indicating that the increase in FA was slowing with age, as we would expect.

3.3 Age x Sex Interaction Effects

Using Model 3, we modeled age x sex interaction effects on FA as well. We corrected for multiple comparisons across FA analyses of age, sex, and age x sex, using FDR. Age and sex were de-meaned in the interaction variable to account for co-linearity. We found a significant interaction effect in several small clusters, including the right frontal callosal fibers and the right inferior fronto-occipital fasciculus (IFOF). Females had a more positive association between FA and age than males in these areas.

4. DISCUSSION

We examined WM development along tract in a large cohort of young adults, finding linear and nonlinear age effects. FA and AD increased while MD and RD decreased with age. This has been shown in prior papers, but none has mapped age effects along tracts in such a large sample.

Examining within-tract averaged measures, Kochunov et al. (2012) found that the cingulum and fronto-occipital fasciculi had the latest maturational peaks (1). We found the same trends, with the most extensive age effects in the bilateral IFOF. The left IFOF showed more pronounced age effects in the linear model than the right IFOF. The left temporal lobe includes Wernicke's area, and is closely connected with Broca's area in the frontal cortex to support language functions (13, 14). Language involves a complex set of functions that typically improve through adolescence and into early adulthood, and are supported by development of these WM tracts (15).

We examined age x sex interaction effects, and found several small clusters in the frontal callosal fibers and IFOF, with females showing a more positive age effect on FA than males. Prior studies also shown similar age x sex interaction effects on FA (16).

AutoMATE allows us to localize the parts of the tract that show age effects, as measures are sampled densely along parametric curve models. Most of the tracts for which we found age effects had significant clusters in the main body of the tract, suggesting that we may be detecting effects of increased myelination, although it is also possible that our resolution to detect group effects was simply better midline along the tract rather than at the termini; the presence of crossing fibers may also affect the tensor-derived metrics and more advanced metrics may be useful here (17). We did find some significant age effects in the tract termini, however, especially in the projections of the *corpus callosum* in the frontal cortex.

5. CONCLUSION

By age 18 we may consider individuals adults, which suggests that development has completed, but many studies shown that both structural and functional brain maturation continues into early adulthood. Our results echo prior studies on this topic, giving further detail by mapping age effects along tracts. Some of the tracts to show age-related effects in our young-adult sample are the long anterior-posterior tracts that connect the temporal lobe to the rest of the brain, particularly those in the left hemisphere.

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Figure 1.

Linear age effects on tract-wise FA. Colors correspond to the p -value along the tract, with *blue* indicating a p -value at or above the FDR threshold (not significant) and *green-red* indicating increasingly significant p -values, as shown in the color bar.

Figure 2. Nonlinear age effects on tract-wise FA. Colors correspond to the p -value along the tract, with *blue* indicating a p -value at or above the FDR threshold (not significant) and *green-red* indicating increasingly significant p -values, as shown in the color bar.

Figure 3. Age x Sex interaction effects on FA. Colors correspond to the p -value along the tract, with *blue* indicating a p -value at or above the FDR threshold (not significant) and *green-red* indicating increasingly significant p -values, as shown in the color bar.