Radiology

ORIGINAL RESEARCH • NEURORADIOLOGY

White Matter by Diffusion MRI Following Methylphenidate Treatment: A Randomized Control Trial in Males with Attention-Deficit/Hyperactivity Disorder

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Supported by faculty resources of the Academic Medical Center, University of Amsterdam, and grant 11.32050.26 from the European Research Area Network Priority Medicines for Children (Sixth Framework Programme).

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Conflicts of interest are listed at the end of this article.

Radiology 2019; 00:1–7 • https://doi.org/10.1148/radiol.2019182528 • Content codes: NR MR PD

Background: Methylphenidate (MPH) is highly effective in treating attention-deficit/hyperactivity disorder (ADHD). However, not much is known about its effect on the development of human brain white matter (WM).

Purpose: To determine whether MPH modulates WM microstructure in an age-dependent fashion in a randomized double-blind placebo-controlled trial (Effects of Psychotropic Medication on Brain Development–Methylphenidate, or ePOD-MPH) among ADHD referral centers between October 13, 2011, and June 15, 2015, by using diffusion-tensor imaging (DTI).

Materials and Methods: In this prospective study (NTR3103 and NL34509.000.10), 50 stimulant treatment–naive boys and 49 young adult men diagnosed with ADHD (all types) according to *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* criteria were randomized to undergo treatment with MPH or placebo for 16 weeks. Before and 1 week after treatment cessation, study participants underwent MRI, including DTI. The outcome measure was change in fractional anisotropy (FA), which was assessed in three regions of interest (ROIs), as well as in a voxel-based analysis in brain WM. Data were analyzed by using intention-to-treat linear mixed models for ROI analysis and a permutation-based method for voxel-based analysis with family-wise error correction.

Results: Fifty boys (n = 25 MPH group, n = 25 placebo group; age range, 10–12 years) and 48 men (n = 24 MPH group, n = 24 placebo group; age range, 23–40 years) were included. ROI analysis of FA yielded no main effect of time in any of the conditions. However, voxel-based analysis revealed significant ($P < .05$) time-by-medication-by-age interaction effects in several association tracts of the left hemisphere, as well as in the lateral aspect of the truncus of the corpus callosum, due to greater increase in FA (standardized effect size, 5.25) in MPH-treated boys. Similar changes were not present in boys receiving a placebo, nor in adult men.

Conclusion: Four months of treatment with methylphenidate affects specific tracts in brain white matter in boys with attention-deficit/hyperactivity disorder. These effects seem to be age dependent, because they were not observed in adults treated with methylphenidate.

Online supplemental material is available for this article.

Attention-deficit/hyperactivity disorder (ADHD) is the most frequently diagnosed neurodevelopmental disorder, with symptoms arising in childhood and often persisting into adulthood (1). Methylphenidate (MPH) is commonly prescribed for treatment of ADHD, and its efficacy is considered to be 60%–80% (2). ADHD has been associated with alterations in white matter tract development. A previous meta-analysis (3) identified compromised white matter integrity in several tracts in both pediatric and adult patients with ADHD. However, the studies included in this meta-analysis were all retrospective in nature, and the possible confounding effects of medication were not taken into account.

A retrospective study by Castellanos et al (4) reported an increase, or apparent normalization, of white matter volume in children with medicated ADHD compared with children who were not receiving medication. However, medication status of the children and adolescents was not well accounted for, and most participants were already receiving ADHD medication at the time of the study. In a preclinical study in rats, we observed an increase in fractional anisotropy (FA) only in the corpus callosum (CC) of adolescent rats treated with MPH but not in adult rats or in rats treated with a saline solution (5). These preclinical findings suggest that the effect of MPH on brain white matter is modulated by age. The adolescent brain is

Abbreviations

ADHD = attention-deficit/hyperactivity disorder, ATR = anterior thalamic radiation, CC = corpus callosum, DTI = diffusion-tensor imaging, ePOD-MPH = Effects of Psychotropic Medication on Brain Development–Methylphenidate, FA = fractional anisotropy, MPH = methylphenidate, ROI = region of interest, TBSS = Tract-Based Spatial Statistics

Summary

This randomized clinical trial on the influence of methylphenidate on brain development using diffusion-tensor MRI found fractional anisotropy to increase in specific brain areas of boys with attention-deficit/hyperactivity disorder but not in young adult men or boys receiving a placebo.

Key Results

- In boys with attention-deficit/hyperactivity disorder (ADHD), 4 months of treatment with methylphenidate (MPH) was associated with increased white matter fractional anisotropy (FA) after 16 weeks (standardized effect size of 5.25 at whole-brain voxel-based analysis)
- In adult men with ADHD and in both boys and adult men receiving placebo, changes in FA measures were not present, suggesting that the effects of MPH on brain white matter are modulated by age.

a rapidly developing system maintaining high levels of plasticity. For instance, the maturation and development of white matter continues well into adulthood (6).

We hypothesized that FA would increase in children treated with MPH but not in children treated with placebo or in adults. We therefore designed a randomized clinical trial titled the Effects of Psychotropic Medication on Brain Development–Methylphenidate, or ePOD-MPH, study (7). Our current study aimed to investigate whether the effects of MPH on the human brain, including white matter, are modulated by age.

Materials and Methods

The trial protocol for this prospective study adhered to the Declaration of Helsinki (2013) and was registered by the Central Committee on Research Involving Human Subjects (an independent registry) on March 24, 2011 (identifier NL34509.000.10), and subsequently at the Netherlands National Trial Register (identifier NTR3103), with enrollment of the first study participant on October 13, 2011. In addition, the institutional review board of the Amsterdam Medical Centers approved the study. The full protocol is available in Appendix E1 (online). The trial ended on June 15, 2015. All study participants and, for the children, either both parents or their legal representatives provided written informed consent.

Experimental Design

The ePOD-MPH study was a 16-week double-blind randomized controlled trial with MPH to evaluate its effects on the developing brain in the greater Amsterdam area in the Netherlands. A blinded end-point evaluation in stimulant treatment–naive boys and young adult men with ADHD was performed (7). Study participants were randomly assigned to receive either a placebo or treatment with MPH. The effect of age and MPH treatment on white matter structure was assessed by means of diffusion-tensor imaging (DTI) at baseline and at the end of the trial, after a 1-week washout in week 18 to ensure drug clearance (the half-life of MPH is 2–3 hours). The primary outcome measure of ePOD-MPH was to report on the modification by age of MPH treatment on the outgrowth of the dopamine system by using pharmacologic MRI, and second primary outcome measures included DTI for white matter assessment (8).

Randomization and Blinding

After baseline MRI assessment, every study participant was stratified by age and randomized to receive either MPH or placebo treatment (1:1) by using a permuted block scheme generated by the local clinical research unit. The hospital pharmacy in Triversum, Alkmaar, the Netherlands received the information sealed and prepared the assigned treatment (ie, MPH or placebo). Study participants, the treating physicians (including C.B.), and research personnel were blinded to the type of treatment. The treating physician prescribed the study medication (MPH) according to clinical guidance (change in ADHD symptoms), in accordance with Dutch treatment guidelines. The placebo tablet matched the MPH tablet in appearance. It was manufactured and labeled according to Good Manufacturing Practice guidelines (2003/94/EG). Therapy compliance was monitored in five control visits. The ePOD-MPH trial was monitored by the Clinical Research Unit of the Academic Medical Center.

Study Participants

Baseline DTI values have been published elsewhere (with a similar analysis plan and regions of interest [ROIs] as used here) (9). Inclusion criteria were as follows: ADHD diagnosis (all subtypes); male sex; age, 10–12 years or 23–40 years; and stimulant treatment–naive status. Study participants were recruited in the outpatient clinics of Triversum (Alkmaar, the Netherlands), De Bascule Academic Center for Child and Adolescent Psychiatry (Amsterdam), and PsyQmental health facility (the Hague, the Netherlands). All study participants were given a diagnosis by an experienced psychiatrist on the basis of the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*. The diagnosis was subsequently confirmed with a structured interview—the Diagnostic Interview Schedule for Children (National Institute of Mental Health Diagnostic Interview Schedule for Children Version IV, or DISC-IV [10]) and the Diagnostic Interview for ADHD (DIVA 2.0 [11]) for adults. Inclusion criteria were at least six of nine symptoms of inattention or hyperactivity/impulsivity on the DISC-IV (for children) and on the DIVA 2.0 (for adults). Patients were excluded if they were given a diagnosis with a comorbid axis I psychiatric disorder requiring pharmacologic treatment at study entry or if they had general contraindications for MRI such as implanted electric and electronic devices, metal implants, or claustrophobia (Fig 1). After study inclusion, one adult patient was excluded because of undisclosed prior treatment with MPH. Adult study participants received coaching sessions (five sessions on practical topics such as using an agenda, planning, setting priorities, dealing with pro-

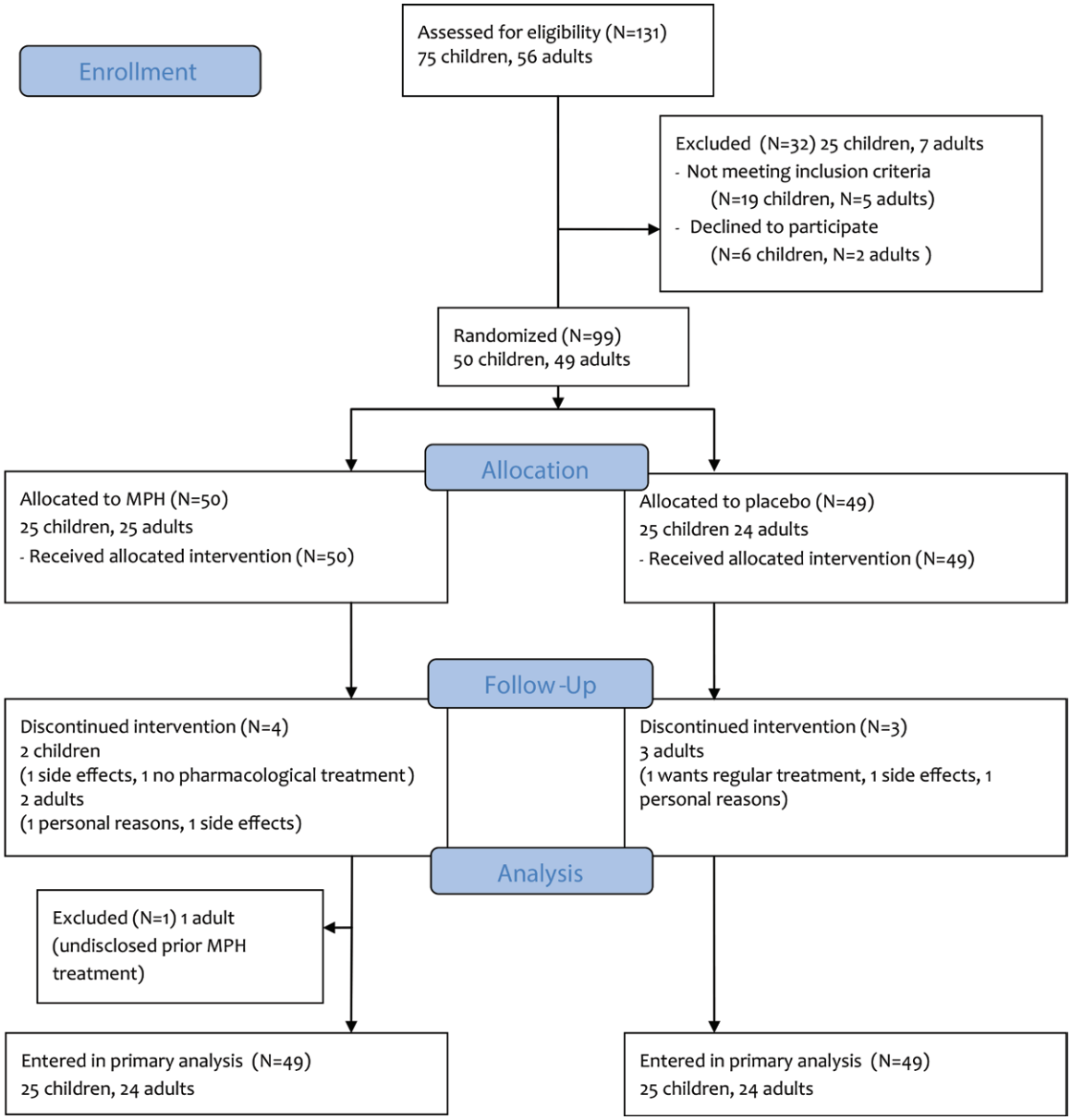

Figure 1: Consolidated Standards of Reporting Trials diagram shows enrollment of the study participants. MPH = methylphenidate.

crastination, and making choices in education and work), and parents of children received psychoeducation.

Image Acquisition

FA is a scalar measure that provides information about the degree of fiber organization and integrity (12). Processes that lead to alterations in axonal architecture, such as altered axonal outgrowth, can result in FA changes (13–15). Therefore, the primary dependent variable of interest was brain white matter FA.

All MRI studies were performed with a 3.0-T MRI unit equipped with a sensitivity encoding eight-channel head coil and body coil transmission (Philips Medical Systems, Best, the Netherlands). DTI studies were performed at baseline (week 0) and after treatment. The MRI parameters were as follows: field of view, 224 × 224 mm; section thickness, 2 mm; repetition time msec/echo time msec, 8135/94; imaging time, 6 minutes 47 seconds; sensitivity encoding factor, two; number of sections, 60; 46 gradient directions with a b value of 1000 sec/mm^2; four averaged images with a b value of 0 sec/mm^2; half-scan, 0.797; and fat suppression SPIR, 250 Hz.

DTI Processing

Preprocessing of diffusion-weighted (DW) images is discussed in detail in Appendix E1 (online). Briefly, DW images were corrected for distortions due to eddy currents and head motion (16). On the basis of the latter correction, an overall motion score was calculated for each study participant representing the degree of study participant movement during imaging (17). Diffusion tensors were estimated from the DW images, after which the tensors' FA statistic was calculated. The preprocessing of the

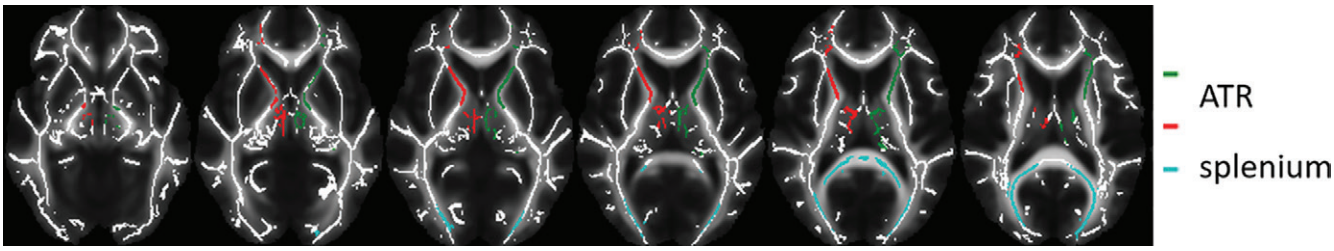

Figure 2: Images of regions of interest (colored lines) in the white matter skeleton representation. Data from left and right anterior thalamic radiation (ATR) were averaged.

DTI data was partially performed by using in-house developed software written in Matlab (MathWorks, Natick, Mass). This was performed by using the Academic Medical Center Neuroscience Gateway, using resources of the Dutch e-Science Grid with the support of the SURF Foundation (18). Average values of the diffusion statistics were computed over the whole white matter (4) within a central ROI in the truncus of the CC (5), as well as in the bilateral anterior thalamic radiation (ATR), as determined by the Johns Hopkins University white-matter tractography atlas (19). The choice of whole-brain FA and CC was based on previous findings, while we included the ATR ROI because it is an important tract in the frontal lobe and one of the last to mature (6,20,21) (Fig 2). Therefore, a white matter skeleton representation was generated by using Tract-Based Spatial Statistics (TBSS) software (22). Mean FA values for the whole brain and the ROIs were computed based on the white matter skeleton.

Statistical Analysis

To our knowledge, no other previous trial has examined the effects of MPH on the brain in children and young adults using MRI. Therefore, there were only limited and indirect data available to perform a sample size calculation. Our goal for this research was to be able to detect differences in the age-dependent effect of MPH on the outgrowth of the dopaminergic system if these differences were in the magnitude of a standardized effect size of 1.25. Our study protocol (Appendix E1 [online]) contains several pieces of evidence supporting the view that the expected differences will lead to standardized effect sizes of at least 1.25, including the DTI assessments we report here. Our findings on dopamine function (assessed by using pharmacologic MRI) have been reported elsewhere (8).

All ROI analyses were intent to treat, with the significance level set at $P < .05$ (two-sided). Linear mixed models were used to estimate the effect of time, group, and age and the corresponding interaction effects in the three ROIs. A compound symmetry covariance matrix and a fixed intercept were asserted; the model parameters were estimated by using a maximum-likelihood approach. Demeaned motion was added as a covariate to the model. Furthermore, missing values of the covariates (dropout and technical failure [see below]) were imputed by population averages. The data were analyzed by using SPSS Statistics (version 22.0; IBM, Armonk, NY).

For the exploratory voxelwise statistical analysis, data were analyzed per protocol (ie, study participants with missing data were not included in the analysis). TBSS was performed to create a white matter skeleton to evaluate differences in FA by using nonparametric permutation testing with Randomize (500 permutations) (23). All analyses were initially thresholded at $P < .05$ (two sided), with a family-wise error correction for multiple comparisons using threshold-free cluster enhancement (24). Conditions were compared over time with demeaned motion scores as covariates, similar to the ROI analyses.

Results

Demographics and Treatment

Our study, which started on October 13, 2011, and ended June 15, 2015, included 50 stimulant treatment–naive Dutch boys (10–12 years of age) and 48 stimulant treatment–naive young Dutch adult men (23–40 years of age).

Neither the children nor the adult groups differed in age, ADHD symptom severity, or extent of clinical impairment prior to treatment administration (Table). No serious adverse events were noted in any of our study participants. Covariates were imputed for seven study participants because of dropout (no follow-up) and for one participant because of technical failure of the MRI study (at baseline), amounting to a total rate of imputed data of 4.1% (eight of 196).

ROI-based Analysis

At baseline, no differences were observed in the children or in the adult group between the two medication groups for any of the ROIs ($P > .2$ for all). We found no three-way interaction between time, age, and medication in any of the ROIs (whole brain: $F = 0.43$ [$df = 1, 88.6$], $P = .51$; ATR: $F = 0.03$ [$df = 1, 85.7$], $P = .86$; CC: $F = 0.13$ [$df = 1, 90.9$], $P = .72$) (Fig 3). We did not find a two-way interaction between time and medication in either the young or the adult study participants (in children, whole brain: $F = 2.23$ [$df = 1, 46.78$], $P = .13$; ATR: $F = 0.30$ [$df = 1, 46.34$], $P = .59$; CC: $F = 0.33$ [$df = 1, 47.60$], $P = .57$; in adults, whole brain: $F = 1.86$ [$df = 1, 42.40$], $P = .18$; ATR: $F = 0.58$ [$df = 1, 39.43$], $P = .45$; CC: $F = 0.09$ [$df = 1, 43.24$], $P = .76$). Finally, no main effect of time was found on FA in any of the ROIs ($P > .2$ for all). Hence, we observed no changes in FA in any of the ROI analyses.

Voxel-based Analysis

Because of missing data, the voxelwise analysis included only 47 children and 43 adults (demographics of this subset are described in Tables E1 and E2 [online]). There were no demographic differences between treatment groups within age strata nor between the medication groups in either the children or

Characteristics of the Study Groups for the ROI Analysis (Intention to Treat)

Characteristic	Children Treated with MPH (*n* = 25)	Children Treated with Placebo (*n* = 25)	Adults Treated with MPH (*n* = 24)	Adults Treated with Placebo (*n* = 24)
Age (y)	11.4 ± 0.8	11.3 ± 0.9	28.6 ± 4.6	29.0 ± 4.9
Estimated intelligence quotient*	104.8 ± 21.0	103.4 ± 15.1	107.9 ± 8.8	107.9 ± 6.4
ADHD subtype†				
Inattentive	14	14	11	5
Hyperactive/impulsive	0	1	0	0
Combined	11	10	13	19
ADHD symptoms				
DBD-RS inattention score	21.7 ± 3.2	22.8 ± 3.4	…	…
DBD-RS hyperactivity score	15.0 ± 5.0	16.4 ± 6.3	…	…
ADHD-SR	…	…	30.6 ± 10.0	30.4 ± 9.3
Adherence (%)	84 ± 15	80 ± 18	90 ± 8	86 ± 8

Note.—Unless otherwise specified, data are means ± standard deviations. ADHD = attention-deficit/hyperactivity disorder, ADHD-SR = Attention Deficit Hyperactivity Disorder-Self Report, DBD-RS = Disruptive Behavior Disorders Rating Scale, ROI = region of interest. Mean motion scores were as follows: 0.16 ± 0.42 (standard deviation) in children at baseline, 0.098 ± 0.43 in children at follow-up, −0.18 ± 0.24 in adults at baseline, and −0.09 ± 0.27 in adults at follow-up.

* Data are numbers of participants.

† Determined in children by using the Wechsler Intelligence Scale for Children; determined in adults by using the National Adult Reading Test.

adults at baseline. Additionally, no significant changes in FA were observed between baseline and posttreatment studies in either age group.

However, we found several clusters with significant differences in the changes from baseline to after treatment (ie, an interaction effect) between children and adults in whom MPH was administered (see Fig 4, left, for the time-by-medication-by-age interaction effects), illustrating small but significant increases in FA in children with MPH. The change in mean FA of all the significant voxels was extracted and plotted in Figure 4, right.

Discussion

In this trial, we studied whether the effects of methylphenidate (MPH) treatment on the white matter of stimulant-naive study participants with attention-deficit/hyperactivity disorder (ADHD) are modulated by age. We did not find a significant age-by-time-by-treatment interaction in the ROI analyses with standardized effects sizes between 0.15 and 0.58. However, our voxel-based analyses demonstrated a different change in FA values in children after treatment with MPH than the change in adults treated with MPH in specific brain regions, with a standardized effect size of 5.25, suggesting that the effects of MPH on brain white matter are modulated by age.

Our results are in line with the limited available literature on ADHD medications and brain white matter. First, Castellanos et al (4) reported an 8.9% increase in white matter volume in children with medicated ADHD compared with children who were not receiving medication. In a preclinical study in rats, we observed an increase of 9.2% in FA only in the CC of adolescent rats treated with MPH, but not in adult rats nor in saline-treated rats (5). The combined results of these studies and our current findings provide further evidence that MPH seems to affect white matter maturation. Our current findings may be mediated, in part, by increased expression of striatal genes involved in the formation of new axons that were upregulated (>1.5-fold change) by periadolescent MPH treatment (25). However, there is not much overlap between the tracts we found here and those mentioned in a previous meta-analysis (3). However, the studies in the meta-analysis were all retrospective in nature, and the possible confounding effects of medication were not taken into account.

The observation of interaction effects only in voxelwise comparisons and not in the selected ROIs suggests that the effects of MPH are particularly subtle: Small, local differences may be averaged out over the ROI. Furthermore, the locations in which significant interactions were found might indicate that brain regions other than the ATR are more susceptible to the stimulating effects of MPH. For instance, our CC ROI was placed central and more anteriorly in the truncus of the CC than the location where the voxel-based analysis detected an interaction effect; the lack of overlap likely explains the discrepancy between the two analyses. Moreover, changes after such a short period of time are likely small and therefore restricted to subclusters of tracts rather than the entire tract. Our voxel-based analyses suggest that the white matter in several association fibers (parts of the left superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus) seem to be particularly sensitive to the modulating effects of age. However, it is well known that these regions are rich in crossing fibers (26).

A strength of our current study was its prospective design, in which the effects of confounders such as age and sex are likely to be relatively small. The selective inclusion of stimulant treatment–naive study participants was also critical for addressing our objective. However, our study also had some limitations. We included only boys to limit variation, as girls and boys differ considerably in brain white matter development (27). Another potential weakness was the limited statistical power. Because of its complexity, the power of our study was limited, especially because we examined three different brain regions, which could have increased the risk of a type I error. The performed TBSS analysis particularly assessed small

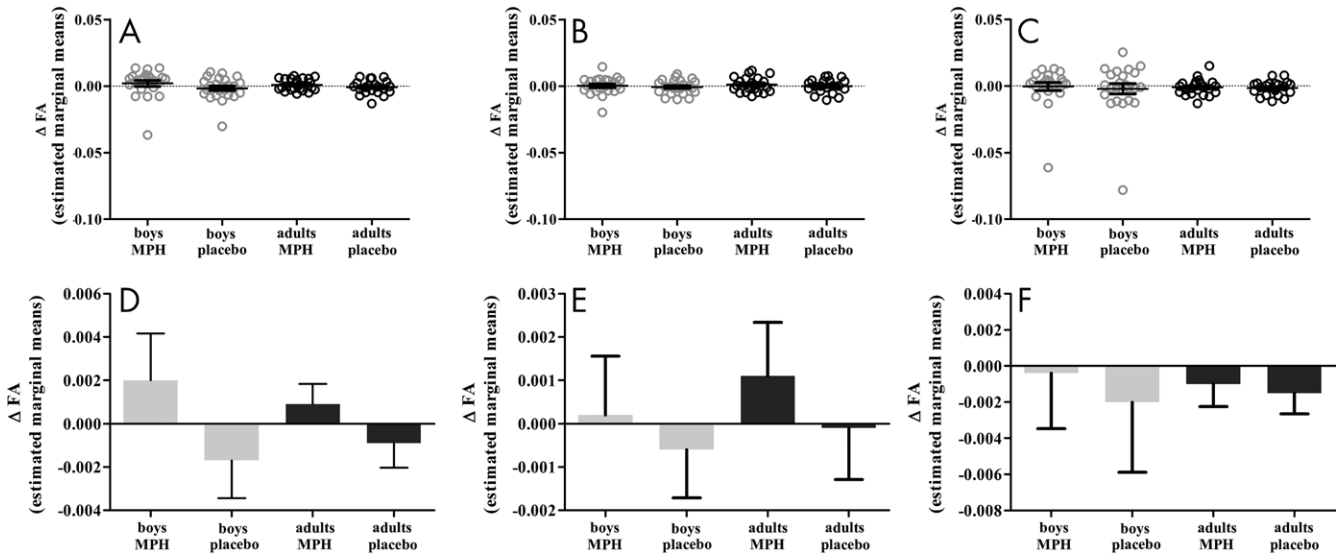

Figure 3: *A–F,* Graphs show results of region of interest analysis. *A–C,* Scatterplots of changes in raw fractional anisotropy (FA) values from baseline to after treatment in, *A,* whole-brain white matter, *B,* anterior thalamic radiation, and, *C,* splenium. *D–F,* Box-and-whisker plots show estimated marginal means and standard errors for change in FA values from baseline to after treatment in, *D,* whole-brain white matter, *E,* anterior thalamic radiation, and, *F,* splenium. Error bars = standard errors of the mean. MPH = methylphenidate.

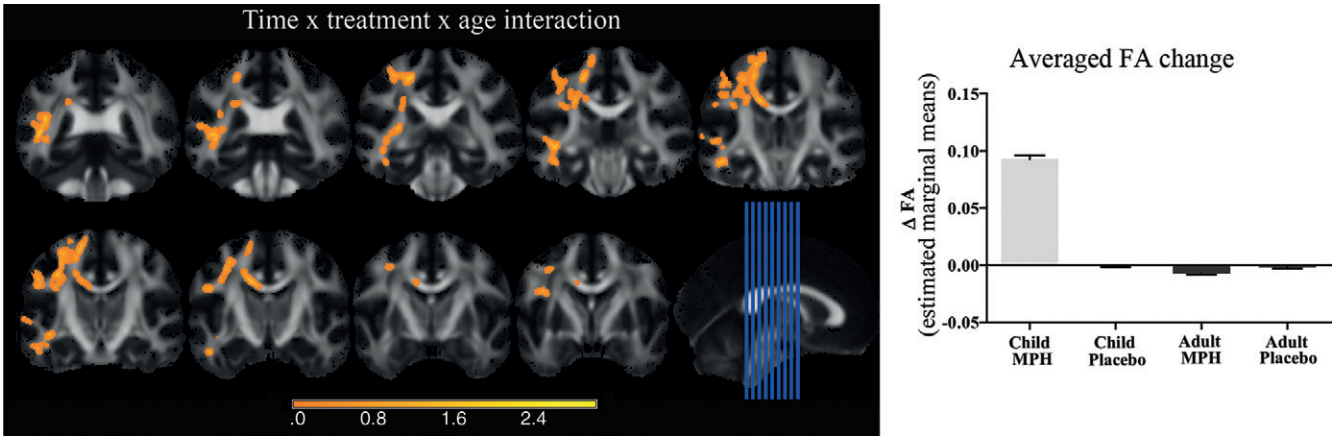

Figure 4: Images show whole-brain voxel-based analysis. Voxelwise fractional anisotropy (FA) comparison by Tract-Based Spatial Statistics software (22) showed significant treatment-by-age interaction effects. Left: Coronal sections that correspond to the sagittal section locations in the image in the bottom row far right. The areas in which the difference between baseline and after treatment in children treated with methylphenidate (MPH) was higher than that in adults treated with MPH are color-coded orange ($P < .05$) and are located in several association fibers (parts of the left superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus) and commissural fibers (lateral in the truncus of the corpus callosum). Right: Graph shows averaged FA change. Estimated marginal means and standard errors for change in FA values from baseline to after treatment of all significant voxels in the left image were extracted and plotted per group.

microstructural differences. The adopted 1.25 effect size was based on evidence of such subtle differences. This may have resulted in insufficient power for the ROI analysis (Fig 3), because our standardized effect sizes were between 0.15 (ATR ROI) and 0.58 (CC ROI). However, the standardized effect size in the voxelwise analysis (Fig 4) was 5.25. The diffusion-weighted MRI acquisition used in our study was limited to a single *b* value of 1000 sec/mm^2 only. Although FA was our predefined outcome measure, we also analyzed other values of white matter integrity, including mean diffusivity, axial diffusivity, and radial diffusivity. However, none of these demonstrated any clusters with significant differences in the changes from baseline to after treatment between children and adults in our voxel-based analyses. We hypothesize that FA may be more sensitive to the observed changes between groups, as we have previously demonstrated in a preclinical study with the same study design (5). In addition, our voxelwise analysis showed changes only in the left hemisphere. We investigated whether this finding may reflect hemispheric dominance. Because nearly all of our subjects were right handed, it is conceivable that the left hemisphere is more sensitive to the vulnerability of the imprinting effects of MPH, although we did not observe such a lateralization effect in our preclinical work in which we also measured FA values (5). Clearly, the potentially confounding effect of dominant handedness requires further investigation.

In conclusion, in line with clinical and preclinical data, we provide further evidence that the effects of methylphenidate (MPH) on brain white matter are modulated by age. The group difference was due to a more rapid increase in FA in children treated with MPH and was not seen in children receiving a placebo or adults. Future studies are needed to investigate whether our findings can be extrapolated to the female sex and to young/older children and/or adolescents, with more advanced protocols using multiple (at least two) *b* values, which would allow researchers to distinguish additional white matter details, such as fiber crossings, which cannot be reliably estimated otherwise.

Author contributions: Guarantor of integrity of entire study, L.R.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, C.B., O.G.F., L.R.; clinical studies, C.B., A.S., L.R.; experimental studies, L.R.; statistical analysis, C.B., O.G.F., A.S., M.W.A.C., F.M.V.; and manuscript editing, all authors

Disclosures of Conflicts of Interest: **C.B.** disclosed no relevant relationships. **O.G.F.** disclosed no relevant relationships. **A.S.** disclosed no relevant relationships. **M.W.A.C.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: owns stock or stock options in Nico.lab. Other relationships: disclosed no relevant relationships. **F.M.V.** disclosed no relevant relationships. **L.R.** disclosed no relevant relationships.

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