

The effect of methylphenidate intake on brain structure in adults with ADHD in a placebo-controlled randomized trial

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Background: Based on animal research several authors have warned that the application of methylphenidate, the first-line drug for the treatment of attention-deficit/hyperactivity disorder (ADHD), might have neurotoxic effects potentially harming the brain. We investigated whether methylphenidate application, over a 1-year period, results in cerebral volume decrease. **Methods:** We acquired structural MRIs in a double-blind study comparing methylphenidate to placebo. Global and regional brain volumes were analyzed at baseline, after 3 months and after 12 months using diffeomorphic anatomic registration through exponentiated lie algebra. **Results:** We included 131 adult patients with ADHD into the baseline sample, 98 into the 3-month sample (54 in the methylphenidate cohort and 44 in the placebo cohort) and 76 into the 1-year sample (37 in the methylphenidate cohort and 29 in the placebo cohort). Methylphenidate intake compared with placebo did not lead to any detectable cerebral volume loss; there was a trend toward bilateral cerebellar grey matter increase. **Limitations:** Detecting possible neurotoxic effects of methylphenidate might require a longer observation period. **Conclusion:** There is no evidence of grey matter volume loss after 1 year of methylphenidate treatment in adult patients with ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by early childhood onset and persistent symptoms of attention deficit, motor hyperactivity and impulsivity causing psychosocial impairments in different areas of life.¹ The persistence rate into adulthood varies between 15% and 65% depending on the diagnostic criteria applied.² Based on meta-analyses of population-based epidemiological studies the average prevalence of adult ADHD is 2.5%–4.9%.³

Pharmacotherapy, with stimulants in general and methylphenidate (MPH) in particular, is widely accepted as an effective treatment in both children and adults.¹ This therapy regime is recommended by all relevant guidelines for children, adolescents and adults if symptoms are severe and socially debilitating.⁴

In general MPH is well tolerated,^{5,6} however, there is controversy in the media and scientific literature about whether treatment with MPH is safe with respect to cerebral health.⁷ Limited evidence from animal research indicated that MPH

administration to young rats caused persistent reduction in the density of striatal dopamine (DA) transporters.⁸ This report sparked a public discussion about potential long-term damage from MPH to the basal ganglia, inducing symptoms of Parkinson disease.^{7,9–13} Several papers, mainly from animal research, reported negative long-term physiologic consequences of stimulant drugs, including induced abnormalities of krebs cycle enzymes, oxidative stress or altered dendritic spine formation.^{14–19} One recent study on mice reported that following chronic administration of 10 mg/kg of MPH using stereological counting methods, a significant reduction in DA neuron numbers in the substantia nigra pars compacta was observed, as well as a significant increase in the number of activated microglia in the substantia nigra.²⁰ Other authors also stress the differences between MPH and amphetamines and suggest that MPH might even be neuroprotective.^{21,22} In human research, several neuroimaging studies and meta-analyses concluded that MPH exerts normalizing effects on brain structures, with volume reductions being present in childhood and adolescence, but not in adulthood.^{23–27}

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However, thus far ADHD literature is lacking data from prospective human studies. All authors agree that such research is necessary to assess the safety of MPH for cerebral health in patients with ADHD.^{23–26,28}

This government-funded imaging study is part of a larger project comparing the effects of group psychotherapy (GPT) and clinical management (CM) and the effects of MPH and placebo in a factorial 2×2 , double-blind, multicentre study (COMPAS trial; EudraCT Number: 2006–000222–31; Current Controlled Trials ISRCTN54096201; BMBF 01GV0606).^{29,30} Following a baseline assessment (week 0) patients were randomized either to GPT + MPH, GPT + placebo, CM + MPH or CM + placebo. Group psychotherapy took place in weekly closed groups of 6–9 patients until week 13, followed by monthly sessions until week 52. Participants randomized to CM received weekly (monthly after week 13) supportive counselling in individual sessions that lasted 15–20 min.^{29,30} The results of the clinical trial are published elsewhere.³¹ Neuroimaging measurements were obtained at baseline (week 0), after 3 months (week 13) and after 1 year (week 52).

Given the discussion of the possible neurotoxic effects of MPH, the primary aim of the present study was to test the hypothesis that long-term administration of MPH alters global or regional cerebral volume. Because the study was implemented within the COMPAS trial we also analyzed the interaction between GPT and CM within these brain structures.

Methods

The study was approved by the Ethics Commission of the University Medical Center Freiburg and performed in accordance with the standards laid out in the Declaration of Helsinki.³² We obtained written informed consent from all participants before including them into the imaging subproject.

Patient recruitment and assessment

Within the COMPAS trial, after a prescreening procedure of 1480 patients, 518 were evaluated for trial participation and 433 were randomized into 4 arms at 7 study centres. The study protocol and diagnostic procedure were implemented within the clinical COMPAS trial.^{29,30} Appendix 1, Table S1, available at jpn.ca, lists the eligibility criteria for study participation. Appendix 1, Table S2 lists the applied diagnostic instruments. For the imaging study, patients were recruited from 2 clinical centres (Freiburg and Mannheim) in order to acquire all imaging data with only 1 MRI scanner (Freiburg site), therefore avoiding any additional signal variance.

Randomization and masking

Eligible patients were randomized in groups of 14–15; 1 group had only 12 participants and 1 group had 16 participants. The randomization scheme allowed GPT to take place in groups of 6–9 patients. Group psychotherapy or CM plus a medication number (coding for MPH or placebo) were centrally assigned to each patient.^{29,30} Treatments were allocated with a 1:1:1:1 ratio, stratified by centre.³¹

Patients and therapists were blinded for medication, but were aware of the assignment to either GPT or CM. However, the observers rating the symptoms of ADHD (using the Conner Adult ADHD Rating Scale [CAARS], the Diagnostic checklist for diagnosis of ADHD in adults and the Clinical Global Impressions Scale) were blind to the allocation of treatment.

Sample definition

Patients from the Freiburg and Mannheim study centres who passed prescreening were invited to participate in the imaging study (baseline sample, week 0). Because the screening process was not finalized at this time, participants could still be excluded from randomization if they did not fulfill all of the eligibility criteria (see Appendix 1, Table S1).^{29,30} The cross-sectional structural findings of this sample have been published elsewhere.³³ Every patient was invited to participate in 2 further MRI sessions (subsequently referred to as visits), which occurred 13 weeks and 52 weeks after therapy onset. The patients for whom we were not able to obtain full data sets at week 13 were excluded from the 3-month sample (week 0–13). The 1-year sample (week 0–52) included all patients for whom we were able to obtain full data sets for the duration of the study.

Imaging procedures

We acquired all MRI data at the Freiburg study site. An MPRAGE T_1 -weighted scan was obtained (repetition time [TR] 2200 ms, echo time [TE] 4.11 ms, flip angle 12° , field of view $256 \times 256 \text{ mm}^2$, voxel size $1 \times 1 \times 1 \text{ mm}^3$) on a Siemens 3 T TIM-Trio magnetom scanner equipped with a 12-channel head coil. All images were controlled for artifacts and image integrity, striation and fuzziness of MPRAGE images. Head motion or technical artifacts led to exclusion.

We used the VBM8 toolbox for longitudinal data (<http://dbm.neuro.uni-jena.de/467/>), as implemented in SPM8 running under MATLAB (MathWorks) software, to analyze the MRI data. We first segmented T_1 -weighted images into grey matter, white matter and cerebrospinal fluid (CSF). The latter analyses of global structural volumes used these VBM8-derived segment volumes. The grey matter and white matter segments were then used to obtain an across-subject registration template using DARTEL, which created an individual flow field for each participant by iteratively warping the individual tissue probability maps into alignment with the across-subject registration model. To avoid registration bias with 3 visits, normalization parameters were estimated from the averaged individual imaging after affine registration. In a further modulation step we spatially normalized the segments into Montreal Neurological Institute (MNI) space. After this modulation step, the value in each voxel represents the local volume of the respective tissue type. Images were smoothed using a 10 mm full-width at half-maximum Gaussian kernel.

Statistical analyses

The main focus of this project was on the effect of MPH vs. placebo across visits. However, because the COMPAS trial

also studied the efficacy of GPT compared with CM, we took this contrast (GPT v. CM) into account in all statistical analyses of the effects of MPH compared with placebo.

Comparison of cohorts

We calculated 2 different basic comparisons. First we compared global and regional brain volumes between patients randomized to the MPH or placebo cohorts at week 0 and week 13 (3-month sample). Second we analyzed the dynamics of global and regional brain volumes over a 1-year period comparing the MPH and placebo cohorts at 3 visits (week 0, week 13 and week 52; 1-year sample).

Comparison of psychometric and demographic data

We compared the structural equality of the MPH and placebo cohorts for both the 3-month and 1-year samples using χ^2 tests for all categorical variables and t tests or analyses of variance (ANOVA) where appropriate for dimensional data.

Global structural volumes

For the comparison of global signals we calculated a linear mixed model, with global structure volume as a dependent variable to assess the interaction between cohorts (MPH v. placebo) and visit (week 0 v. week 13 in the 3-month sample and week 0 v. week 13 v. week 52 in the 1-year sample). To assess a possible confounding effect of GPT compared with CM we added this category as a co-factor. All linear mixed model analyses were calculated in R software³⁴ using the afex package.³⁵ In each linear mixed model the random factor "subject" was included to allow for random intercepts across different participants. We dealt with multiple comparisons over 3 different global structural volumes using Bonferroni correction.

Regional structural volumes

For the analysis of the effect of MPH on brain structure we performed a $2 \times 2 \times 2$ mixed-effects ANOVA for the 3-month sample, and a $2 \times 2 \times 3$ mixed-effects ANOVA for the 1-year sample. We used the GLM-flex toolbox (http://nmr.mgh.harvard.edu/harvardagingbrain/People/AaronSchultz/GLM_Flex.html) to model effects of medication (2 levels: MPH v. placebo) as between-subjects factors and the repeated-measures effect of the visits (week 0 v. week 13 v. week 52) as a within-subjects factor. We focused on the grey matter segment and included all voxels with at least 10% probability of containing grey matter. After family-wise error (FWE) correction at the voxel level to correct for multiple comparisons across voxels, we applied a statistical threshold of $p < 0.05$. In addition, we performed exploratory analyses with uncorrected thresholds of $p < 0.001$ and $p < 0.01$ for the contrast between MPH and placebo to detect more subtle effects of MPH on brain volumes. We focused on the effects of visit, medication (MPH v. placebo) and psychotherapy (GPT v. CM) as well as the visit \times medication and visit \times psychotherapy interactions on grey matter volumes. To ensure that grey matter segments did not differ between groups on entering the study (baseline sample at week 0), we first ran a 2×2 ANOVA with only the baseline data included (data not shown).

Criterion of significance

The significance level for reporting was set to $p < 0.05$ after correction for multiple comparisons. In exploratory analyses we applied an uncorrected threshold of $p < 0.001$ and $k > 20$ voxels. For region-of-interest-based (ROI) analyses we used ROIs from the cross-sectional study³³ based on an earlier study by Seidman and colleagues.³⁶ Because the GLM-flex toolbox does not allow small-volume correction for multiple comparisons within an ROI, we extracted all voxels from the ROIs and corrected for multiple comparisons using false discovery rate (FDR) correction across all voxels of the corresponding ROI.

Results

Baseline, 3-month and 1-year samples

Figure 1 illustrates the selection process for the baseline sample. Of the 187 patients who consented to participate, 56 had to be excluded from further analysis for reasons listed in Figure 1. Thus the final patient sample at baseline consisted of 131 full data sets.

In 98 of the 131 baseline cases we were able to obtain full data sets at week 13. Of these 98 patients, 54 were receiving MPH and 44 were receiving placebo. The remaining 33 patients were excluded from the 3-month sample for reasons summarized in Figure 1. Table 1 summarizes the demographic and time-insensitive clinical data of this sample, with additional information being presented in Appendix 1, Table S3a. Appendix 1, Table S4a provides the medication details and Table S5a provides details on previous and current psychiatric comorbidity.

At the end of study, we were able to obtain full data sets from 66 patients (37 receiving MPH and 29 receiving placebo). The remaining 32 patients were lost to follow-up for reasons listed in Figure 1 and were excluded from the 1-year sample (see also Table 1 and Appendix 1, Tables S3b, S4b and S5b).

Matching of the 3-month and 1-year samples

Table 1 illustrates that cohorts of both the 3-month and 1-year samples were well matched with respect to age, sex, IQ and Wender Utah Rating Scale — German short version (WURSK) figures. As expected, the final dose of medication was significantly higher in the placebo cohort than the MPH cohort.

Prospective analysis of the effect of MPH on brain structure in the 3-month sample

Global structural volumes

Table 2 illustrates that there was a significant reduction of grey matter volumes and increase of white matter volumes after 3 months across both cohorts. However, there was no significant effect of cohort (MPH v. placebo) on global volumes and no significant cohort \times visit interaction.

Regional structural volumes

Overall there was no significant effect of MPH compared with placebo. In particular there was no evidence of volume loss in brain areas related to Parkinson disease (basal ganglia,

midbrain). Even when performing exploratory analyses we found no evidence of grey matter volume reduction.

Prospective analysis of the effect of MPH on brain structure in the 1-year sample

Global structural volumes

Table 3 illustrates that overall there was no significant effect of visit on global structural volumes. As in the 3-month sample,

there was no significant effect of cohort (MPH v. placebo) on global volumes and no significant cohort \times visit interaction.

Regional structural volumes

When comparing the cohorts in the 1-year sample across weeks 0, 13 and 52 we again found no evidence of grey matter volume reduction in any brain region. Even exploratory analyses revealed no evidence of grey matter volume loss. The effect of the cohort \times visit interaction on grey matter volume

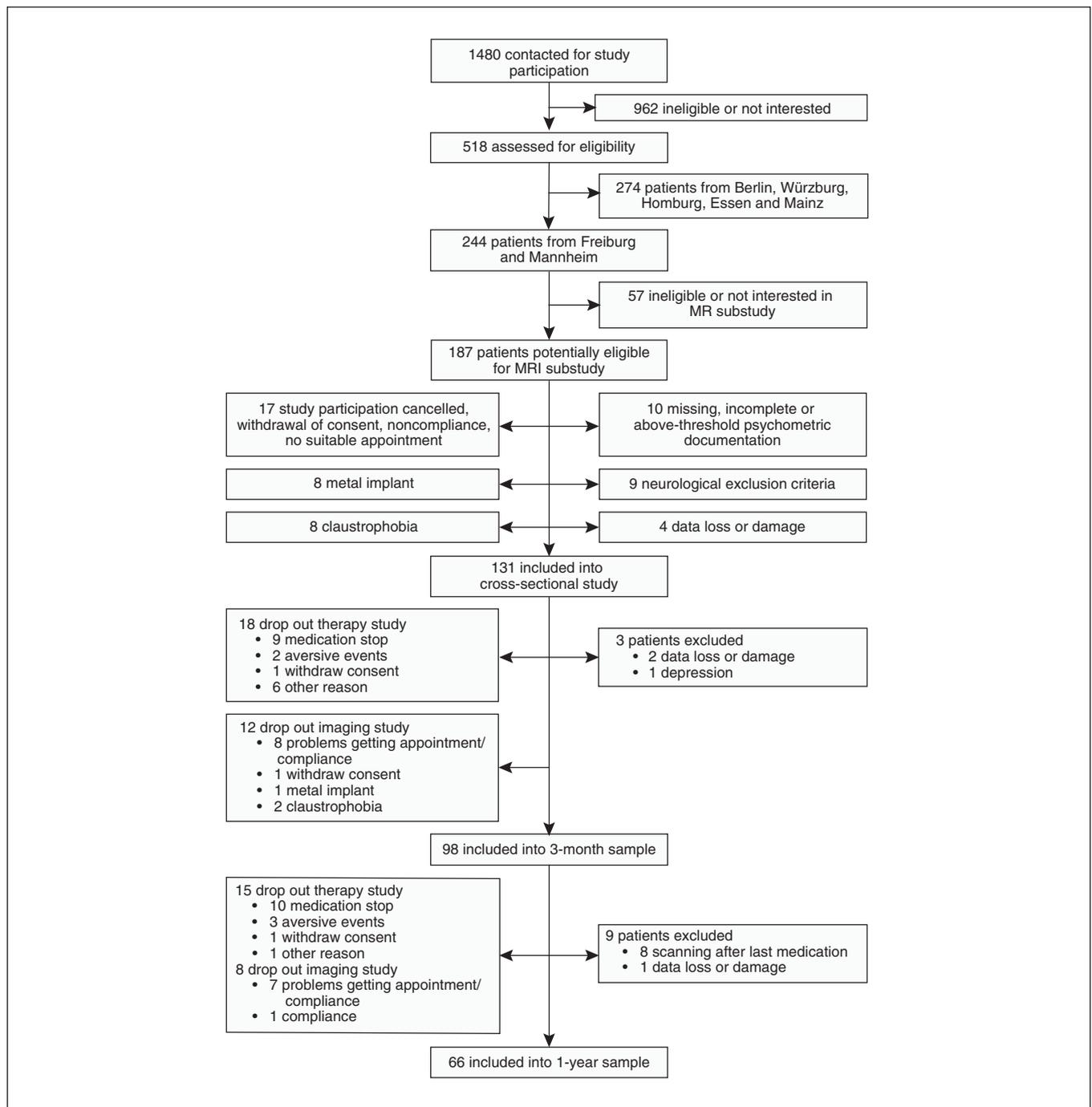


Fig. 1: Study enrolment process.

reached trend-level significance in the bilateral cerebellum (Fig. 2 and Table 4).

Effect of psychotherapy (GPT v. CM) on global and regional brain volumes

In the 3-month sample 44 of the 98 patients were receiving GPT compared with 54 who were receiving CM. In the 1-year sample 34 of the 66 patients were receiving GPT compared with 32 who were receiving CM (Table 1). In all statistical calculations mentioned previously, we included a comparison of GPT versus CM as a co-factor. The GPT \times visit and CM \times visit interactions did not reach statistical significance for global or regional brain volumes.

Discussion

Here we present longitudinal data of, to our knowledge, the only prospective, double-blind, placebo-controlled clinical trial analyzing the effects of MPH on brain structure in adults with ADHD. Our main finding was that administration of MPH over

a period of 1 year did not result in grey matter volume reduction compared with placebo. In particular we found no signs — even in less conservative testing — in regions that are classically involved in the modulation of symptoms related to Parkinson disease, including midbrain structures and the basal ganglia.

Possible implications of the main finding

It is of clinical importance that we could not detect evidence of grey matter loss as a consequence of treatment with MPH, as this reassures patients taking MPH as well as physicians prescribing the drug. However, this finding does not prove that there is no neuronal cell loss in the substantia nigra or other areas of the brain, because such processes might be too subtle to be picked up by voxel-based morphometry (VBM) or in an observation period of 1 year.³⁷ Of note, alterations in neuronal and glial cell physiology of the substantia nigra have been reported in young and developing rodents^{8,20} but not in adult animals, whereas we observed the structural dynamics of only adult human brains exposed to MPH. It may be that the same study done in children or adolescents

Table 1: Demographic and clinical characteristics of patients receiving methylphenidate compared with placebo in the 3-month and 1-year samples

Variable	Group; no. or mean \pm SD			Statistic	<i>p</i> value
	MPH	Placebo	Total		
3-month sample					
Participants	54	44	98		
Sex, female:male	29:25	22:22	51:47	$\chi^2 = 0.133$	0.72
ADHD subtype, iADHD:cADHD:hADHD	28:26:0	20:22:2	48:48:2	$\chi^2 = 2.674$	0.26
Psychotherapy, GPT:CM	24:30	20:24	44:54	$\chi^2 = 0.010$	0.92
IQ	113.89 \pm 15.3	113.89 \pm 15.4	113.81 \pm 15.3	$t_{96} = 0.059$	0.95
Age, yr	34.02 \pm 10.1	37.09 \pm 9.3	35.40 \pm 9.8	$t_{96} = -1.552$	0.12
WURS-k	39.63 \pm 9.4	41.82 \pm 8.0	40.61 \pm 8.8	$t_{96} = -1.224$	0.22
CAARS*	104.43 \pm 32.4	112.86 \pm 35.6	108.21 \pm 34.0	$t_{96} = -1.225$	0.22
ICV, mm ³ *	1386.37 \pm 131.1	1384.76 \pm 134.0	1385.64 \pm 131.7	$t_{96} = 0.060$	0.95
BDI*	11.55 \pm 6.9	12.72 \pm 9.8	12.08 \pm 8.3	$t_{75.089} = -0.664$	0.51
Dose, mg/kg	0.646 \pm 0.27	0.826 \pm 0.29	0.726 \pm 0.29	$t_{91} = -3.069$	0.003
1-year sample					
Participants	37	29	66		
Sex, female:male	17:20	14:15	31:35	$\chi^2 = 0.035$	0.85
ADHD subtype, iADHD:cADHD:hADHD	20:17:0	16:12:1	36:29:1	$\chi^2 = 1.357$	0.51
Psychotherapy, GPT:CM	18:19	16:13	34:32	$\chi^2 = 0.277$	0.60
IQ	114.22 \pm 16.1	109.76 \pm 14.6	112.26 \pm 15.5	$t_{64} = 1.164$	0.25
Age, yr	33.97 \pm 9.1	36.52 \pm 9.9	35.09 \pm 9.5	$t_{64} = -1.085$	0.28
WURS-k	38.24 \pm 8.1	39.90 \pm 7.1	38.97 \pm 7.7	$t_{64} = -0.866$	0.39
CAARS*	104.90 \pm 30.8	106.31 \pm 30.9	105.52 \pm 30.6	$t_{64} = -0.185$	0.85
ICV, mm ³ *	1394.29 \pm 137.0	1373.58 \pm 130.6	1385.19 \pm 133.6	$t_{64} = 0.622$	0.54
BDI*	11.35 \pm 8.13	13.62 \pm 9.6	12.35 \pm 8.1	$t_{64} = -1.134$	0.26
Dose, mg/kg	0.660 \pm 0.24	0.833 \pm 0.29	0.736 \pm 0.27	$t_{64} = -2.667$	0.010

ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; CAARS = Conner's Adult ADHD Rating Scale; cADHD = combined subtype; CM = clinical management; GPT = group psychotherapy; hADHD = hyperactive-impulsive subtype, iADHD = inattentive subtype; ICV = intracranial volume; MPH = methylphenidate; WURS-k = Wender Utah Rating Scale.

*Measured at baseline.

would have led to different results.³⁸ Still, it is reassuring that we could not detect evidence for grey matter loss in the diencephalon, the basal ganglia, or in fact in any brain area.

We detected only a trend-level inverse grey matter signal in patients treated with MPH and placebo in the bilateral cerebellum. This finding has to be treated with caution because it might represent a type-I error. When considering this observation as a relevant trend its significance is unclear. The finding might add to the increasing body of evidence that the cerebellum plays a critical role in the organization of higher cognitive and behavioural processes.³⁹ More precisely, cerebellar abnormalities have been reported in several imaging studies in childhood and adult ADHD in respective meta-analyses.^{28,40,41}

Discrete grey matter signal increase in VBM studies, secondary to behavioural or cognitive interventions, is most commonly reported as a cerebral correlate of adaptive neural plasticity and learning, which is generally not regarded as an indicator of pathological processes, such as neurodegeneration.^{42–44} Thus a trend toward a cerebellar grey matter signal increase secondary to MPH exposure might be a direct pharmacological effect or an indirect consequence of cognitive or behavioural change induced by the medication and nonpharmacological treatment. Why patients treated with placebo showed an inverse pattern remains unclear and might indicate that the signal decrease may not represent a true neuronal alteration. Future studies might clarify this issue.

Table 2: Comparison of change in global brain structures between patients receiving methylphenidate versus placebo after 13 weeks (3-month sample)

Variable	Visit; mean \pm SD, mm ³				Statistic	<i>p</i> value	
	Week 0		Week 13				
Grey matter							
MPH	643.91	63.5	641.44	63.5	Cohort	$F_{1,96} = 0.50$	0.44†
Placebo	634.82	59.1	630.76	59.2			
Visit	$F_{1,96} = 8.42$; $p = 0.005^*$				Cohort \times visit	$F_{1,96} = 0.61$	0.48‡
White matter							
MPH	520.12	66.1	522.42	67.4	Cohort	$F_{1,96} = 0.01$	0.94†
Placebo	520.81	61.2	523.63	62.7			
Visit	$F_{1,96} = 11.53$; $p = 0.001^*$				Cohort \times visit	$F_{1,96} = 0.12$	0.73‡
CSF							
MPH	222.34	28.0	221.57	27.1	Cohort	$F_{1,96} = 1.05$	0.31†
Placebo	229.13	38.9	228.52	39.1			
Visit	$F_{1,96} = 1.01$; $p = 0.32^*$				Cohort \times visit	$F_{1,96} = 0.01$	0.91‡

CSF = cerebrospinal fluid; MPH = methylphenidate.
 *Effect of visit in mixed-model statistic with covariate group psychotherapy versus clinical management.
 †Effect of cohort in mixed-model statistic with covariate group psychotherapy versus clinical management.
 ‡Cohort \times visit interaction in mixed model statistic with covariate group psychotherapy versus clinical management.

Table 3: Comparison of change in global brain structures between patients receiving methylphenidate versus placebo after 52 weeks (1-year sample)

Variable	Visit; mean \pm SD, mm ³			Statistic	<i>p</i> value	
	Week 0	Week 13	Week 52			
Grey matter						
MPH	647.24 \pm 67.0	644.45 \pm 67.1	646.89 \pm 67.4	Cohort	$F_{1,63} = 1.02$	0.32†
Placebo	631.54 \pm 60.5	628.78 \pm 58.9	628.20 \pm 56.7			
Visit	$F_{2,128} = 1.44$; $p = 0.24^*$			Cohort \times visit	$F_{2,128} = 0.54$	0.58‡
White matter						
MPH	523.99 \pm 69.8	526.07 \pm 71.7	524.93 \pm 69.0	Cohort	$F_{1,63} = 0.27$	0.60†
Placebo	514.36 \pm 57.1	516.32 \pm 57.3	516.84 \pm 59.9			
Visit	$F_{2,128} = 1.88$; $p = 0.16^*$			Cohort \times visit	$F_{2,128} = 0.34$	0.71‡
CSF						
MPH	223.06 \pm 28.0	222.50 \pm 26.7	222.84 \pm 27.9	Cohort	$F_{1,63} = 0.34$	0.56†
Placebo	227.68 \pm 40.2	227.00 \pm 40.5	227.32 \pm 42.6			
Visit	$F_{2,128} = 0.22$; $p = 0.80^*$			Cohort \times visit	$F_{2,128} = 0.00$	> 0.99‡

CSF = cerebrospinal fluid; MPH = methylphenidate.
 *Effect of visit in mixed-model statistic with covariate group psychotherapy versus clinical management.
 †Effect of cohort in mixed-model statistic with covariate group psychotherapy versus clinical management.
 ‡Cohort \times visit interaction in mixed-model statistic with covariate group psychotherapy versus clinical management.

Association with other findings

We have summarized the relevant literature in another recent paper.³³ Although no studies in the literature report data from a randomized controlled trial, there is some indirect evidence from case-control studies looking at the long-term outcome of patients who had received stimulants in the past. In addition, there are 2 meta-analyses^{23,24} that report evidence for basal ganglia volume loss in children (particular in the putamen, pallidum and caudate) that tends to normalize with age, par-

ticularly in patients receiving pharmacological treatment.^{23,24} A long-time prospective study is required to clarify whether MPH is involved in the normalization of brain volumes altered in childhood and adolescence.

Limitations

Methodological issues and limitations of this study have to be considered. As mentioned, the present study is part of a larger multicentre, double-blind clinical trial comparing the effect of

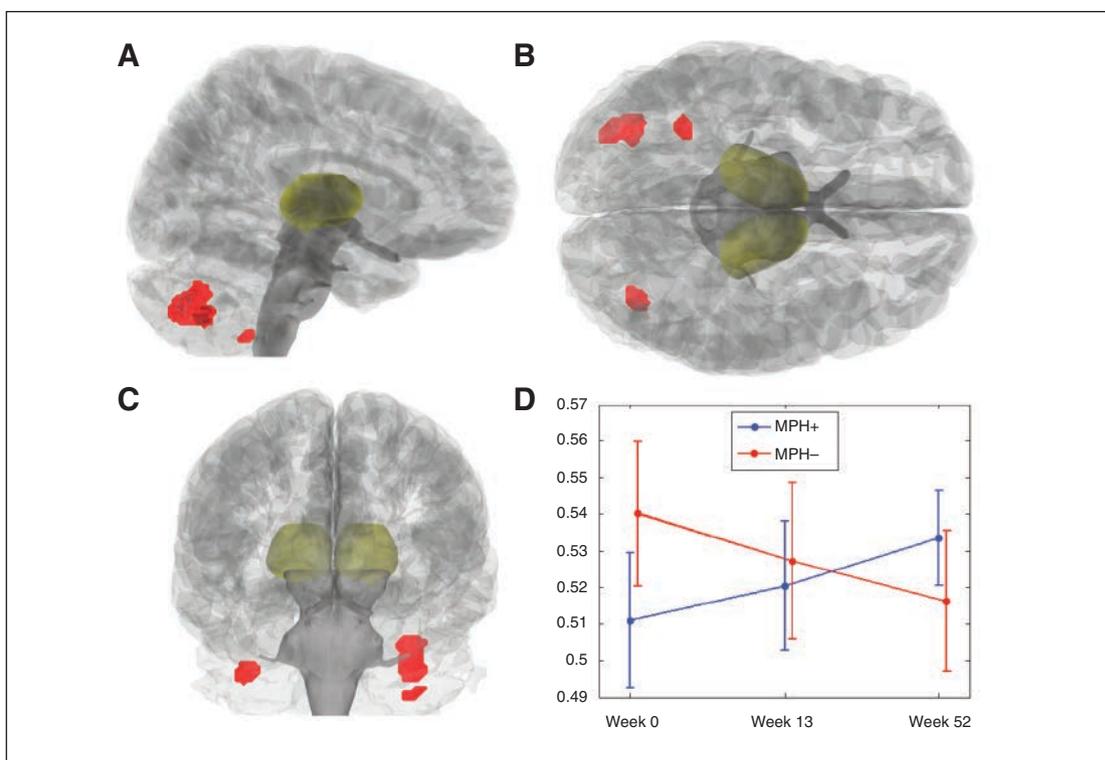


Fig. 2: Long-term effect of methylphenidate (MPH) versus placebo after 1 year. Depicted are those areas bilaterally in the cerebellum where a steady increase of grey matter signal was found over time in the MPH cohort, whereas in the placebo cohort there was a signal reduction (medication \times visit interaction across week 0, week 13 and week 52; $p < 0.01$, uncorrected, $k = 50$). (A) Sagittal view from the right side. (B) Transversal view from the top. (C) Coronal view from the front. (D) Plot of the mean peak voxel grey matter contrast estimates with 95% confidence intervals across the 3 visits. MPH- = placebo.

Table 4: Region-of-interest-based analysis for GLM-flex comparison of patients receiving methylphenidate versus placebo after 13 weeks (3-month sample) and 52 weeks (1-year sample)*

Area	3-month sample			1-year sample		
	Statistic	p value	p value, FDR†	Statistic	p value	p value, FDR†
ACC	$F_{1,94} = 14.19$	< 0.001	0.999	$F_{2,124} = 5.67$	0.005	0.99
DLPFC	$F_{1,94} = 13.39$	< 0.001	1.000	$F_{2,124} = 5.21$	0.007	> 0.99
IPL	$F_{1,94} = 10.07$	0.002	1.000	$F_{2,124} = 5.77$	0.004	0.91
Cerebellum	$F_{1,94} = 11.49$	0.001	0.604	$F_{2,124} = 7.30$	0.001	0.53
Caudate	$F_{1,94} = 5.75$	0.018	0.975	$F_{2,124} = 2.57$	0.004	0.99
Putamen	$F_{1,94} = 3.94$	0.05	1.000	$F_{2,124} = 3.55$	0.032	> 0.99

ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; FDR = false discovery rate; IPL = inferior parietal lobule.
 *Peak voxel F and uncorrected p values for $2 \times 2 \times 2$ mixed-effects analysis of variance for the 3-month sample and a $2 \times 2 \times 3$ mixed-effects analysis of variance for the 1-year sample using GLM-flex toolbox for different regions of interest. No cluster filter has been applied to the uncorrected p and F values.
 †FDR-corrected p values have been adjusted for the number of voxels in the corresponding regions of interest.

MPH and placebo and comparing the effect of GPT and CM in adults with ADHD. All diagnostic and therapeutic procedures followed the highest standards and were monitored throughout the studies' progress.^{29,30} The study sample had a slightly above-average mean intelligence; however, the clinical, socio-demographic and psychometric characteristics of our sample mirror those of most other VBM studies and meta-analyses in adults with ADHD.^{23,24} Demographic characteristics of the MPH and placebo cohorts were comparable (Table 1). In contrast to cross-sectional VBM studies³³ we decided not to consider sex or linear and quadratic age effects owing to the longitudinal design of the study.

All images were acquired using the same MRI scanner, and the protocol and scanner were not modified during the study.

Still there are relevant limitations. The dropout rate was much higher than anticipated, possibly owing to the disorder itself in addition to the duration of the study (1 year in total). Also, we had additional exclusions owing to data quality (e.g., movement artifacts), which also could be partially explained by the symptoms of ADHD (restlessness).

Future studies should precisely record the duration and intensity of pretreatment stimulus prescription, which was not fully documented in the present study. Further, possible detrimental effects of MPH might be too subtle to be picked up by VBM and during an observation period of 1 year.

Conclusion

To our knowledge, this is the largest imaging study in adults with ADHD, and the only study prospectively comparing MPH with placebo in a placebo-controlled, double-blind trial. Applying well-established VBM methods we found no evidence of global or regional cerebral volume loss as a consequence of the administration of MPH over a period of 1 year. In particular, we found no evidence of volume loss in brain areas related to dopaminergic dysfunction (midbrain, basal ganglia).

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