ORIGINAL ARTICLE

Evidence of Developmental Alterations in Cortical and Subcortical Regions of Children With Attention-Deficit/Hyperactivity Disorder

A Multivoxel In Vivo Phosphorus 31 Spectroscopy Study

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Context: There is mounting evidence of neurodevelopmental alterations implicating the prefrontal cortex (PFC) and basal ganglia in children with attention-deficit/hyperactivity disorder (ADHD). The brain undergoes substantive structural and functional changes with a differential timing between brain regions during development from childhood to adolescence. In vivo phosphorus 31 magnetic resonance spectroscopy (^{31}P MRS) is a noninvasive neuroimaging approach that is sensitive in assessing developmental changes of overproducing/pruning of synapses.

Objective: To provide support for a developmental mechanism targeting a bottom-up dysfunction of the basal ganglia impairing the fine-tuning of prefrontal functions in ADHD.

Design: Cross-sectional study.

Setting: Pittsburgh, Pennsylvania, and the surrounding areas.

Participants: Thirty-one psychostimulant-naive children with ADHD (mean [SD] age, 8.1 [1.2] years; range, 6.1-10.0 years) and 36 healthy control subjects (mean [SD] age, 8.1 [1.3] years; range, 6.1-10.4 years).

Main Outcome Measure: Membrane phospholipid (MPL) precursor levels (ie, phosphomonoesters that are anabolic metabolites of MPL) were assessed in the PFC and basal ganglia as well as in 4 other brain regions using in vivo ^{31}P MRS.

Results: Lower bilateral MPL precursor levels in the basal ganglia and higher MPL precursor levels in the inferior parietal region (primarily right side) were noted in the children with ADHD as compared with healthy control children. There was a group × age interaction in the PFC and inferior parietal region, with relatively older psychostimulant-naive children with ADHD showing significantly lower PFC and higher inferior parietal MPL precursor levels. No differences between groups were noted in the superior temporal, posterior white matter, or occipital regions.

Conclusion: Though based on cross-sectional data, these results are suggestive of possible progressive, nonlinear, and sequential alterations implicating a bottom-up developmental dysfunction in parts of the cortico-striato-thalamo-cortical network in ADHD.

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ATTENTION-DEFICIT/HYPERactivity disorder (ADHD) is one of the most prevalent childhood behavioral disorders, affecting 8% to 12% of the population worldwide.[1] Attention-deficit/hyperactivity disorder, which appears in early childhood, is characterized by the inability to focus attention, control impulses, and refrain from extraneous motor activity.[2] The inhibitory regulation,[3] executive function (eg, attention regulation and working memory), motivational processes, perception, and motor control[4-6] have all been implicated in ADHD. Consistent with these cognitive deficits, neuroimaging studies have shown structural and functional alterations in the prefrontal cortex (PFC), basal ganglia (BG), cerebellum, and inferior parietal lobe of children with ADHD.[7-9] Castellanos and colleagues[10] have reported in a large longitudinal study developmental trajectories of gray matter volumes in children with ADHD paralleling those of healthy children but with smaller volumes in all regions except the caudate. They have suggested that early influences on brain development in ADHD may be fixed and nonprogressive. However, a more recent study assessing cortical thickness has shown a delay in the maturation of the cortex by approximately 2 years in children with ADHD compared with healthy con-

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trols.[11] Also, there is evidence of a lag or delay in cognitive and social development in children with ADHD,[12-17] which would suggest regional progressive trajectories differing between children with and without ADHD.

During childhood and adolescence, the brain undergoes substantive structural and functional changes in a heterochronous (or differential timing) manner between brain regions.[18-27] For example, longitudinal structural magnetic resonance imaging (MRI) studies of healthy subjects have shown a pattern of increasing gray matter volumes in children followed by decreasing gray matter volumes into adolescence. The peak of gray matter volume occurs earlier in the somatosensory and visual cortices, followed by temporal and parietal association cortices, and then by the slower-developing PFC and lateral temporal cortex.[22-25] In the subcortical region, the caudate nucleus decreases in volume during childhood and adolescence.[23,28,29] The sequential timing of these regions parallels cognitive milestones. The maturation of primary motor and sensory functions comes first, followed by basic language skills, attention and spatial memory, and then by higher-order executive functions and motor coordination.[30] These changes in cortical volume coincide with changes in the formation of synapses on dendritic spines and shafts and on somas[18-20]; the processes of eliminating overproduced neuronal connections or synapses and acquiring synaptic efficiency (ie, decreasing gray matter volumes) appear to parallel the fine-tuning or maturation of cognitive performance.[31,32] This also is supported by functional MRI studies that show increased focal activation with increasing cognitive performance.[33] Considering the heterochronous behavior of overproducing/pruning of synapses associated with maturation, one may speculate that an alteration of an earlier-developing region may influence the development of a later or slower-developing region.[34] In pediatric ADHD, alterations in the development of the BG may influence the later development of the PFC.

In vivo phosphorus 31 magnetic resonance spectroscopy (^{31}P MRS) is a noninvasive neuroimaging approach sensitive in assessing neurodevelopment.[35-38] Specifically, ^{31}P spectroscopy provides information on metabolites that are part of the anabolic and catabolic pathway of membrane phospholipids (MPLs). These include phosphomonoesters (PMEs) phosphoethanolamine and phosphocholine, which are precursors of MPLs, and phosphodiesters (PDEs) glycerophosphoethanolamine and glycerophosphocholine, which are breakdown products of MPLs.[39-41] In tissue, MPLs naturally form membrane bilayers that at the cellular level separate functional compartments, such as dendrites and synaptic connections. Early in postnatal brain development, several in vivo human and ex vivo rat brain extract ^{31}P spectroscopy studies have consistently shown high MPL precursor levels and low levels of MPL breakdown products. This reflects the high production demand of MPLs for the rapid development of dendritic and synaptic connections. This is followed by decreases in precursor levels and increases in breakdown products that then plateau as the brain reaches maturation.[37,38] Burri et al[42] also have shown in early brain development an inverse correlation between decreasing MPL precursor levels and increasing concentration of MPLs. In addition, it has been shown that MPL precursor levels significantly increase at the time and site of neuritic sprouting.[43] Recently, in vivo ^{31}P spectroscopy data of healthy subjects have shown similar trajectories of increasing MPL precursor levels in children followed by decreasing levels in adolescents.[44] The timing of the peak in the PFC is consistent with that of anatomical MRI data.[22,23] Collectively, this suggests that the quantification of MPL precursor levels is a sensitive measure of synthesis activity of MPLs (ie, the density of dendrites and synaptic connections). In a pilot in vivo ^{31}P spectroscopy study, we have shown deficits in MPL precursor levels in the BG as well as in the slower-developing PFC region of children with ADHD aged 7 to 12 years as compared with healthy comparison subjects.[45] These deficits suggested a possible underdevelopment of neuronal processes and synapses in ADHD. However, it also is possible that the earlier-developing BG may influence the slower-developing PFC, leading to progressive developmental alterations in ADHD. The purpose of this study was to investigate the MPL precursor levels in relatively younger children with ADHD (than the initial study) using the identical ^{31}P spectroscopy methods.[45] We hypothesized that MPL precursor deficits in the BG would be seen across the age range of children with ADHD but that the PFC MPL precursor level deficits would only be observed in the relatively older children with ADHD. This would provide support where PFC alterations are not apparent until the onset of fine-tuning processes in the PFC of children with ADHD. The novelty of this study is the examination of age effects in very young psychostimulant-naive children with ADHD.

METHODS

SUBJECTS

Thirty-one psychostimulant-naive children with *DSM-IV* ADHD[2] and 36 healthy comparison subjects participated in this study. This is an independent sample from our previous study.[45] Attention-deficit/hyperactivity disorder and other psychiatric diagnoses were determined using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL),[46] which was administered to the subject and his or her parent/guardian. The Disruptive Behavior Disorders Scale (DBD)[47,48] and the Iowa Connors Hyperactivity/Impulsivity Scale[49] questionnaires were given to the parent/guardian and the subject's teacher and were used to augment the K-SADS-PL diagnostic interview in determining ADHD status. The Kaufman Brief Intelligence Test was administered to measure verbal and nonverbal intelligence.[50] Subject exclusion criteria included (1) *DSM-IV* disorder, including schizophrenia or other psychotic disorders, pervasive developmental disorders, tic disorders, eating disorders, mood disorders, or anxiety disorders; (2) severe depressive symptoms that require prompt, more intensive clinical attention; (3) a diagnosis of a *DSM-IV* substance abuse disorder within 3 months; (4) a significant medical and/or neurological illness past or current (eg, hypertension, thyroid disease, diabetes mellitus, asthma requiring prophylaxis, seizures, or significant head injury);

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Table. Subject Group Characteristics

	Mean (SD) [Range]					
	Healthy Comparison Children			Psychostimulant-Naive Children With ADHD		
	Younger	Older	Total	Younger	Older	Total
Sample size	17	19	36	15	16	31
Sex distribution	13 boys; 4 girls	14 boys; 5 girls	27 boys; 9 girls	14 boys; 1 girl	11 boys; 5 girls	25 boys; 6 girls
Age, y	6.9 (0.5) [6.1-7.8]	9.2 (0.7) [8.1-10.4]	8.1 (1.3) [6.1-10.4]	7.1 (0.6) [6.1-8.1]	9.1 (0.6) [8.2-10.0]	8.1 (1.2) [6.1-10.0]
ADHD subtype				9 combined; 6 inattentive	6 combined; 10 inattentive	15 combined; 16 inattentive
Comorbidity				3 ODD; 2 CD	4 ODD	7 ODD; 2 CD
Full-scale IQ	106 (15)	117 (15)	111 (16)	109 (17)	110 (14)	110 (17)
Child Global Assessment Scale score	92 (5)	93 (5)	92 (5)	54 (5)	59 (6)[a]	56 (6)
DBD[47,48] inattentive score[b]	0.2 (0.4) [0.2 ± 0.5]	0.2 (0.3) [0.1 ± 0.1]	0.2 (0.4) [0.2 ± 0.3]	2.3 (0.5) [2.1 ± 0.7]	2.1 (0.7) [2.0 ± 0.9]	2.2 (0.6) [2.1 ± 0.8]
DBD hyperactive/impulsive score[b]	0.2 (0.8) [0.3 ± 0.3]	0.2 (0.3) [0.2 ± 0.3]	0.2 (0.3) [0.2 ± 0.3]	1.8 (0.8) [1.7 ± 1.0]	1.4 (0.7) [1.4 ± 1.0]	1.6 (0.8) [1.6 ± 1.0]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; DBD, Disruptive Behavior Disorders Scale; ODD, oppositional defiant disorder.

[a] Significantly different when compared with that of the younger psychostimulant-naive children with ADHD group (P=.02).

[b] Mean score ±1 SD from parent report and teacher report in brackets.

(5) a history of or a current psychiatric disorder, including schizophrenia or other psychotic disorders, mood disorders, or a hereditary neurological disorder in a first-degree relative; and (6) an IQ of 70 or lower. There were 7 children with ADHD who had comorbid oppositional defiant disorder and 2 children with comorbid conduct disorder. All children were naive to any psychostimulant medication at time of the scan. After a complete description of the study to the subjects and guardians, written informed consent was obtained from the parents/guardians and assent, from the child. The University of Pittsburgh institutional review board approved the study and consent. The **Table** includes a summary of subject characteristics.

MRS AND MRI PROCEDURE

No children were sedated during the scanning procedure. Prior to the examination, the children familiarized themselves with the MRI system and the sounds of scanning sequences using our MRI simulator. For data collection, a doubly tuned transmit/receive volume head coil was used to acquire the multivoxel ^{31}P spectroscopy data on a GE LX 1.5-T whole-body MRI system (GE Medical Systems, Milwaukee, Wisconsin). A 3-plane MRI localizer was first collected, followed by a set of sagittal and axial scout MRIs using the 2-dimensional fast spin-echo sequence that were used to prescribe the ^{31}P spectroscopy measurement. A single-slice selective excitation RF pulse followed by phase-encoding pulses to spatially encode the 2 in-plane dimensions (termed *FIDCSI* on a GE system) was used to acquire the multivoxel in vivo ^{31}P spectroscopy data (ie, the 2-dimensional chemical shift imaging). Based on sagittal scout images, the ^{31}P 2-dimensional chemical shift imaging axial slice was positioned parallel with the anterior-posterior commissure line (**Figure 1**A). Prior to ^{31}P spectroscopy measurement, automatic and manual shimming on the axial slice were applied using the FIDCSI sequence in the proton hydrogen 1 (^{1}H) mode. The acquisition parameters were field of view (FOV) $=240\times360$ mm^2, slice thickness=30 mm, 8×8 phase-encoding steps (nominal voxel volume=40.5 cm^3 or 3.0×4.5 cm$\times$3 cm^3), repetition time (TR)=2000 milliseconds, complex data points=1024, spectral bandwidth=5.0 kHz, preacquisition delay=1.7 milliseconds, number of averages=16, and acquisition time approximately 34 minutes. A 3-dimensional volume of T1-weighted images covering the entire brain (spoiled gradient recalled acquisition, TR=25 milliseconds, echo time=5 milliseconds, flip angle=400°, FOV=240×180 mm, slice thickness=1.5 mm, 124 coronal slices, number of excitations=1, matrix=256×192, and scan time=7 minutes 44 seconds) was then collected for tissue-segmentation analysis of the ^{31}P spectroscopy voxels followed by a set of T2-weighted/proton density images (2-dimensional fast spin-echo; TR=3000 milliseconds; echo times=17 and 102 milliseconds; echo-train length=8; FOV=240×240 mm^2; approximately 24 axial slices, 5-mm thick, and no gap; number of excitations=1; matrix=256×192; and scan time 5 minutes 12 seconds) to screen for neuroradiological abnormalities. The acquisition protocol was identical to the previously published study.[45]

MRS QUANTIFICATION

The 6 different right and left regions of interest included the PFC (including the anterior cingulate gyrus, superior frontal gyrus, and prefrontal white matter), BG (including the head of the caudate, putamen, anterior portion of the thalamus, anterior horn of the lateral ventricle, and white matter tracts between and around these structures), superior temporal (including the superior temporal gyrus and precentral and postcentral gyrus), inferior parietal (including the supramarginal gyrus and angular gyrus), posterior white matter (including the supramarginal gyrus and forceps major), and the occipital (including the cuneus, precuneus, posterior cingulate, and calcarine sulcus) regions. To optimize the voxel placement for each region, the 8×8 multivoxel grids, which were superimposed on their respective axial scout MRIs, were shifted accordingly (Figure 1C). In the k-space domain, a mild spatial apodization (ie, Fermi window with 90% diameter and 5% transition width) resulting in an effective voxel size of approximately 46.4 cm^3 was applied, whereas in the chemical shift domain a 5-Hz gaussian apodization was applied. In fitting the PME, PDE, inorganic orthophosphate (Pi), phosphocreatine (PCr), and adenosine triphosphate (2 doublets and a triplet) resonances, the ^{31}P spectroscopy signals extracted from the regions of interest were modeled with 11 gaussian-damped si-

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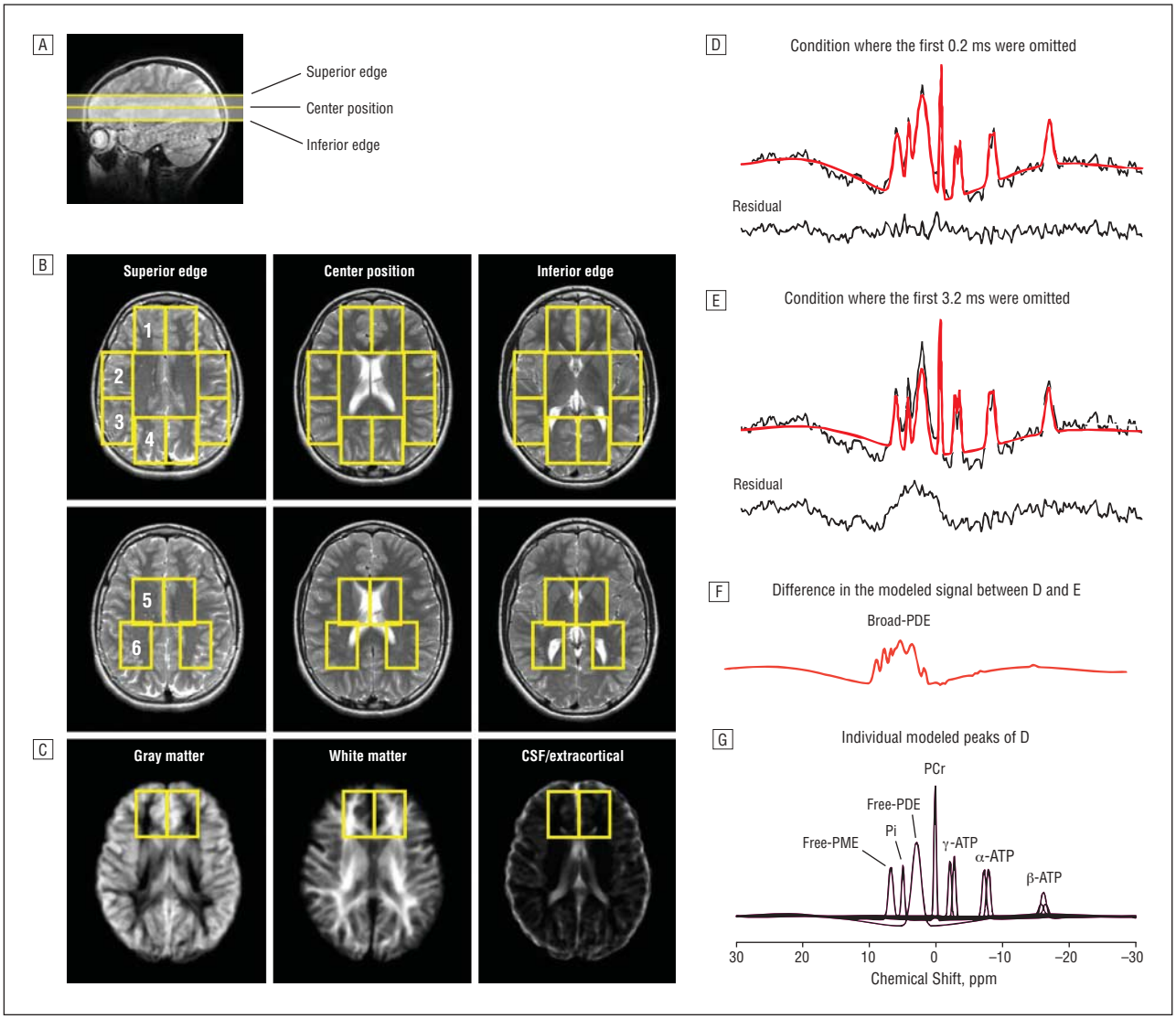

Figure 1. A, The cross-sectional view of the 2-dimensional chemical shift imaging (CSI) 3-cm-thick axial slice. B, The in-plane view of the 2-dimensional CSI and the 6 different right and left regions of interest as indicated by the yellow voxels (1=prefrontal, 2=superior temporal, 3=inferior parietal, 4=occipital, 5=basal ganglia, and 6=posterior white matter). The Figure depicts the superior and inferior edges and center position of the 30-mm-thick 2-dimensional CSI axial slice. C, Example of tissue-segmented images with the prefrontal voxel superimposed. An example of modeling an in vivo phosphorus 31 (^{31}P) spectrum in the time domain by omitting the first 0.2 milliseconds and 3.6 milliseconds of the ^{31}P signal are shown in parts D and E, respectively. D and E, The Fourier transformation of the acquired (black line) and modeled (red line) signal and the residual below (ie, the difference between acquired and modeled signal). F, The difference in the modeled signal between parts D and E, in which the area under the curve represents the level of the broad signal underlying the phosphodiester resonance (broad-PDE). G, The individual modeled peaks of part E and the assignment of the spectral peaks. ATP indicates adenosine triphosphate; CSF, cerebrospinal fluid; free-PME, freely mobile membrane phospholipid precursors; free-PDE, freely mobile membrane phospholipid breakdown products; PCr, phosphocreatine; and Pi, inorganic orthophosphate.

nusoids in the time domain, omitting the first 3.2 milliseconds and using the Marquardt algorithm.[51] The omission of the first 3.2 milliseconds was chosen to ensure that the broad signal underlying the PDE and PME resonances (termed *broad-PDE*) had negligible influence or contribution in the modeling as illustrated in the residual of Figure 1D.[41] The broad-PDE signal was then estimated by taking the difference in the modeled signal between modeling the total acquired signal using minimal omission (in this case, 0.2 milliseconds) and using an omission of 3.2 milliseconds (ie, the difference between parts C and D in Figure 1). Also, this approach ensured that the quantified PME and PDE primarily reflected the freely mobile MPL precursors and breakdown products (termed *free-PME* and *free-PDE*, respectively).[41] The metabolite levels were expressed as a mole percentage (ie, relative to the total modeled amplitude when omitting 3.2 milliseconds of the ^{31}P spectroscopy signal). A typical example of quantifying the ^{31}P spectroscopy signal of a voxel is shown in Figure 1.

In addressing the variability in the composition of tissue types within the ^{31}P spectroscopy voxels, the proportions of gray and white matter tissue and cerebrospinal fluid (CSF)/extracortical space were estimated for each extracted ^{31}P spectroscopy voxel. In a fully automated procedure, the T1-weighted images were coregistered to the axial scout images and corrected for any B_1 field bias, the brain was extracted, and the images were segmented into partial volume maps of gray and white matter tissue and CSF/extracortical space using FreeSurfer and FSL tools (eg, FLIRT, NU_CORRECT, BET, and FAST).[52,53] The tissue fractions were then estimated by extracting from the segmented images the region of interest matching the coordinates and size of the ^{31}P spectroscopy voxel using the FSL tools (eg, AVWROI, AVWSTATS, and AVWMATHS) as illustrated in Figure 1C.

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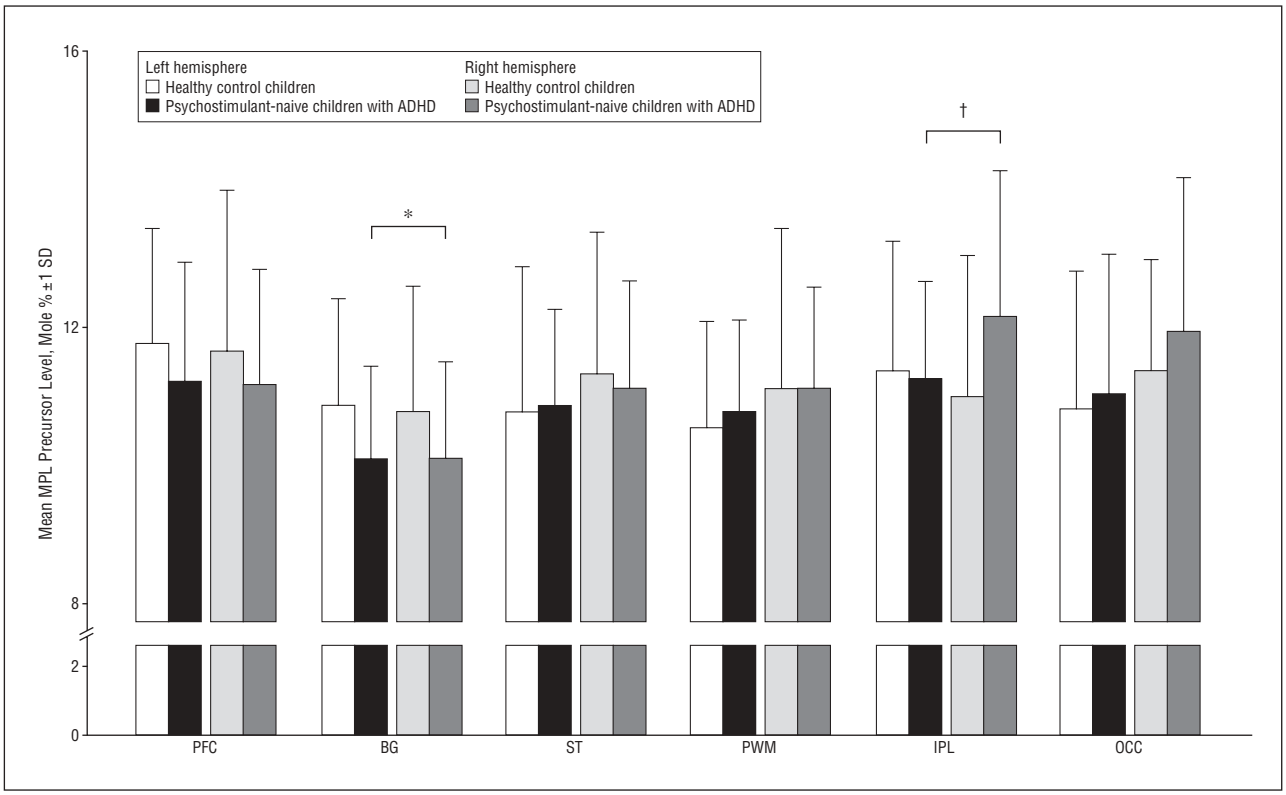

Figure 2. Mean membrane phospholipid (MPL) precursor levels of healthy control children and psychostimulant-naive children with attention-deficit/hyperactivity disorder (ADHD) in the left and right hemisphere for the 6 different regions of interest (prefrontal cortex [PFC]; basal ganglia [BG]; superior temporal [ST]; posterior white matter [PWM]; inferior parietal lobe [IPL]; and occipital cortex [OCC]). * and † significantly different between psychostimulant-naive children with ADHD and healthy comparison subjects (independent of hemisphere; $P=.02$ and $P=.046$, respectively).

STATISTICAL ANALYSIS

Regression analyses based on the generalized estimating equation method (PROC GENMOD; SAS Institute Inc, Cary, North Carolina) with subject group (ADHD and healthy comparison), age, sex, hemisphere (right and left), and gray matter fraction (relative to gray plus white matter fractions only, as the concentration of ^{31}P metabolites is negligible in CSF) as the main effect terms were used to test group differences with a region of interest. To test lateral/bilateral differences, a model with an additional group × hemisphere interaction term was used. Post hoc comparisons for significant group × hemisphere interactions were done using the differences of least squares means. Also, to test age effects, a model with a group × age interaction term was used. The statistical results of the GENMOD analyses (ie, the score statistics for type 3 generalized estimating equation analyses) were based on the χ^2 statistics and associated P values.[54] In addressing the primary hypotheses, these models were applied with free-PME level as the dependent variable for the PFC and BG regions; subsequent analyses with free-PDE, broad-PDE, PCr, and β–adenosine triphosphate levels and PCr/Pi and free-PME/free-PDE ratios as dependent variables for the 6 different regions also were conducted. The right and left measurements were treated as repeated measurements in each analysis and P values of .05 or less were considered significant.

RESULTS

Neither age nor full-scale IQ was significantly different between psychostimulant-naive children with ADHD and healthy comparison children ($t_{65}=0.15$; $P=.89$ and $t_{65}=0.35$; $P=.76$) (Table). Mean (SD) age was not significantly different between children with combined subtype ADHD (n=15) and predominantly inattentive subtype ADHD (n=16) (8.0 [1.2] years vs 8.3 [1.2] years; $t_{29}=0.74$; $P=.47$) or between psychostimulant-naive children with ADHD with and without comorbidity (7.9 [1.3] years vs 8.2 [1.1] years; $t_{29}=0.73$; $P=.47$). Furthermore, in each region of interest there were no significant group differences in the proportion of gray (or white) matter tissue within the ^{31}P spectroscopy voxels.

REGIONAL EFFECTS

Independent of hemisphere, free-PME levels were significantly lower in the BG of psychostimulant-naive children with ADHD compared with healthy comparison children ($\chi^2=5.69$ and $P=.02$) (**Figure 2**). In the inferior parietal region, both free-PME levels and free-PME/free-PDE ratios were significantly higher in the psychostimulant-naive children with ADHD compared with healthy comparison children ($\chi^2=3.98$ and $P=.046$; $\chi^2=8.57$ and $P=.003$) (Figure 2). There were no other significant differences in metabolite levels or ratios in the PFC, superior temporal, posterior white matter, or occipital regions between psychostimulant-naive children with ADHD and healthy comparison children.

HEMISPHERE EFFECTS

The only significant group × hemisphere interaction was observed in the inferior parietal free-PME/free-PDE ratios ($\chi^2=5.29$ and $P=.02$) (Figure 2), with post hoc analy-

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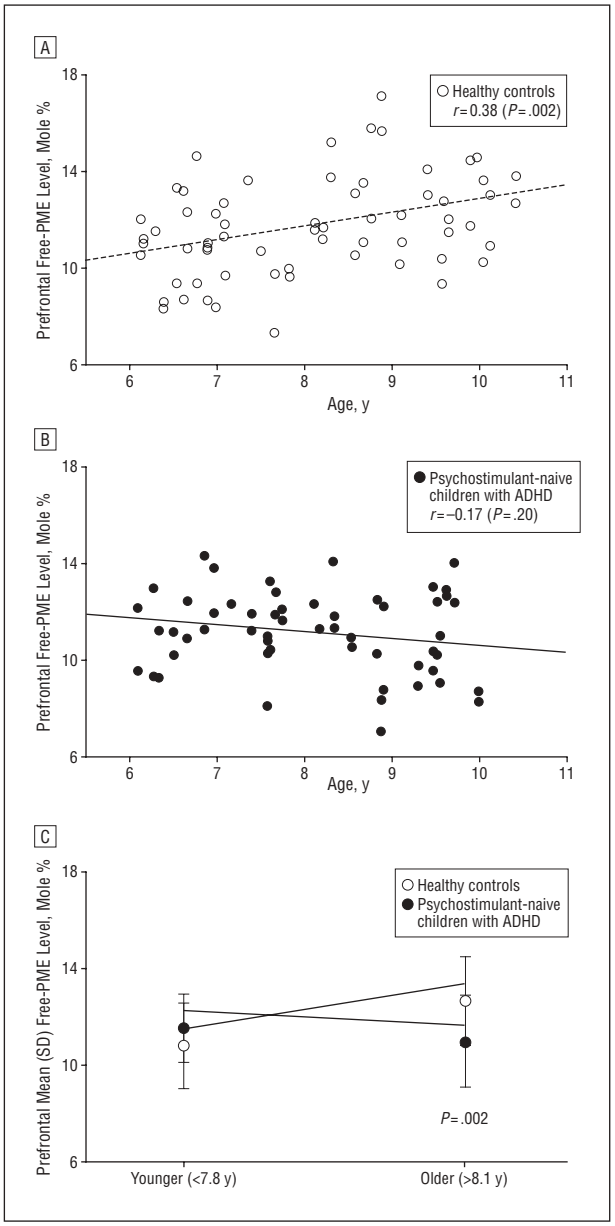

Figure 3. A and B, Scatterplots of freely mobile membrane phospholipid (MPL) precursor levels (free-PME) vs age from the prefrontal cortex (PFC) of healthy controls (A) and psychostimulant-naive children with attention-deficit/hyperactivity disorder (ADHD) (B). The correlations are as indicated and there is a significant group × age interaction (P=.01) as noted in the text. C, Plot showing the mean (SD) MPL precursor levels from the PFC of healthy controls and psychostimulant-naive children with ADHD dichotomized based on age (ie, younger and older).

ses showing increased ratios on the right side of the inferior parietal region of psychostimulant-naive children with ADHD compared with healthy comparison children (χ^2=14.3 and P<.001). The inferior parietal free-PME levels failed to reach significance (χ^2=3.62 and P=.06) (Figure 2), but post hoc analyses also showed a similar right-sided effect (χ^2=7.34 and P=.007).

AGE EFFECTS

Regarding any group × age interactions, both the PFC free-PME (χ^2=6.54 and P=.01) and inferior parietal free-PME (χ^2=4.85 and P=.03) levels were significant. In the PFC, free-PME levels positively correlated significantly with age in healthy comparison children (r=0.38 and P=.002) (**Figure 3**A), which contrasted the negative free-PME correlation with age in the children with ADHD (r=−0.17 and P=.20) (Figure 3B). In the inferior parietal, a stronger negative association between free-PME levels and age was observed in the healthy comparison children (r=−0.51 and P<.001) compared with children with ADHD (r=−0.19 and P=.14).

To further investigate whether there were age-related group differences in PFC and inferior parietal free-PME levels, the children were dichotomized into younger and older groups based on the age median. There were 15 younger children with ADHD (14 boys and 1 girl aged between 6.1 and 8.1 years; 9 combined subtype and 6 inattentive subtype) and 16 older children with ADHD (11 boys and 5 girls aged between 8.2 and 10 years; 6 combined subtype and 10 inattentive subtype) and 17 younger healthy comparison children (13 boys and 4 girls aged between 6.1 and 7.8 years) and 19 older healthy comparison children (14 boys and 5 girls aged between 8.1 and 10.4 years). There were no significant differences in the DBD inattentive or hyperactive/impulsive symptom scores between the 2 psychostimulant-naive ADHD subgroups except for significantly higher Child Global Assessment Scale scores in the older compared with younger psychostimulant-naive children with ADHD (Table). The 4-group subject term with age, sex, gray matter fraction, and hemisphere as covariates was significant for both PFC (χ^2=8.58 and P=.04) and inferior parietal (χ^2=9.6 and P=.02) free-PME levels. Post hoc analyses showed lower PFC free-PME levels in the older psychostimulant-naive children with ADHD compared with the older healthy comparison children (χ^2=9.23 and P=.002) (Figure 3C), whereas the inferior parietal free-PME levels were significantly higher in the older children with ADHD compared with older healthy comparison children (χ^2=12.5 and P<.001).

COMMENT

In this study, a multivoxel in vivo ^{31}P spectroscopy technique was used to assess the level of metabolites associated with MPL and high-energy phosphate metabolism in 6 different right and left brain areas of psychostimulant-naive children with ADHD and healthy comparison children. Lower bilateral MPL precursor levels in the BG and higher MPL precursor levels in the inferior parietal region (primarily right side) were noted in the psychostimulant-naive children with ADHD as compared with healthy comparison subjects. These findings, which corrected for the proportion of gray matter tissue volume within the ^{31}P spectroscopy voxels in the analyses, are consistent with MRI studies noting structural changes in these regions.[8,55-57] No differences between groups were noted in the superior temporal, posterior white matter, or occipital regions. Additionally, for the first time to our knowledge, this study identified an age interaction in the PFC and inferior parietal region, with relatively older psychostimulant-naive children with ADHD showing lower

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PFC and higher inferior parietal MPL precursor levels. To place these findings in the context of brain development, one needs a closer look at the biochemical significance of ^{31}P spectroscopy measurements.

Though ^{31}P spectroscopy may lack in spatial resolution because of the lower sensitivity of the ^{31}P nuclei relative to the ^{1}H nuclei, there is a high degree of specificity in assessing biochemical changes of MPL precursor levels in brain development. During a growth spurt in the neuropil with the branching of dendrites and the formation of new synapses, one would expect increased activity in the MPL synthesis that is reflected by increased MPL precursor levels and likewise decreased levels during the process of synaptic elimination or pruning.[42,43] This is demonstrated by the decrease in MPL precursor levels coinciding with the heterochronous pruning behavior of overproduced dendrites and synaptic connections from childhood to adolescence[18-27] as shown in **Figure 4**A and B. Because of the age limit of 10 years in this study, the age range has been extended with older healthy controls to illustrate the broader developmental age trends (albeit based on cross-sectional data) of MPL precursor levels in the PFC and BG (Figure 4A and B). Also, because of differences in developmental trajectories between males and females,[59] and the subjects in this study being predominantly male, only data of male subjects are shown in Figure 4. Over this broader age range, the peaking or plateau of MPL precursor levels in the BG and PFC of males occurs approximately at the age of 9 and 10 to 11 years, respectively, and is consistent with structural MRI data[10,29,59] as well as with the maturation of cognitive and behavioral milestones at that age range.[30-32] Also, the MPL precursor measurements reaffirm the timing of overproducing/pruning of dendrites/synapses occurring earlier in the BG relative to the PFC. Therefore, the lower bilateral MPL precursor levels in the BG of children with ADHD, which primarily parallel the trajectory of healthy children, are consistent with our recent report assessing relatively older children with treated ADHD (Figure 4F vs Figure 4D).[45] This suggests the density of dendrites and synapses is less with decreased activity in MPL synthesis in children with ADHD potentially because of an underdevelopment of dendritic branching and synaptic formations. This is in line with smaller caudate volumes being observed in children with ADHD in several structural MRI studies as well as reduced globus pallidus and putamen volumes.[8,55,57,60] In general, structural MRI studies have shown bigger effects in right caudate volume in children with ADHD, suggesting a loss of normal right-greater-than-left caudate asymmetry,[61] which was not observed in this study with the MPL precursor levels. Though this psychostimulant-naive ADHD cohort was too young to compare "normalization" effects with prior reports,[10] it would be interesting to extend the age range in a future investigation using ^{31}P spectroscopy.

In contrast to the BG, MPL precursor level alterations in the PFC of children with ADHD were only significant in the relatively older psychostimulant-naive children with ADHD, again, a finding consistent with our earlier independent report (Figure 3C and Figure 4C and E).[45] The proportion of ADHD subtypes between the younger and older children with ADHD was not balanced, but the lack of differences in DBD inattentive and hyperactive/impulsive symptom scores between the younger and older psychostimulant-naive children with ADHD suggests that the potential of symptoms influencing changes in MPL precursor levels is unlikely. The novelty of this study is the identification of a significant age effect observed in very young psychostimulant-naive children with ADHD. There are several structural MRI studies that have shown reduced PFC volumes in ADHD,[9,55,57,60] but in most cases, these studies involved relatively older children with ADHD and therefore were unable to identify this age effect. The PFC trajectory of the relatively younger children both with and without ADHD shows increasing MPL precursor levels, but then the psychostimulant-naive children with ADHD deviate prior to the maximum peaking of the healthy comparison children (Figure 4C). This suggests that the ability to overproduce dendrites and synapses with decreased activity in MPL synthesis is significantly less in the relatively older psychostimulant-naive children with ADHD (ie, their ability to "fine-tune" the maturation of the PFC may be interpreted as underachieved). Additionally, the BG has projections to and from the PFC and, as noted earlier, the timing of the fine-tuning in healthy comparison children occurs ahead of the PFC. Based on our findings, one may speculate that the underdeveloped BG is altering the fine-tuning maturation process of the PFC.[9,34,62] This indicates a developmental mechanism targeting a bottom-up dysfunction impairing the fine-tuning of control processes or executive functions in the PFC.[3,6,9,62] In all, the data on the MPL precursor levels from the PFC and BG suggest possible progressive nonlinear and sequential alterations in parts of the cortico-striato-thalamo-cortical network in ADHD as part of an attempt to reorganize the neuropil during these growth spurts. Caution is warranted as the data are based on cross-sectional measurements and definitively addressing this issue requires future longitudinal studies.

In the inferior parietal region, MPL precursor levels were significantly higher in psychostimulant-naive children with ADHD compared with healthy comparison children and were more pronounced in the right hemisphere and in the relatively older psychostimulant-naive children with ADHD. This absence of decreasing MPL precursor levels with age in the inferior parietal region of psychostimulant-naive children with ADHD compared with healthy comparison children, which resulted in a greater contrast in the relatively older psychostimulant-naive children with ADHD, is suggestive of less synaptic pruning (with higher MPL synthesis activity) or fine-tuning in the right inferior parietal region in ADHD. The right inferior parietal region plays an important role in visual sustained attention and attention or set shifting[63] and has been implicated in children with ADHD by structural MRI studies. Interestingly, in a recent structural MRI study, Sowell and colleagues[64] reported a bilateral increase in gray matter density in the inferior parietal region of children with ADHD as well as reductions in the size of prefrontal regions, which is consistent with this study when comparing the relatively older psychostimulant-naive children with ADHD. However, reduced bilateral gray and white

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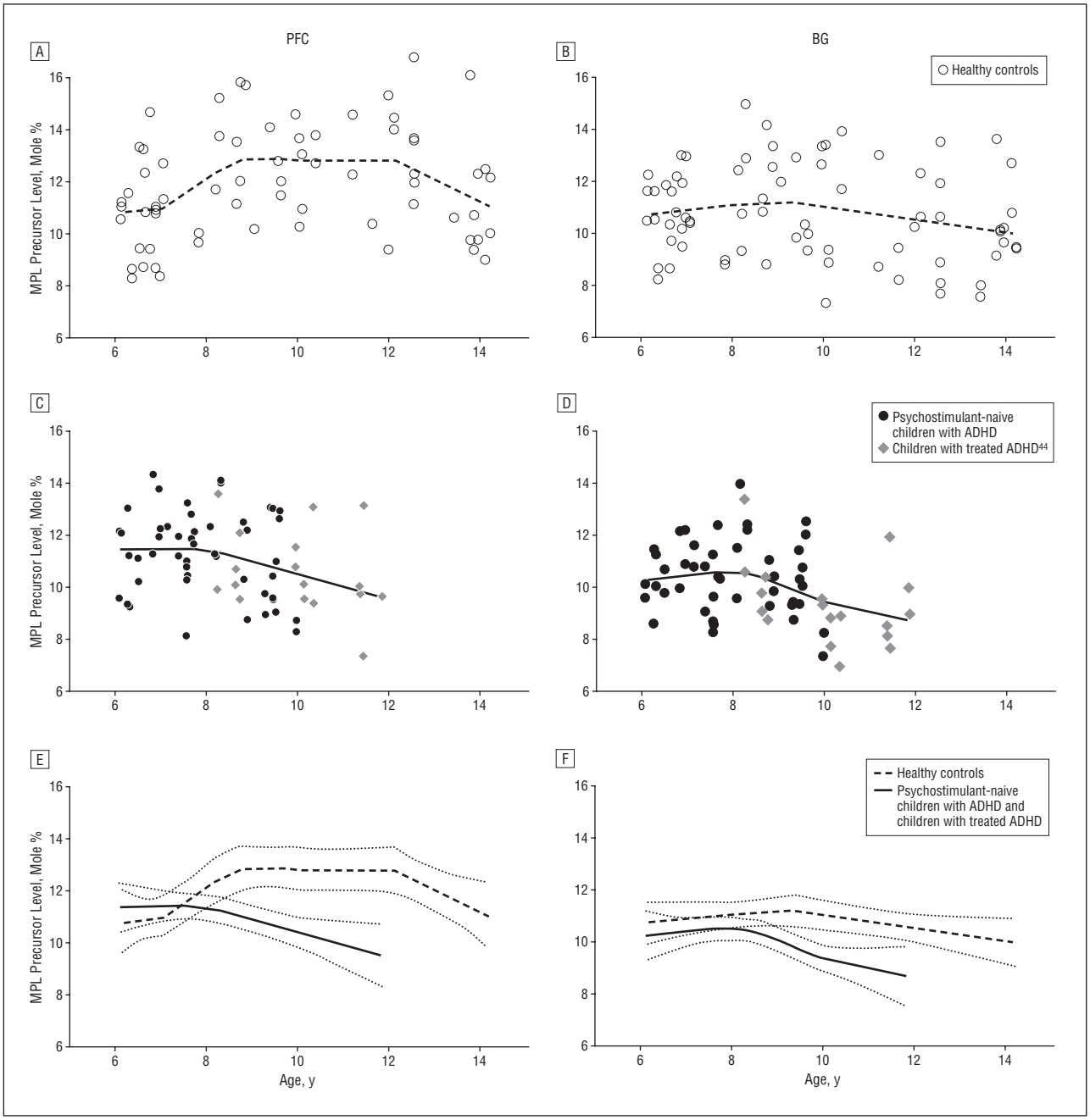

Figure 4. A-F, Scatterplots of membrane phospholipid (MPL) precursor levels vs age in the prefrontal cortex (PFC) (A, C, and E) and basal ganglia (BG) (B, D, and F) of healthy controls (A and B), psychostimulant-naive children with attention-deficit/hyperactivity disorder (ADHD), and children with treated ADHD (C and D) (data published by Stanley el al[45]). All data points are of male subjects only. To qualitatively illustrate trajectories of MPL precursor levels in normal brain development, 15 additional older healthy controls (excluded from the Table description) were added in parts A and B. The modeled curves were derived by using the generalized additive model (PROC GAM; SAS Institute Inc, Cary, North Carolina), which is a nonparametric regression approach where, unlike the LOESS model, the smoothing is optimized by minimizing the sum of squared residual.[58] Also, this approach avoids the assumption of a specific function in describing the mean age trends (eg, a parabola or quadratic function, which forces a discrete peak to be estimated). In parts E and F, only the modeled curves are shown along with their 95% confidence intervals based on the goodness of fit (dotted lines).

matter volumes have been seen in the inferior parietal region of ADHD,[10,65] though not by all.[66] Functional MRI studies using sustained visual attention tasks also have shown reduced activation in the right inferior parietal region of children with ADHD compared with healthy comparison children.[67-69] Additionally, there is evidence from electroencephalography studies of multiple brain growth spurts during development, which include a growth spurt beginning at about the age of 6 years.[70] The decreasing MPL precursor levels in healthy comparison subjects are suggestive of an earlier peaking in the right inferior parietal region. It is not known whether the psychostimulant-naive children with ADHD who did not show decreasing MPL precursor levels with age also had an earlier overproduction of synapses. These results stress the importance of studying younger children with ADHD.

The characterization of these deviations in MPL precursor level trajectories with age in the PFC and

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inferior parietal region of psychostimulant-naive children with ADHD is limited to a certain degree by the cross-sectional design. However, the sample size is respectable, with a balanced distribution of ADHD subtypes across a difficult-to-study age range of 6 to 9 years. Nevertheless, to truly assess individual developmental courses, longitudinal studies are needed.[71] The relatively large voxels question whether these changes in MPL precursor levels with age are due to changes in white matter tissue. However, the maturation trajectory of white matter volumes increases approximately linearly from early childhood to adolescence,[59] which cannot account for the nonlinear changes in MPL precursor levels with age in the PFC and BG of healthy comparison children (Figure 4A and B). Differences in the proportions of gray and white matter volume within the voxels were not significant between subject groups. Note that voxel tissue content is a different metric than measuring the true volume of a structure. The proportion of gray matter within the voxels was also accounted for as a covariate in the analyses and the significant differences persisted. Interestingly, ^{31}P spectroscopy was able to identify these developmental trajectories based on cross-sectional data, which was only possible for structural MRI studies by conducting longitudinal measurements on much larger samples.[22] Collectively, this suggests that in vivo ^{31}P spectroscopy may have greater sensitivity in identifying developmental changes in healthy controls as well as in detecting biochemical alterations in children with ADHD as compared with conventional structural MRI approaches.

In conclusion, these cross-sectional results provide support for regionally specific changes in MPL synthesis activity in ADHD that are suggestive of being progressive and raise the possibility of a bottom-up dysfunctional mechanism of the BG, impairing the fine-tuning of cortical control processes or executive functions in the slower-developing PFC of children with ADHD.

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