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Brain abnormalities in children with attention-deficit/hyperactivity disorder assessed by multi-delay arterial spin labeling perfusion and voxel-based morphometry

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Abstract:	Purpose: To obtain an understanding of the correlation between hemodynamic differences and morphological changes as well as potential sex differences in children with ADHD using multi-delay pseudo-continuous arterial spin labeling (pCASL) imaging and voxel-based morphometry (VBM), especially given that previous findings are limited for girls. Materials and methods: We recruited 23 children with ADHD (mean age, 8.3 years; 19 boys; 4 girls) and 24 children without ADHD (mean age, 9.1 years; 13 boys; 11 girls) as controls. All participants underwent 3D multi-delay pCASL and T1-weighted imaging. The voxel-based statistical parameter mapping (SPM) method was used for group-wise comparisons.

	Results: Compared with controls, children with ADHD exhibited decreased regional cerebral blood flow (rCBF) and gray matter volume (GMV) in the left middle frontal gyrus and left postcentral gyrus. Analysis by sex revealed reduced rCBF and GMV in the left lingual gyrus and left inferior occipital gyrus in boys with ADHD versus controls and increased rCBF and GMV in the left superior frontal gyrus in girls with ADHD. Conclusion: Although our results are preliminary because of small sample sizes, several brain regions exhibit changes in both cerebral perfusion and GMV in the same direction in patients with ADHD, with boys with ADHD showing decreased activity and girls with ADHD displaying increased activity in the fronto-parietal cortices.
Secondary Abstract:	In the present study, we evaluated cerebral perfusion and volumetric abnormalities along with sex differences in children with ADHD using multi-delay pseudo-continuous arterial spin labeling and voxel-based morphometry. Children with ADHD exhibited several abnormalities in both cerebral perfusion and gray matter volume in the same direction.
Author Comments:	

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Abstract

Purpose:

To obtain an understanding of the correlation between hemodynamic differences and morphological changes as well as potential sex differences in children with ADHD using multi-delay pseudo-continuous arterial spin labeling (pCASL) imaging and voxel-based morphometry (VBM), especially given that previous findings are limited for girls.

Materials and methods:

We recruited 23 children with ADHD (mean age, 8.3 years; 19 boys; 4 girls) and 24 children without ADHD (mean age, 9.1 years; 13 boys; 11 girls) as controls. All participants underwent 3D multi-delay pCASL and T1-weighted imaging. The voxel-based statistical parameter mapping (SPM) method was used for group-wise comparisons.

Results:

Compared with controls, children with ADHD exhibited decreased regional cerebral blood flow (rCBF) and gray matter volume (GMV) in the left middle frontal gyrus and left postcentral gyrus. Analysis by sex revealed reduced rCBF and GMV in the left lingual gyrus and left inferior occipital gyrus in boys with ADHD versus controls and increased rCBF and GMV in the left superior frontal gyrus in girls with ADHD.

Conclusion:

Although our results are preliminary because of small sample sizes, several brain regions exhibit changes in both cerebral perfusion and GMV in the same direction in patients

with ADHD, with boys with ADHD showing decreased activity and girls with ADHD displaying increased activity in the fronto-parietal cortices.

Keywords: Attention-Deficit/Hyperactivity Disorder, Cerebral Blood Flow, Magnetic Resonance Imaging, Pediatrics.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset neurodevelopmental disorder characterized by age-inappropriate inattention, hyperactivity, and impulsivity [1, 2]. ADHD exhibits a sex difference, with a prevalence 2.4 times higher in boys than in girls, which persists into adolescence [3]. The limited literature on sex differences in ADHD has shown that boys and girls with ADHD differ in terms of clinical presentation and, to some extent, neuropsychological functioning [4]. Very few studies have explored sex differences in regional brain perfusion in ADHD.

In prior functional studies, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have been widely used to distinguish perfusion alterations in brain regions in children with ADHD. However, these techniques require the administration of contrast material and/or exposure to ionizing radiation. Arterial spin labeling (ASL) imaging has recently become extensively used in clinical practice as a technique that enables the direct and noninvasive quantitative measurement of cerebral blood flow (CBF) in brain regions without the need for contrast material or radiation exposure [5]. ASL imaging uses magnetically labeled water in arterial blood as an endogenous tracer and is suitable for the clinical examination of pediatric patients. Pulsed (or pseudo-) continuous arterial spin labeling (pCASL) has been reported to have higher accuracy and reproducibility than single-pulse labeling for CBF quantitation [6]. However, a transit delay caused by a difference in flow speed and transit length is one of the disadvantages of ASL

imaging. Multiple post-labeling delay (PLD) times have been incorporated to overcome this disadvantage and improve the accuracy of CBF quantification [7]. Previous work has evaluated the reproducibility and robustness of the multi-delay pCASL method [8]. Because a transit delay may depend on childhood development, compensation for a transit delay is considered important when comparing blood flow in children with ADHD. In addition, neuroimaging morphology studies have revealed structural abnormalities in children with ADHD, particularly in the fronto-striato-parietal and fronto-cerebellar regions. Multiple structural MRI studies have reported decreased volumes in the orbitofrontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex (DLPFC), superior frontal cortex, superior occipital cortex, inferior parietal cortex, and cerebellum in patients with ADHD compared with controls [9-14]. Several structural MRI studies reported results in girls and boys with ADHD compared with typically developing counterparts of the same sex [4, 15, 16]. Although structural and functional imaging studies have reported abnormalities in brain regions in children with ADHD, previous work has not comprehensively used multi-delay pCASL and voxel-based morphometry (VBM) methods to investigate brain alterations. Due to the lack of neuroimaging data on female participants, sex-specific studies are still lacking in boys and girls with ADHD relative to controls. Thus, most of the existing literature on sex differences in children with ADHD has mainly recruited male counterparts [17, 18].

Therefore, the aim of this study was to obtain an understanding of the correlation between hemodynamic differences and morphological changes along with the potential effect of a sex difference in children with ADHD using Hadamard-encoded multi-delay pCASL imaging and VBM. Both patients with ADHD and age-matched controls were imaged and we compensated for the transit delay effect to obtain quantified CBF maps and thereby better evaluate the abnormalities and sex differences in cerebral perfusion in ADHD.

Materials and methods

Participants

We recruited patients who were diagnosed with ADHD according to DSM-5 at Tokushima University from September 2017 to March 2020. A total of 23 children with ADHD with a mean ± standard deviation (SD) age of 8.3 ± 2.7 years (range, 3–13 years) were included in this study. Twenty-four children without ADHD or intellectual delay with a mean ± SD age of 9.1 ± 4.2 years (range, 1–16 years) were selected as controls. The ADHD group comprised 19 boys (8.3 ± 2.8 years) and 4 girls (8.2 ± 2.6 years). The control group comprised 13 boys (8.7 ± 4.2 years) and 11 girls (9.5 ± 4.4 years). No significant difference in age was found between male or female patients and the same-sex controls. ADHD patients were diagnosed according to DSM-5 criteria and structured clinical interviews by treating pediatricians and informants. Control subjects underwent an MRI scan to rule out any brain abnormalities for several reasons, such as preventive measures, mild headache, or discomfort.

The inclusion criteria for patients with ADHD were as follows: (a) patients who were diagnosed with ADHD according to DSM-5; and (b) patients with no history of severe physical disease or psychiatric illness. The exclusion criteria were as follows: (a) participants who could not complete the full MRI scan session; (b) participants with morphological abnormalities on MRI; and (c) participants with neurological disorder, mental retardation, or intellectual delay. Children with no abnormalities on MRI and no evidence of ADHD, intellectual delay, or psychiatric illness were selected as controls. **Fig. 1** demonstrates a summary flowchart of the exclusion and inclusion criteria of this study.

Pediatric participants required sedation to complete the MRI examination under the supervision of a pediatrician. Monitoring of the heart rate and pulse oximetry was performed by radiologists using MRI-compatible equipment. The referring physician met with all

parents of the patients to ensure compliance and instruct the parents on pre-sedation preparations. Written informed consent was obtained from the family members of all of the children after the purpose and risks of the study had been fully explained, and all participants assented to the study procedures. The study was approved by the Institutional Review Board

MRI data acquisition

All imaging data were acquired using a 3-T MRI scanner (Discovery 750; GE Healthcare, Waukesha, WI) with 16-channel head coils. Prior to the pCASL imaging, axial 3D spoiled gradient-recalled echo (SPGR) T1-weighted images were acquired with the following parameters: repetition time, 8.6 ms; echo time, 3.5 ms; flip angle, 15; field of view, 220 × 220 mm; and slice thickness, 1.8 mm.

The Hadamard-encoded pCASL method was applied to obtain multiple PLD time data in this study. The imaging parameters were as follows: repetition time, 6797 ms; inversion time, 1000 ms; echo time, 11.2 ms; flip angle, 111°; field of view, 240 × 240 mm; slice thickness, 4 mm; three PLD times, 1.2, 2.2, and 3 s; number of excitations, 1; arms, 6; voxel size, 1.875 × 1.875 × 4; and total scan time, 5 min 36 s.

All perfusion and reference images were acquired with a 3D stack of a spiral rapid acquisition with refocused echoes imaging sequence. Subsequently, transit delay and compensated quantified CBF maps were used for the evaluation. The calculation method used to generate a perfusion map by multi-delay ASL imaging has already been published and the theory of CBF quantification by Hadamard-encoded pCASL methods has been described previously. We generated CBF and arterial transit time maps according to a previous study [19].

Preprocessing of MRI data

All MRI data were preprocessed using Statistical Parameter Mapping 12 (SPM12; Wellcome Centre for Human Neuroimaging, London, UK; https://www.fil.ion.ucl.ac.uk/spm/) running in MATLAB 9.3 (The MathWorks, Natick, MA). We assessed the optimized VBM with the DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) toolbox for SPM.

Preprocessing of VBM

All T1-weighted images were aligned and processed using field bias correction. They were then segmented into GM, white matter, and cerebral spinal fluid. Gray and white matter images were then imported into DARTEL and non-linear deformations for their optimal alignment were estimated by building a template and registering the tissue class images with the template. Subsequently, Jacobian scaled ("modulated") warped tissue class images were created. Finally, GM partitions were smoothed with an 8-mm full width at half maximum Gaussian kernel and used for statistical analysis [20, 21].

Preprocessing of CBF maps

Individual CBF images were realigned and co-registered to the corresponding structural tissue class images. Then, they were spatially normalized to the Montreal Neurological Institute (MNI) coordinate system and smoothed with an 8-mm full width at half maximum Gaussian kernel. After spatial preprocessing, the smoothed, modulated, and normalized CBF maps were used for statistical analysis [22, 23]. **Fig. 2** demonstrates the preprocessing steps of the CBF map of this study.

Statistical analysis

For global volumetric analysis, the independent t-test was used to compare ADHD and control groups. Statistics were computed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). The level of significance was set at $P < 0.05$.

For regional volumetric and perfusion comparisons between groups, the two-sample t-test was used with adjustment for age, sex, and GM volume. In addition, the full-factorial model was used to compare ADHD patients and controls in each group of boys and girls with adjustment for age using SPM12. For the comparison of GM volumes and CBF maps, the level of significance was set at $P < 0.001$, uncorrected for multiple comparisons, and with no extent threshold.

Results

Analysis of all participants with ADHD

Hadamard-encoded pCASL study

Table 1 lists the brain regions with significant perfusion changes using a Hadamard-encoded pCASL study in children with ADHD. The left middle frontal gyrus, left postcentral gyrus, and left precentral gyrus exhibited a significant CBF reduction ($P < 0.001$) in children with ADHD. Furthermore, increased CBF was found in the right posterior cingulate gyrus ($P < 0.001$) in children with ADHD. The transit delay was not significantly different between children with ADHD and controls ($P < 0.001$).

VBM study

A global volumetric analysis found no significant difference in GM, white matter, and total brain volumes between the ADHD and control groups using an independent t-test.

In a regional volumetric analysis, the ADHD group exhibited lower GM volume in the right supramarginal gyrus, right superior occipital gyrus, right inferior frontal gyrus, left

middle frontal gyrus, left central operculum, right parietal operculum, left lingual gyrus, left superior parietal lobe, right fusiform gyrus, left angular gyrus, left inferior occipital gyrus, and left postcentral gyrus versus the control group ($P < 0.001$) **(Fig 3)**. In addition, the ADHD group showed increased GM volume in the right inferior temporal gyrus ($P < 0.001$).

Analysis by sex of children with ADHD

Hadamard-encoded pCASL study

Compared with control boys, boys with ADHD showed reduced CBF in the left lingual gyrus, left inferior occipital gyrus, right superior occipital gyrus, left calcarine cortex, and left middle frontal gyrus ($P < 0.001$). There was no significant increase in CBF at $P < 0.001$.

Compared with control girls, girls with ADHD showed no significant CBF reduction at $P < 0.001$. In addition, increased CBF was found in the right superior frontal gyrus and left supramarginal gyrus ($P < 0.001$) in girls with ADHD versus controls.

The transit delay was not significantly different between boys and girls with ADHD and controls ($P < 0.001$). The regional CBF (rCBF) changes in boys and girls with ADHD relative to sex-matched controls are shown in **Fig. 4**, whereas the regions with significant rCBF differences in boys and girls with ADHD using a Hadamard-encoded pCASL study are listed in **Table 2**.

VBM study

The regions with significant GM volume differences in children with ADHD versus controls are summarized in **Table 3**. Boys with ADHD displayed significant GM volume reductions in the right supramarginal gyrus, right fusiform gyrus, left lingual gyrus, left angular gyrus, right cuneus, left middle temporal gyrus, right superior temporal gyrus, right inferior frontal gyrus, and left inferior occipital gyrus ($P < 0.001$). Furthermore, boys with

ADHD showed increased GM volume in the right inferior temporal gyrus ($P < 0.001$). In contrast, girls with ADHD showed no significant decrease but increased GM volume in the right superior frontal gyrus, right anterior orbital gyrus, left superior frontal gyrus, right precuneus, and left precentral gyrus versus control girls ($P < 0.001$).

Integrated results between perfusion and GM volume

All participants with ADHD showed decreased perfusion and GM volume in the left middle frontal gyrus and left postcentral gyrus. Boys with ADHD exhibited decreased perfusion and GM volume in the left lingual gyrus and left inferior occipital gyrus, whereas girls with ADHD showed increased perfusion and GM volume in the left superior frontal gyrus.

Discussion

In this study, we investigated brain hemodynamic and morphological abnormalities along with sex differences in children with ADHD by using multi-delay pCASL and VBM methods. By compensating for the transit delay, we compared CBF in children with ADHD. Compared with controls, children with ADHD showed reduced cerebral perfusion and GMV in the left middle frontal gyrus and left postcentral gyrus. Boys with ADHD exhibited reduced rCBF and GMV in the left lingual gyrus and left inferior occipital gyrus versus controls, whereas girls with ADHD had increased rCBF and GMV in the left superior frontal gyrus.

Analysis of all participants

Multi-delay pCASL imaging allows the direct estimation of both CBF and transit delay times, which are the two main hemodynamic parameters of perfusion quantification [24]. CBF measured by pCASL imaging is considered to be closely coupled to both glucose metabolism and neuronal activity [17, 25]. Neuronal activity generates metabolic demand

for oxygen and glucose, which increases blood flow to tissue [3], and patients with ADHD have been found to have reduced activity in the frontal, parietal, and occipital regions in prior imaging studies using a variety of measurement techniques, including functional MRI, SPECT, PET, and ASL-MRI [17, 26-31]. In our study, a decreased CBF was found in children with ADHD in the left middle frontal gyrus, left postcentral gyrus, left precentral gyrus, left lingual gyrus, left inferior occipital gyrus, right superior occipital gyrus, and left calcarine cortex compared with controls, which is largely consistent with the previous literature and subsequent meta-analyses.

In addition, VBM results also showed significant GM reductions in the right supramarginal gyrus, right superior occipital gyrus, right inferior frontal gyrus, left middle frontal gyrus, left central operculum, right parietal operculum, left lingual gyrus, left superior parietal lobe, right fusiform gyrus, left angular gyrus, left inferior occipital gyrus, and left postcentral gyrus in children with ADHD compared with controls, findings that are almost the same as those of prior studies [9, 12-14, 18]. These results revealed decreased GM volumes in children with ADHD, particularly in the DLPFCs and occipital and parietal cortices. The DLPFC has been implicated in planning, working memory, and attentional processes [32]. A DLPFC deficit had been reported in previous prospective neuroimaging studies of ADHD patients and subsequent meta-analyses [30, 32-35]. Moreover, the parietal cortex contains regions relevant to attentional functioning that are considered to be important in the cognitive pathophysiology of ADHD. In our study, a decrease in both CBF and GM volume was found in the frontal and parietal lobes, which would contain regions related to cognitive control functions, including response inhibition, working memory, and shifting attention, all of which show impairments in children with ADHD [18]. We found a larger GM volume in the right inferior temporal gyrus in children with ADHD compared with controls. A previous study of 27 children and adolescents with ADHD reported prominent increases in

GM in brain areas, including the temporal lobe, in children with ADHD [36]. The inferior temporal gyrus can be considered a tertiary visual association cortex and a portion of the language formulation area region involving cognitive functions such as language, visual perception, and memory [37].

In our study, not only decreased rCBF, but also increased rCBF were found in the right posterior cingulate gyrus, right superior frontal gyrus, and left supramarginal gyrus. The posterior cingulate gyrus is involved in anticipatory biasing of spatial attention to motivationally relevant events, and enhanced activation in the posterior cingulate gyrus may thus have mediated visuospatial attention to temporal information to compensate for reduced fronto-parietal activation [26, 38]. The supramarginal gyri (secondary somatosensory cortices) are responsible for integrating tactile or pain-based stimuli with higher-order functions such as attention [39], and a previous prospective study reported increased activity in the superior frontal gyrus in children with ADHD compared with healthy controls [40].

Furthermore, no significant transit delay was found in children with ADHD compared with controls. The results of CBF maps suggest that fronto-parietal regions could somehow be affected by the pathophysiology of ADHD.

Analyses of sex differences

We conducted a differentiated analysis of the sex difference in children with ADHD, even though the number of female participants was small. The pCASL results indicated that boys with ADHD had reduced CBF in the occipital and frontal cortices compared with control boys. Meanwhile, structural MRI found decreased GM volumes in the parietal, occipital, temporal, and frontal cortices in boys with ADHD relative to control boys. We found a GM volume reduction in the premotor region including the right inferior frontal gyrus in boys with

ADHD, which is in line with the results of a previous study of 93 children with ADHD [4] showing premotor reductions in bilateral lateral premotor regions in boys. The right inferior frontal gyrus has been associated with various cognitive functions, including attention, motor inhibition, and imagery, as well as social cognitive processes or speech functions [41]. The same tendency as the decrease in CBF and GM volume in boys with ADHD was confirmed in the left lingual gyrus and left inferior occipital gyrus, which would contain regions related to visual processing, and previous studies reported abnormalities in these regions in patients with ADHD [10, 42]. In contrast, girls with ADHD presented increased CBF in the right superior frontal gyrus and left supramarginal gyrus. Morphological analysis revealed increased GM volume in girls with ADHD in the right superior frontal gyrus, right anterior orbital gyrus, left superior frontal gyrus, right precuneus, and left precentral gyrus versus control girls. The left superior frontal gyrus exhibited the same increasing tendency in CBF and GM volumes.

The pathophysiology of ADHD may be more complicated in girls than in boys and associated with more internalizing problems (depression and anxiety) and intellectual impairment [43, 44]. Previous work mainly tended to comprise male participants, and female participants have been underpresented in MRI studies of ADHD [45]. Therefore, few neuroimaging studies of children with ADHD have included sex-matched controls [16, 46-49]. The results of the present study suggest that the fronto-parietal network is related to the pathophysiological abnormality in patients with ADHD, although the activity of the left fronto-parietal network in female pediatric patients will be increased and contrast with the decreased activity of the right fronto-parietal network in male pediatric patients. Other atypical lateralization studies have been reported in the ADHD literature [50, 51].

The limitation of the present study was the relatively low number of girls with ADHD. Thus, we suggest that further research be conducted with a larger sample of girls with ADHD.

Despite this limitation, the results of this study shed light on the pathophysiological abnormalities of ADHD and suggest that further research involving a larger sample of girls with ADHD should be conducted next.

Overall, we determined the potential ability of multi-delay pCASL to evaluate CBF differences in children with ADHD compared with controls. Further investigation of sex differences between boys and girls with ADHD revealed a perfusion reduction, as well as an increase in brain regions relative to sex-matched controls. In addition to the pCASL method, we also investigated brain morphological changes by incorporating VBM. Both perfusion and GMV results indicated abnormalities in the fronto-parietal network. This area could thus be affected in children with ADHD.

In conclusion, our study elucidated the capability of multi-delay pCASL to evaluate abnormalities and sex differences in cerebral perfusion in children with ADHD. By combining brain perfusion and structural analysis, we determined that fronto-parietal regions were somewhat affected in children with ADHD, with the tendencies differing by sex.

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Table 1. Regions with rCBF differences between ADHD and control groups obtained with a Hadamard-encoded pCASL study.

	Region	BA	MNI			Cluster size k	Z-score	P uncorr.
			x	y	z			
CBF map Control > ADHD	Lt. Middle frontal gyrus	9	−26	10	60	34	3.53	<0.001
	Lt. Postcentral gyrus	3	−42	−33	52	61	3.50	<0.001
	Lt. Precentral gyrus	4	−22	−28	74	14	3.26	<0.001
CBF map ADHD > Control	Rt. Posterior cingulate gyrus	23	16	−33	33	13	3.45	<0.001
Delay map	-	-	-	-	-	-	-	-

Lt. = left, Rt. = right, BA = Brodmann area.

Table 2. Analysis by sex results showing brain regions with differences in cerebral perfusion obtained with a Hadamard-encoded pCASL study.

	Region	BA	MNI			Cluster size k	Z-score	P uncorr.
			x	y	z			
Boys' CBF map Control > ADHD	Lt. Lingual gyrus	18	−3	−81	3	376	3.99	<0.001
	Lt. Inferior occipital gyrus	18	−39	−66	2	43	3.34	<0.001
	Rt. Superior occipital gyrus	19	18	−81	27	20	3.29	<0.001
	Lt. Calcarine cortex	17	−4	−66	12	39	3.28	<0.001
	Lt. Middle frontal gyrus	9	−26	9	60	1	3.09	<0.001
Girls' CBF map ADHD > Control	Rt. Superior frontal gyrus	8	16	0	52	112	4.16	<0.001
	Lt. Supramarginal gyrus	40	−39	−39	38	5	3.15	<0.001
Delay map	-	-	-	-	-	-	-	-

Lt. = left, Rt. = right, BA = Brodmann area.

Table 3. Regional GMV differences between ADHD and control groups.

	Region	BA	MNI			Cluster size k	Z-score	P uncorr.
			x	y	z			
All participants Control > ADHD	Rt. Supramarginal gyrus	40	40	−32	33	213	3.98	<0.001
	Rt. Superior occipital gyrus	19	21	−81	24	59	3.67	<0.001
	Rt. Inferior frontal gyrus	44	51	8	10	12	3.47	<0.001
	Lt. Middle frontal gyrus	9	−28	9	33	21	3.41	<0.001
	Lt. Central operculum	43	−40	−15	20	41	3.34	<0.001
	Rt. Parietal operculum	43	46	−22	15	28	3.30	<0.001
	Lt. Lingual gyrus	18	−10	−102	−16	105	3.29	<0.001
	Lt. Superior parietal lobe	5	−30	−66	27	8	3.19	<0.001
	Rt. Fusiform gyrus	37	45	−54	−15	8	3.18	<0.001
	Lt. Angular gyrus	39	−57	−68	27	1	3.12	<0.001
	Lt. Inferior occipital gyrus	18	−30	−98	−18	1	3.10	<0.001
	Lt. Postcentral gyrus	3	−45	−20	54	1	3.09	<0.001

All participants ADHD > Control	Rt. Inferior temporal gyrus	20	32	−6	−54	38	3.79	<0.001
Boys Control > ADHD	Rt. Supramarginal gyrus	40	39	−33	34	186	4.02	<0.001
	Rt. Fusiform gyrus	37	40	−52	−14	128	3.56	<0.001
	Lt. Lingual gyrus	18	−9	−99	−16	99	3.34	<0.001
	Lt. Angular gyrus	39	−33	−64	32	12	3.29	<0.001
	Rt. Cuneus	17	12	−82	26	14	3.26	<0.001
	Lt. Middle temporal gyrus	21	−60	−38	−18	28	3.25	<0.001
	Rt. Superior temporal gyrus	22	62	−36	10	3	3.18	<0.001
	Rt. Inferior frontal gyrus	44	52	9	9	5	3.18	<0.001
	Lt. Inferior occipital gyrus	18	−42	−69	2	2	3.12	<0.001
Boys ADHD > Control	Rt. Inferior temporal gyrus	20	33	−6	−54	67	3.99	<0.001
Girls ADHD > Control	Rt. Superior frontal gyrus	8	16	−8	52	58	3.81	<0.001
	Rt. Anterior orbital gyrus	47	28	50	−26	32	3.51	<0.001

	Lt. Superior frontal gyrus	8	−16	32	30	28	3.50	<0.001
	Rt. Precuneus	7	4	−60	68	13	3.39	<0.001
	Lt. Precentral gyrus	4	−15	−14	52	8	3.20	<0.001

Lt. = left, Rt. = right, BA = Brodmann area.

Figure Legends

Figure 1.

Flow chart of the inclusion and exclusion criteria of this study.

Figure 2.

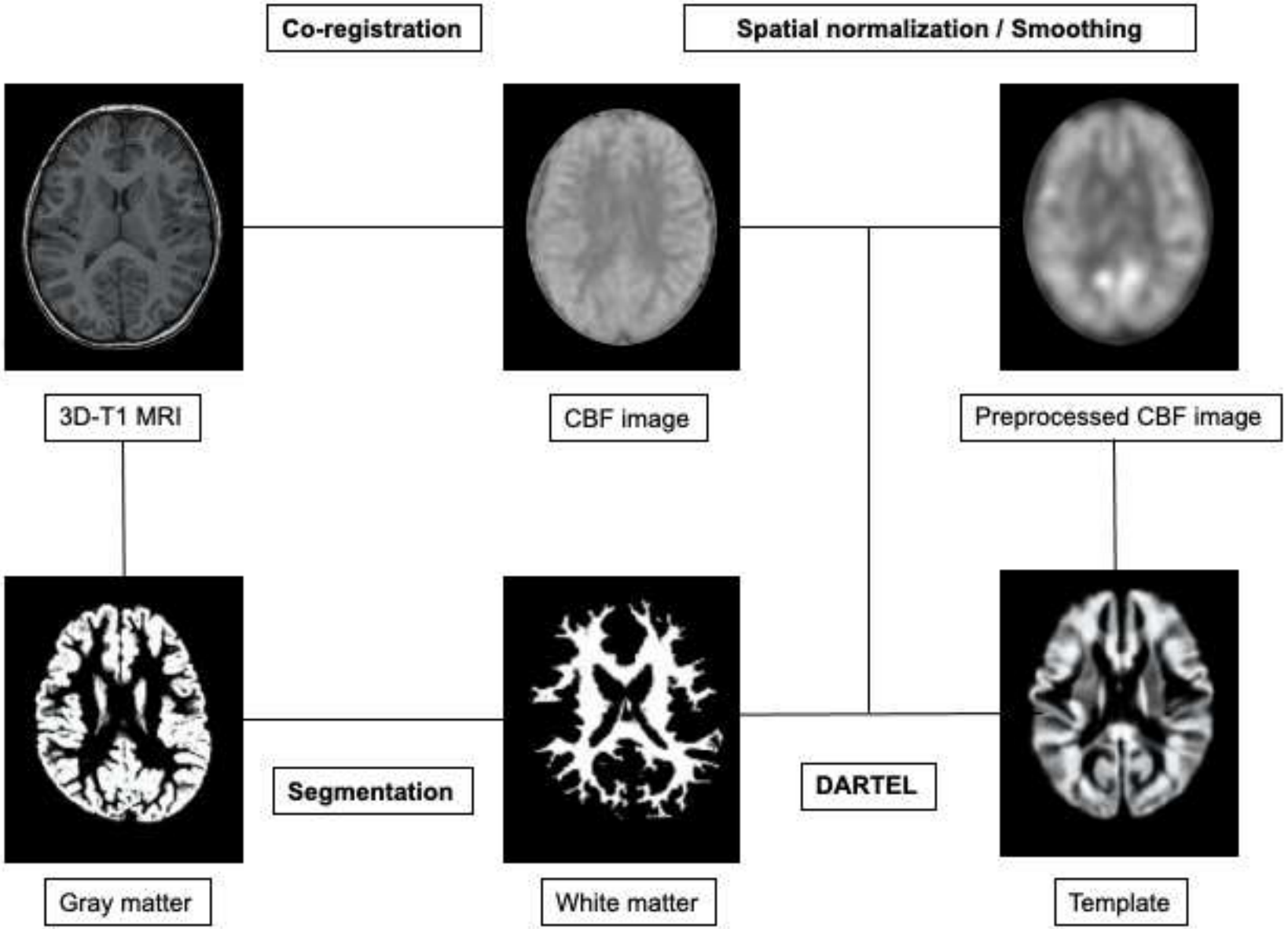
Preprocessing steps of the CBF maps.

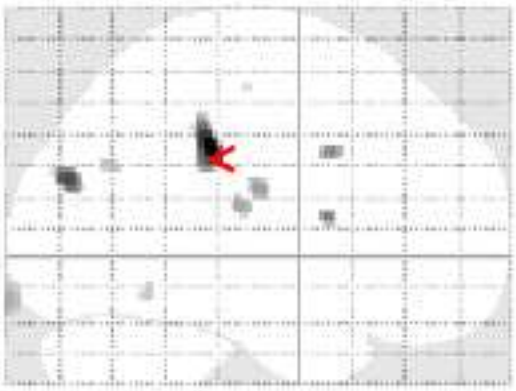
Figure 3.

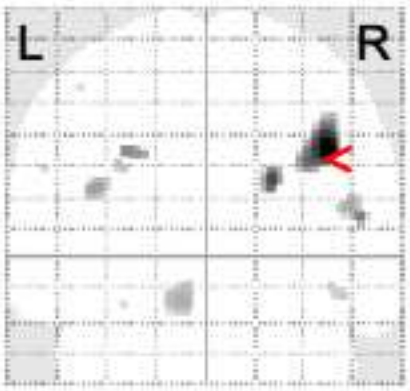
Brain regions with significantly decreased GM volume (largest cluster = right supramarginal gyrus) in the ADHD group compared with the control group ($P < 0.001$, uncorrected).

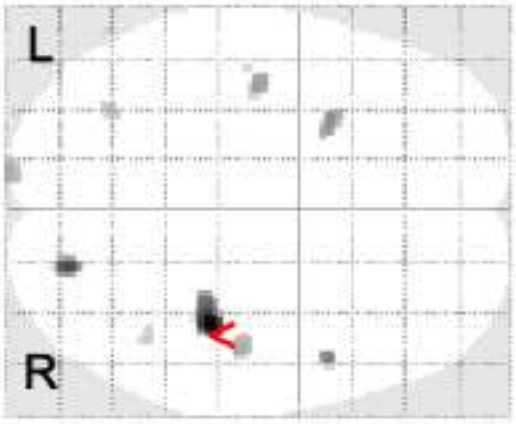
Figure 4.

Regions with decreased cerebral blood flow in (a) boys (left lingual gyrus) and increased cerebral blood flow in (b) girls (right superior frontal gyrus) with ADHD compared with those of controls using a Hadamard-encoded pCASL map ($P < 0.001$, uncorrected). Color scales indicate the *t*-score.









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