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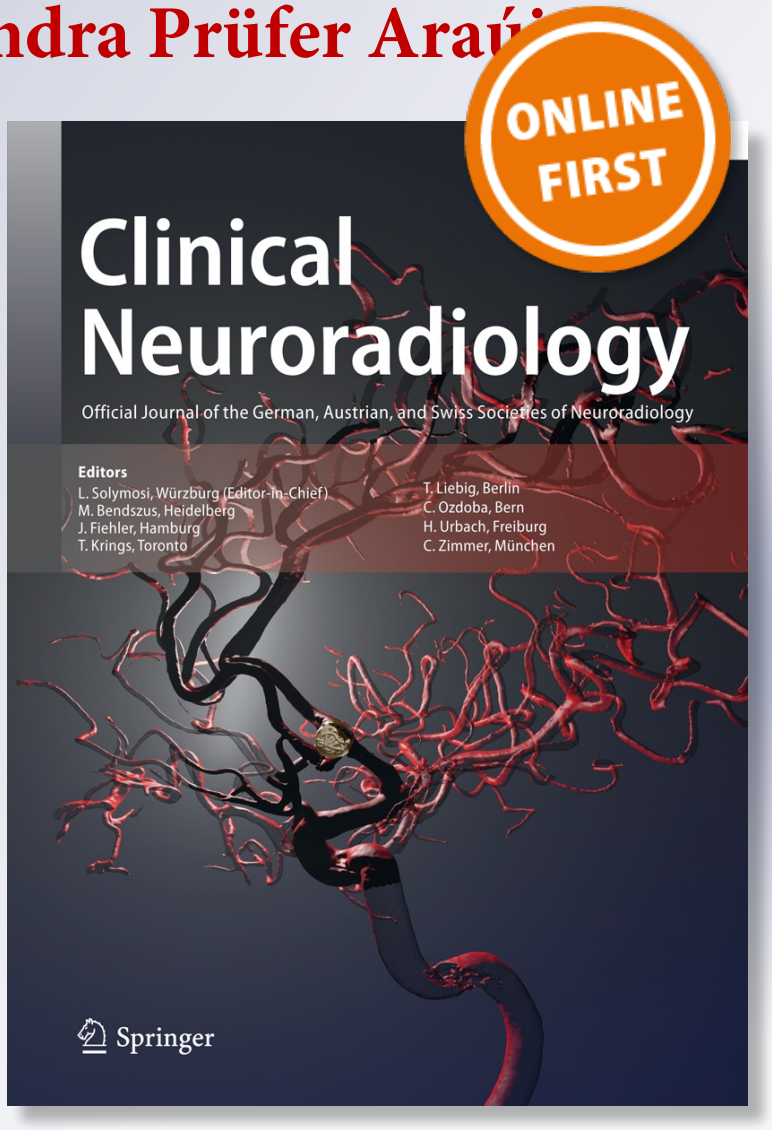

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ORIGINAL ARTICLE

Pilot study of brain morphometry in a sample of Brazilian children with attention deficit hyperactivity disorder: influence of clinical presentation

Giuseppe Pastura[1] · Tadeu Takao Almodovar Kubo[2] · Emerson Leandro Gasparetto[3] · Otavio Figueiredo[4] · Paulo Mattos[5] · Alexandra Prüfer Araújo[6]

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Abstract
Purpose Currently, the diagnosis of attention deficit hyperactivity disorder (ADHD) rests on clinical criteria. Nonetheless, neuroimaging studies have demonstrated that children with ADHD have different cortical thickness and volume measures to typically developing children (TDC). In general, studies do not evaluate the influence of clinical presentation in the brain morphometry of ADHD children. Our objective was to perform a pilot study in order to evaluate cortical thickness and brain volume in a sample of Brazilian ADHD children and compare these to those of TDC, taking into account the influence of clinical presentation.
Methods We performed an analytic study comparing 17 drug-naïve ADHD children of both genders, aged between 7 and 10, and 16 TDC. ADHD subjects were first considered as one group and further separated based on clinical presentation.
Results The brain volume did not differ between patients and TDC. Smaller cortical thicknesses were identified on the left superior, medium and inferior temporal cortex, as well as in the left inferior parietal cortex. When compared to TDC, combined and inattentive ADHD presentations depicted smaller cortical thickness with high significance and power. The same magnitude of results was not observed when comparing inattentive ADHD and TDC.
Conclusions In this pilot study, ADHD is associated with abnormalities involving the cortical thickness of the posterior attentional system. The cortical thickness in the left superior, medium and inferior temporal cortex, as well as in the left inferior parietal cortex may differ according to ADHD presentations.

Keywords Attention deficit hyperactivity disorder · Cortical thickness · Children · Cortex

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Introduction

According to the fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-V), attention deficit hyperactivity disorder (ADHD) is characterized by a persistent pattern of inattention and/or hyperactivity associated with functional impairment [1]. Although not all studies find differences between the ADHD subtypes, and the heterogeneity in clinical presentation of ADHD has been often described, there are many neuroimaging studies that demonstrate a myriad of abnormalities, both anatomical and functional in ADHD.

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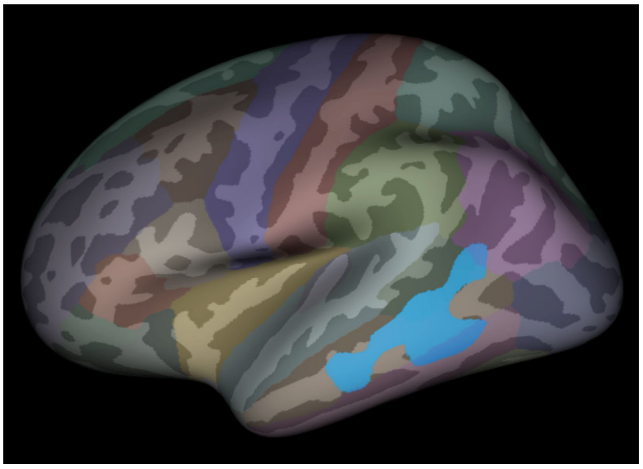

Fig. 1 Left superior, medium and inferior temporal cortex, and left inferior parietal cortex parsed after correction for multiple comparisons

Even though DSM-V has recently abandoned the concept of subtypes in favor of clinical presentations, which may change over time, there is a vast literature on this distinction [1]. According to Castellanos and Tannock [2] and taking into account the former DSM-IV criteria [3], there are differences in the neurobiology of inattentive subtype relative to the other subtypes, regarding age of onset, comorbidity, and social behavior. Others [4] have demonstrated a later age of symptom onset, fewer externalizing symptoms, greater difficulties in social interaction, and a different cognitive profile in the inattentive subtype (ADHD-I). Some studies have documented a different etiological pathway between this and others subtypes [5]. The vast majority of neuroimaging studies (Durston et al. 2003; Schulz et al. 2004) do not take into consideration the clinical presentation of ADHD [6, 7] or investigate only the combined (ADHD-C) presentation of this condition.

Over the years, the methods of assessing the cortical structure have gradually been refined. The initial procedures consisted of manual segmentation of pre-defined regions of interest (ROIs); however, this technique is labor intensive and subject to operator-dependent variations. Later, automated techniques were used, which are less cumbersome, less subject to error, and have the possibility of assessing the cortical and subcortical structures, such as voxel-based morphometry (VBM). While this technique is suitable for gray matter volume calculation, it does not have a great accuracy in the evaluation of cortical thickness, since its determination is based on the distance between the edge of the gray matter and the pial space, which causes inaccuracies in measurements [8]. It is noteworthy that relevant studies were performed using VBM, such as those of Lerch et al. (2005) and Shaw et al. (2006) [9, 10]. On the other hand, there are studies that currently make use of more modern techniques such as surface based morphometry (SBM), which provides better matching of homologous cortical regions than volumetric techniques. Moreover, it allows a distinct analysis of the two components of volume: thickness and surface area [11].

In 2007, Shaw et al. [12] published a study where the trajectory of cortical thickness of ADHD patients was compared to that of typically developing children (TDC). It was observed that, although the development pattern is similar in both groups, there was a remarkable difference in time between them, as the group of ADHD patients reached the maximum value of cortical thickness with a median age of 10.5 years while the control group took 7.5 years. These differences were more prominent in the median prefrontal cortex of ADHD patients. Some years later, Shaw et al. [13] published a paper addressing the development of cortical surfaces and gyrification in a large group of ADHD children and controls. In this study, a maturational delay in the cortical thickness and surface area was observed in ADHD patients, mainly in the right prefrontal cortex.

In one of the longest studies on the trajectory of brain volume in children with ADHD, Castellanos et al. [14] assessed 152 children with this clinical condition and compared them to 139 TDC. Drug-naïve ADHD patients had lower white matter volume when compared to TDCs and medicated patients, and lower cerebellar, temporal gray matter, and total brain volumes when compared only to TDC. Interestingly, within the group of ADHD patients, the smaller the volume of gray matter of the frontal and temporal caudate and cerebellum, the higher the severity of the condition.

The present pilot study aims to compare the cortical thickness and brain volume of a sample of Brazilian ADHD drug-naïve children, taking into account their clinical presentation, and comparing these to those of TDC.

Material and methods

After institutional review board approval, 17 ADHD drug-naïve children of both genders, aged between 7 and 10, from the ADHD outpatient clinic of the Federal University of Rio de Janeiro were invited to participate. All parents signed an informed consent form. A control group comprised 16 TDC of both genders, age-matched, from the elementary school of the same university. Patients underwent the SNAP-IV Rating Scale [15–18] and, if this screening was positive, the Brazilian version of the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS), a semi-structured interview using DSM-IV criteria for ADHD, was used [19, 20]. All patients were drug-naïve and had IQs greater than 70 [21]. It is noteworthy that, when the sample analysis began, the DSM-V had not yet been published. Moreover, there was no change in the

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Tab. 1 Comparison between ADHD patients and TDC concerning variables that could be associated with brain changes detected by MRI

Variable	ADHD	TDC	*p*-value
Gender (male/female)	13/4	12/4	1.000
Age[a]	8 (1.2)	9 (1.3)	0.368
Parent's years of study[a]	12 (3.2)	16 (3.7)	0.115
Monthly family incomes [a]	3,5[b] (3.9)	5[b] (5.7)	0.160
IQ[a]	105 (13.6)	106 (17.5)	0.639

[a]Median (standard deviation)
[b]In number of Brazilian minimum wages

Tab. 2 Comparison between gray and white matter volumes of patients and TDC

Variable	ADHD	TDC	*p*-value
Left white matter[a]	194.191 (25.971)	183.811 (21.058)	0.216
Left gray matter[a]	299.183 (25.226)	297.194 (33.368)	0.849
Right white matter[a]	192.421 (25.204)	185.205 (21.300)	0.380
Right gray matter[a]	301.044 (25.268)	299.870 (30.550)	0.905

[a]Median (standard deviation) in mm^3

criteria and number of symptoms required for the diagnosis. The basic changes occurred in relation to age at the onset of symptoms (rising to 12 years old) and the lowering of the cut-off criteria for adults, which did not affect our sample.

The imaging protocol included the following sequence: images' 3D gradient echo T1-sagittal plane, T2-weighted coronal plane, 3D FLAIR images in the sagittal plane, and diffusion tensor (DTI) orthogonal directions at a 30 gradient.

All images were transferred to a workstation (CENTOS 4.9, Linux) with 8 GB RAM memory and two Quad-Core Intel Xeon processors (2 × 3.2 GHz). Cortical reconstruction was performed using *FreeSurfer* version 5.0.0 (http://surfer.nmr.mgh.harvard.edu). The technical details of these procedures were described previously [22–25]. Briefly, this processing includes: motion correction; removal of non-brain tissue using a hybrid watershed/surface deformation procedure; automated Talairach transformation; segmentation of subcortical WM and deep GM structures, including the thalamus, hippocampus, amygdala, caudate, putamen, and ventricles; intensity normalization; tessellation of the GM/WM boundary; automated topology correction; and surface deformation and inflation of the cerebrum. The results of the automatic segmentations were reviewed and any errors were corrected by a medical physicist (TTAK, with 5 years' experience). Cortical thickness maps were calculated for each subject. The mean cortical thickness in the regions of interest in the patient group and in the control group were computed and statistically compared ($p < 0.01$) by a single-binary application included in the FreeSurfer distribution, Qdec. Correction for multiple comparisons was made by Qdec using Monte Carlo simulation ($p = 0.05$). MNI152 Atlas was used to perform the analysis. After applying correction for multiple comparisons using the Monte Carlo method, some regions of interest are highlighted because this correction eliminates false positives. When regions are evident in the images, they are not necessarily a pre-defined anatomical region, but invade adjacent regions and, in order to estimate their size, ROIs must be created. Procedures for the accuracy of cortical thickness measurements have been validated with histological analysis [26–28]. Only cortical gray matter was evaluated.

Comparisons between ADHD and TDC were made using a t-test after checking normality (Kolmogorov–Smirnoff) and variance homogeneity (Levene's) because statistical Z cannot be used with samples smaller than 30 individuals. A nonparametric Mann–Whitney test was used whenever assumptions for a t-test could not be demonstrated [29, 30]. Power analysis was also performed and allowed us to determine the probability of detecting the effect of $(\bar{x}_{Control} - \bar{x}_{ADHD})$ with 95 % (1-β) confidence with the sample size constraints. If the probability is unacceptably low, we would be wise to alter or abandon the experiment. The power calculations were performed with R project software, using the *pwr* package. The *pwr* package contains functions for basic power calculations using effect sizes based on the theory developed by Cohen [31]. The statistic d is the statistic proposed by Hedges and Olkin [32] and compute adjusted effect size estimates by taking into account the sample size of independent samples.

Results

Among the 17 individuals with ADHD, 13 (76.5 %) were male and 4 (23.5 %) were female. Comorbidities with disruptive disorders were present in 58.8 % of cases. ODD, found in 52.9 % ($n = 9$) of cases, was the most prevalent, followed by CD, found in 17.6 % ($n = 3$) of cases.

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Tab. 3 Mann–Whitney test and power analyses comparing mean cortical thickness (mm^3) between TDC and ADHD patients

Variable	ADHD		TDC	Mann–Whitney U	*d*	Power (1-β)
Left superior temporal cortex	2.53[a]	[b]	2.91[a]	30.5	1.4303	0.9911
SD	0.2911		0.1915			
Left medium temporal cortex	3.12[a]	[b]	3.52[a]	22	1.7917	0.9996
SD	0.2490		0.1621			
Left inferior temporal cortex	2.91[a]	[b]	3.42[a]	65	0.9768	0.8638
SD	0.5679		0.4026			
Left inferior parietal cortex	2.50[a]	[b]	3.02[a]	21	1.6873	0.9990
SD	0.3587		0.2091			

SD Standard deviation
[a]In mm
[b]Significant at 1 % probability level
Hypothesis tested H_0: μ Control = μ ADHD, H_1: μ Control > μ_{ADHD} (μ = 0.05)
Statistic $d = \left(1 - \frac{3}{4\ (n_{Control} + n_{ADHD})}\right) \frac{\bar{x}_{Control} - \bar{x}_{ADHD}}{\sqrt{\frac{(n_{Control}-1)S^2_{Control} + (n_{ADHD}-1)S^2_{ADHD}}{n_{Controll} + n_{ADHD} - 2}}}$

Tab. 4 Mann–Whitney test and power analyses comparing cortical thickness (in mm^3) of patients with ADHD, taking into account inattentive presentation (ADHD-I) vs. TDC

Variable	ADHD-I		TDC	Mann–Whitney U	*d*	Power (1-β)
Left superior temporal cortex	2.64	[a]	2.91	10	1.3705	0.0444
SD	0.1502		0.1915			
Left medium temporal cortex	3.15	[b]	3.52	6	2.0598	0.2634
SD	0.2104		0.1621			
Left inferior temporal cortex	3.27	NS	3.42	31	0.3648	0.9576
SD	0.3026		0.4026			
Left inferior parietal cortex	2.68	[b]	3.02	8	1.6281	0.8520
SD	0.1912		0.2091			

NS Non significant
SD standard deviation
[a]Significant at 5 % probability level
[b]Significant at 1 % probability level

The most prevalent presentation of ADHD was the combined one, followed by the inattentive and hyperactive (ADHD-H), with frequencies of 64.7 % (n = 11), 29.4 % (n = 5), and 5.8 % (n = 1), respectively.

ADHD and TDC were similar regarding intrinsic and extrinsic (environmental) factors that might influence brain structure and could account for possible differences on MRI: gender, age, parental education, family income, and IQ (Tab. 1).

Brain volume measures showed no differences between the two groups in either gray or white matter (Tab. 2).

After applying correction for multiple comparisons (Monte Carlo method), only four regions were parsed: left superior, medium and inferior temporal cortex, and left inferior parietal cortex (Fig. 1).

A nonparametric Mann–Whitney test for independent samples and the power analyses for each of these regions were carried out in TDC and ADHD patients (Tab. 3). It is noteworthy that the presence of ADHD is associated with a lower cortical thickness in the four highlighted regions, and the results are significant at the 1 % probability level.

The cortical thickness was stratified by hyperactive and combined presentations, in combination, and inattentive presentation of ADHD. For each region shown in Tab. 3, the cortical thickness of each group was compared between the groups and with the TDC.

Tab. 4 depicts that the value of the cortical thickness is important for distinguishing between ADHD-I and TDC in the left inferior parietal cortex (power [1-β] = 0.8520 and is significant at the 1 % probability level). On the other hand, the differences in the cortical thickness of the left

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Tab. 5 Mann–Whitney test and power analyses comparing cortical thickness (in mm^3) of patients with ADHD taking into account combined (ADHD-C) plus hyperactive (ADHD-H) presentation forms vs. inattentive presentation (ADHD-I)

Variable	ADHD-C and ADHD-H		ADHD-I	U	*d*	Power (1-β)
Left superior temporal cortex	2.48	NS	2.64	22	0.5223	0.9158
SD	0.3269		0.1502			
Left medium temporal cortex	3.11	NS	3.15	29	0.1494	0.5425
SD	0.2712		0.2104			
Left inferior temporal cortex	2.76	[a]	3.27	11	0.9264	0.2482
SD	0.5916		0.3026			
Left inferior parietal cortex	2.42	NS	2.68	18	0.6900	0.0446
SD	0.3913		0.1912			

NS Non significant
SD standard deviation
[a]Significant at 5 % probability level

Tab. 6 Mann–Whitney test and power analyses comparing the cortical thickness (in mm^3) of patients with ADHD taking into account combined (ADHD-C) plus hyperactive (ADHD-H) presentation forms vs. TDC

Variable	ADHD-C and ADHD-H		TDC	U	*d*	Power (1-β)
Left superior temporal cortex	2.48	[a]	2.91	20.5	1.5901	0.9773
SD	0.3269		0.1915			
Left medium temporal cortex	3.11	[a]	3.52	16	1.8612	0.9983
SD	0.2712		0.1621			
Left inferior temporal cortex	2.76	[a]	3.42	34	1.3101	0.8011
SD	0.5916		0.4026			
Left inferior parietal cortex	2.42	[a]	3.02	13	1.9495	0.9960
SD	0.3913		0.2091			

NS Non significant
SD standard deviation
[a]Significant at 5 % probability level

inferior temporal cortex between ADHD-I and TDC were not statistically significant, although they were important.

Tab. 5 shows that the cortical thickness of these four regions has low capacity of distinction between ADHD presentation forms. Even when we look at the left inferior temporal cortex, the difference between the cortical thickness of ADHD-C plus ADHD-H and ADHD-I is significant at a 5 % probability level, but with low power (power [1-β] = 0.2482).

Tab. 6 exhibits a clear difference between the cortical thickness of ADHD-C plus ADHD-H in these four regions when compared to the TDC group. The four variables are significant at the 1 % probability level and with high power [> 0.80].

Discussion

In the present study, ADHD was associated with abnormalities involving the cortical thickness of the posterior attentional system. ADHD presentation may be an important element in determining the cortical thickness in the left inferior temporal cortex. As far as we are aware, this pilot study is the first one to proceed with a brain cortical thickness analysis in a Brazilian sample of ADHD children, taking into account clinical presentation.

In the present study there were no differences between ADHD and TDC clinical profiles (IQ, age, gender, paternal education, and family income) that could account for the results. Besides this fact, we emphasize that all of the ADHD children in this research were drug-naïve, which eliminated the influence of medication on the results.

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Considering that no difference was detected between the brain volumes of the groups, our results differ from those of Castellanos et al. [14], who demonstrated smaller total brain volumes, and also from those of Mostofsky et al. [33], who demonstrated a smaller volume of the frontal lobe. Our sample was much smaller than that of the former, which may explain these differences. In our study, the regions presenting smaller cortical thickness are those belonging to the top-down attentional system, encompassing the parietal and frontal posterior dorsal cortex, and responsible for performing cognitive selection of sensory information [34]. In general, the association cortices in the posterior region of the brain analyze the information received in terms of its intrinsic characteristics, such as color, motion, and sound. On the other hand, the attentional network located in the frontal region of the brain, primarily the pre-frontal cortex (PFC), regulates attention inhibiting distractors [35]. The sensory association cortices are located in the posterior region of the brain, i.e., occipital, temporal, and parietal lobes. Although we did not detect any differences in frontal cortical thickness, our results are in agreement with this theory, as we observed a smaller cortical thickness on the left superior, medium, and inferior temporal cortex, as well as on the left inferior parietal cortex.

The role of the medial temporal lobe in default-mode network attention was demonstrated in an elegant study by Weissman et al. using fMRI, where an increased target-related activity in this region was associated with smaller task-induced deactivations and, therefore, fewer momentary lapses in attention [36].

In a large longitudinal follow-up, Proal et al. followed a cohort of 207 patients from infancy to an average age of 41 years [37]. When their MRI images were compared to 16 controls, a smaller cortical thickness in the dorsal attentional system, including the parietal and temporal regions, was depicted.

In our pilot study, ADHD-C and ADHD-H in combination depicted a smaller cortical thickness with high significance and power, when compared to TDC. Such a significant outcome was not observed when comparing ADHD-I with TDC. The 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) of the American Psychiatric Association [1] eliminated the subtypes and replaced it with specifiers to classify the current manifestation of ADHD at the time of assessment [38]. In the present study, we still used the former classification, and our results show that combined and hyperactive presentations may represent a different cerebral architecture, mainly in the temporal region.

The present study demonstrated cortical differences in children with ADHD when compared to TDC, including decreases in cortical thickness in the posterior attentional network and the influence of the clinical presentation in these findings. To our knowledge, this is the first study to assess the brain volume and cortical thickness of ADHD children as a whole, separating them according to the clinical presentation.

One limitation of this study was the small sample size, which precludes generalization to the ADHD population in general. Another limitation is inherent to cross-sectional studies, which precludes the investigation of cause–effect correlations. Studies with larger and cohort samples are necessary in order to further validate those preliminary findings.

Compliance with ethical guidelines

Conflict of interest G. Pastura, T.T.A. Kubo, E.L. Gasparetto, O. Figueiredo, P. Mattos and A. Prüfer Araújo state that there are no conflicts of interest.

The authors state that this study has been approved by the Federal University of Rio de Janeiro Ethics Committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent prior to their inclusion in the study, and details that might disclose the identity of the subjects under study were omitted.

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