NEUROIMAGING AND NEUROPSYCHOLOGICAL ANALYSES IN A SAMPLE OF CHILDREN WITH ADHD - INATTENTIVE SUBTYPE

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Abstract

Objective: The investigation of distinctive neuropsychological characteristics in patients with the inattentive subtype of Attention Deficit Hyperactivity Disorder (ADHD) and their association with volumetric measures may improve our understanding of this disorder and contribute to discussions about the definition of the subtypes of ADHD.

Method: In this study, a sample of 12 children diagnosed with ADHD-inattentive subtype and 11 typically developing children with ages ranging from 6 to 14 years were submitted to neuropsychological assessment and Magnetic Resonance Imaging, including morphological and morphometrical investigations (region of interest and voxel-based morphometry). For the ADHD-i group, the volumetric measures obtained using the region of interest (ROI) approach were also correlated with their neuropsychological performance.

Results: The results did not reveal differences between the ADHD-i group and the control group with respect to the morphologic data, but the morphometric analysis indicated a reduction of the volume of the left medial frontal gyri, the left anterior cingulate, the left caudate, the left thalamus and the right postcentral gyrus grey matter in the ADHD-i group. The ADHD-i group performed worse on neuropsychological tasks related to selective and sustained attention, semantic and phonological verbal fluency, working memory and the time of execution on the selective attention tasks. Significant correlations were found between the volumetric measurements and the neuropsychological data.

Conclusions: Our results suggest that structural volume differences between the ADHD-i group and the control group can be identified using a more refined method of analysis, such as VBM, and that the ADHD-i group presents worse performance with respect to attention, working memory and phonological fluency compared to controls. Thus, our findings contribute to our understanding of the volumetric abnormalities and the neuropsychological indicators of ADHD-i, strengthening the clinical characterization of the inattentive subtype.

Key words: ADHD, magnetic resonance imaging (MRI), voxel based morphometry (VBM), morphometry, neuropsychology

Declaration of interest: none

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Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterised by a heterogeneous set of behavioural symptoms, including inattentiveness, motor hyperactivity and impulsivity, starting before 7 years of age. The estimated prevalence in childhood is between 5% and 8% (Guevara and Stein 2001). Among children with ADHD, approximately 50% to 70% may present learning disabilities (Polanczyk et al 2007). Social adjustment and emotional well being may also be affected (Jensen et al 1997, Pfiffner et al. 2000).

The diagnosis of ADHD is usually based on reports of a poor ability to focus, difficulties sustaining and switching attention focus and/or developmentally

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inappropriate behaviour, such as poor inhibitory control of responses. According to the frequency and intensity of these three sets of complaints, this disorder can be classified under three subtypes (combined, predominantly inattentive and predominantly hyperactive). Evidence indicates that the inattentive subtype is different from the other subtypes with respect to its neuropsychological profile, specifically regarding the abilities and attentional processes related to the executive functions (Capdevila-Brophy et al. 2005, Romero-Ayuso et al. 2006). Although individuals with the combined subtype of ADHD are more likely to be referred for clinical services, the predominantly inattentive subtype is the most common subtype in the population (Willcutt 2012). Therefore, an analysis of different process related to executive functioning and attention in the different subtypes of ADHD is important to the understanding of the peculiarities of each subtype.

Some Nuclear Magnetic Resonance (NMR) studies have proposed that ADHD may be related to structural grey and white matter modification due to the delayed maturation of some brain networks, mainly the fronto-striatal cortical (Shaw et al. 2007), and this perspective is corroborated by neuropsychological evidence (Rubia et al. 1999, El-Sayed et al. 2003). These structural imaging studies have revealed that the global cerebral volume is 3% to 4% smaller in ADHD subjects, specifically in the regions of the lateral prefrontal cortex, the cingulated cortex, the striatum, the cerebellum and the corpus callosum (Castellanos et al. 1996, Semrud-Clikeman et al. 2006, Valera et al. 2007). These regions have all been identified as part of a widespread neural circuit underlying attention and executive function (Bush et al. 2005, Bush 2010). Despite the large amount of evidence demonstrating developmental impairment in those networks, there are few studies discussing the relationship between the structural findings and the symptomatic expressions in ADHD subjects. Casey et al. (1997) reported the relation between structural differences and executive functioning in ADHD, indicating that the performance on response inhibition tasks was positively correlated with the volume o of the right frontal lobe, right caudate nuclei and globus pallidus. The study developed by Hill et al. (2003) indicated that in an ADHD group but not in the control group, greater right superior prefrontal volume predicted poorer performance on a test of sustained attention. Depue et al. (2010), in their turn, showed that in a sample of young adults with combined-type ADHD a poorer behavioral performance on processing speed and on response inhibition and an increase on response variability correlated significantly with reduced grey matter volume in the right inferior frontal gyrus and in superior parietal lobule.

Given the inexpressive amount of existing studies that correlate brain volumetric measures and performance on neuropsychological tasks in patients with ADHD, more studies become necessary in order to produce more conclusive evidence over the issue, allowing a better understanding of the relationships between structural brain changes and neuropsychological functioning on this disorder. Moreover, controversies remain about the extent to which white or grey matter volume reductions in different brain regions are related to the inattentive subtype of ADHD.

Therefore, the main objective of this study was to examine the differences between a group of participants with ADHD with the inattentive type and a control group with respect to their neuropsychological performance, behavioural characteristics and cerebral white and grey matter volume analysed by quantitative morphology and voxel-based morphometry. We expected to contribute with the characterization of the inattentive subtype, to better comprehend the differences between the existing subtypes. Furthermore, we aimed to correlate the findings of the neuropsychological performance with the results of morphometric analysis for the ADHD group. Our hypothesis was that the ADHD group would present worse performance in the neuropsychological assessment as well as smaller volume in some brain regions.

Methods

Participants

Twelve male children diagnosed with ADHD-inattentive subtype ranging in age from 6 to 14 years (mean age ±SD = 10.67± 1.77) and eleven typically developing children (control subjects) (mean age +/- SD = 9.09 ± 2.07) were included in the study. The control group and the ADHD group did not differ with respect to age (U= 37; p= 0.71) and to anthropometric measures, including the cephalic perimeter (U= 64.5; p= 0.92), the biparietal distance (U= 48.5; p= 0.27), anteroposterior distance (U= 61.5; p= 0.77) and the interpupillary distance (U= 52.5; p= 0.30).

The participants were selected through the parents' voluntary enrolment in the ADHD Outpatient Service at NANI-UNIFESP (Federal University of São Paulo). All subjects who were eligible were invited (through their parents) to participate in the study as they were seen. Only children classified as having ADHD of the inattentive subtype (at least 6 out of the 9 criteria defined by DSM-IV for inattention, starting before the age of 7, with less than 6 symptoms of hyperactivity and impulsivity) were included in the study. The ADHD-i subjects were not taking medications for at least three months before the acquisition of the images and the neuropsychological assessment. All participants (ADHD-i and controls) showed normal intellectual performance (IQ above 85) according to results obtained using the Brazilian version of the Wechsler Children Intelligence Scale (WISC-III) (Wechsler 2002). All of the participants were attending regular schools.

The children were submitted to structural Magnetic Resonance Imaging (MRI) and neuropsychological assessment. The Ethics Committee approved the present study (CEP 1086/09), and informed consent was obtained from all parents before enrolment.

Procedures

We compared the ADHD-i children to the control group in regard to morphometry, to voxel-based morphometry, neuropsychological performance (mainly attention and executive functions) and behavioural characteristics.

MRI data acquisition

All ADHD subjects underwent an MRI of the skull in standard 3.0T according to the same protocol, which involved T1-weighted "steady state" isometric volumetric data acquisition by ultrafast incoherent gradient echo (GRE). The protocol also included reconstruction of the axial, coronal and sagittal planes; axial acquisition spin-eco T2-weighted imaging, axial acquisition with inversion and recovery with fluid

attenuation (FLAIR); acquisition during inversion and recovery with an intermediate inversion time (500 ms) and with the same reference (parallel plan to intercommissural line). The analysis of the data consisted on the structural evaluation of the T2-weighted and FLAIR spin-echo images to detect structural differences.

MRI data processing and analysis: VBM

The present study employed the VBM5 toolbox (http://dbm.neuro.uni-jena.de), which utilises and extends the new unified segmentation approach implemented in Statistical Parametric Mapping (SPM5) (Ashburner and Friston 2005, Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm), executed in Matlab 7.0 (Mathworks, Sherborn, MA). Unified segmentation provides a generative model of VBM preprocessing that integrates tissue classification, image registration, and MRI homogeneity bias correction. The VBM5 toolbox extends the unified segmentation model as it increases the quality of segmentation by applying a Hidden Markov Field (HMRF) model on the segmented tissue maps (Cuadra et al. 2005). The sagittal T1 DICOM files were converted to the NIFTI-1 (http://nifti.nimh.nih.gov) format. The converted files were then segmented into grey and white matter and normalised using the unified model cited above. The voxel values were modulated by the Jacobian determinants derived from the spatial normalisation, thus allowing a reduction of the total counts of the brain structures for which the volumes decreased after spatial normalisation by an amount that was proportional to the degree of volume discounted (Ashburner and Friston 2000). The final voxel resolution after normalisation was 1 mm^3. The obtained grey matter (GM) images were finally smoothed with a Gaussian filter at full width and at a maximum height equal to 8 mm, and they were entered into the statistical analysis. Additionally, the global grey matter, white matter and cerebral spinal fluid volumes, as well as the total intracranial volumes, were computed using the native-space tissue maps of each subject.

Neuropsychological assessment

All participants were submitted to an assessment of the intellectual performance level, and they underwent a battery of neuropsychological tests, including:

Attention measures. For the assessment of attention functions, we used the Conners' Continuous Performance Test (CCPT) (Conners 2002) and a cancellation task (Weintraub and Mesulam 1985).

The CCPT is a computerised visual task that requires distinguishing non-target (X letters) from target (non-X letters) stimuli. The subject is instructed to press the space bar of the computer keyboard for any letter that appears on the screen, except for the letter X. Because the task lasts 14 minutes, it assesses, among other measures, sustained attention abilities. Therefore, the program generates several measures related to inattention, impulsivity and sustained attention problems. In this study, the following scores were adopted to investigate attentions skills: the number of omission errors (measure of inattentiveness), the number of commission errors (measure of response inhibition failure), the mean hit reaction time (measure of processing speed) and the mean inter-interval block change score (measure of sustained attention). A study developed by Miranda et al. (2012) found that an ADHD sample performed worse than the normative sample in almost all of the measures of the CCPT, except in the case of the reaction time and the response style.

A cancellation task that requires functions such as selective attention and visual search (screening) was also used to assess attentive abilities. For this task, a white sheet with several designs was presented to the subject. The subject was then required to mark (cancel) with a pen all the exemplars of one target design. The performance was analysed considering the total time of execution (measure of speed of execution) and the number of omissions errors (measure of visual scanning).

Working memory measures

The Brazilian version of the WISC-III Digit Span subtest (Wechsler 2002) was used as a measure of phonological working memory. On the Corsi blocks test (Milner 1971), the subjects were asked to reproduce a forward and backward sequence of visual stimuli (blocks) in a visual-spatial design after a model was presented by the examiner. This test was used for assessing the visual working memory. The scores of the forward and backward span were considered separately because the main interest was in the span measures.

Semantic and phonological verbal fluency (Lezak et al. 2004)

In these tests, the subjects were asked to say as many words as possible in 60 seconds, according to a given semantic category (here, we used the categories animals and fruits) or according to the first letter of a word (F, A and S). The subjects were scored based on the total number of words generated for each category separately (Semantic Fluency) and for all letters (Phonological Fluency). The task required the evocation of a word according to a criterion (e.g., the initial letter) - Controlled Oral Word Association test (COWAT); therefore, this test was also used as a measure of executive functions.

Inhibition control and decision-making measures

Inhibition control skills are related to the ability to delay a reward in a decision-making context. These skills were investigated by the Iowa Gambling Test (IGT) (Bechara et al. 1994). The IGT is a paradigm that is believed to model real-life decision-making situations, particularly ambiguous situations where the reward rate is unknown. Briefly, the subjects are required to choose one card at a time from 4 available decks (A, B, C, and D). The task requires the subjects to make 100 choices (100 trials), and in each trial, the subjects may win or lose a certain amount of money. Two of the decks yielded a relatively high immediate gain, but they incurred higher loss in the long run. Thus, they were disadvantageous. In contrast, the other decks yielded relatively lower gains, but they incurred smaller losses in the long run and were thus advantageous. To measure performance, the choices were divided into five blocks with 20 choices each. For each block, a net score [number of cards selected from the advantageous (good) decks minus the number selected from the disadvantageous (bad) decks] was generated. The total net score from all blocks was also obtained. The

blocks, as well as the total net scores, were used as the dependent measures.

Visual constructive abilities and visual memory measures

The Copy of the Complex Figure of Rey (Rey 1941) was used to assess the visual constructive functions. The visual memory was also evaluated on this task through the immediate recall of the Complex Figure of Rey. The performance was evaluated according to rules defined in the test manual, considering the presence and the quality of each component of the figure reproduced and recalled.

Behavioural assessment

For the behavioural assessment, a Brazilian version of the Child Behavioral Checklist – CBCL was used (Bordin et al. 1995). The scores obtained through the CBCL can be used to screen for the presence or absence of several behavioural problems at a clinical level (e.g., Anxious/Depressed, Withdrawal Problems, Somatic Complaints, Social problems, Thought Problems, Attention Problems, Rule-Breaking Behaviour and Aggressive Behaviour). The CBCL was completed by one of the parents of each subject, usually the mother.

Statistical analyses

The SPSS (Statistical Package for Social Sciences) software version 15.0 was used to analyse the data. The Shapiro-Wilk test for small samples was used to analyse the normal distribution of the samples. Because the samples were not normally distributed, a nonparametric test (Mann-Whitney) was applied with a significance level of 5%. The magnitude of the effect measures was demonstrated to have a greater sensibility to neuropsychological tests, so the analysis of the differences between the two independent groups was conducted based on the magnitude of the effect, which was calculated using the model proposed by Cliff (1966). Negative results for the magnitude of effect indicate the lower performance of the clinical group. For the anatomical-functional correlations, the Rho of Spearman was used to analyse the results obtained by the neuropsychological assessment and the morphologic and the morphometric data.

Results

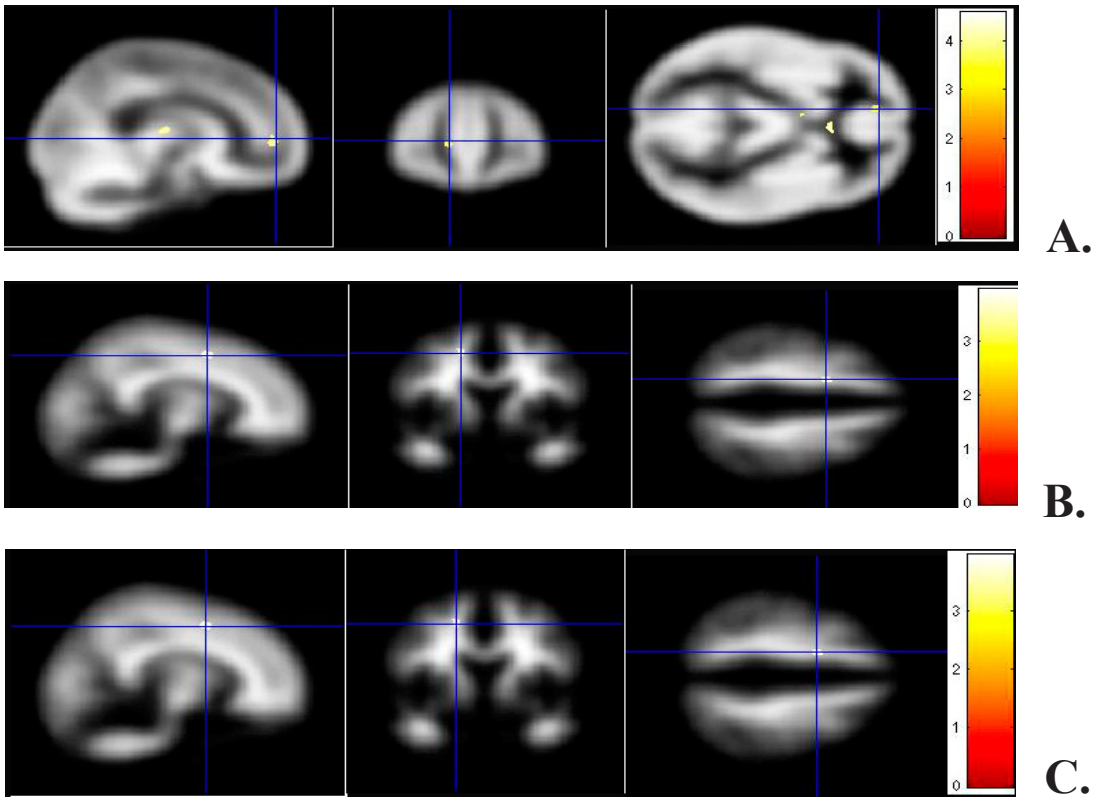
VBM analysis results

The voxel-based analysis of the ADHD-i subjects revealed a reduced volume of the left medial frontal gyri (Z=3.43, pFDR<0.05), the left anterior cingulate (Z= 3.74, pFDR<0.05), the left caudate (Z=3.47, pFDR<0.05), the left thalamus (Z=3.65, pFDR<0.05) and the right postcentral gyrus grey matter concentration (Z=3.72, pFDR<0.05) (see **figure 1**) in comparison to the controls. Compared with the control group, the ADHD-i subjects showed volume reductions in the grey matter in specific cerebral regions, including the left median frontal areas (anterior, motor and right somatosensory cortex), the anterior cingulate cortex, the parietal lobe and the left caudate.

Neuropsychological results

Regarding the neuropsychological performance of children in the ADHD group, when compared to

Figure 1. *Grey matter map displaying reduced left anterior cingulate (A), left caudate (B), and right postcentral gyri (C) in the ADHD group compared to the controls*



controls, a significantly lower performance was found for most of the neuropsychological tests, including the tests of attention, working memory and phonological fluency. The results of the analysis of the effect size based on Cliff's δ are presented in **table 1**.

The tests that were used to measure semantic verbal fluency, working memory and time of execution for the selective attention task showed a high effect size. A moderate effect size was observed for phonological verbal fluency, selective and sustained attention indicators.

Table 1. *Comparison of the performance on neuropsychological tests between the ADHD group and the control group using the effect sizes indicated by Cliff's δ*

Tests	ADHD		Controls		
	M	Dp	M	Dp	δ
CPT – Omissions	20.63	16.44	11.27	3.77	0.42*
CPT – Commissions	21.54	5.12	21.90	6.77	-4.95
CPT – Hit Reaction Time	475.51	97.95	427.27	91.83	0.25
CPT – Hit Reaction Time Block Change	128.12	274.48	43.05	11.16	0.30*
Rey – Copy	23.81	8.76	24.90	7.18	-0.15
Rey – Memory	14.84	8.31	15.45	6.48	-0.14
Digits Span Forward	4.16	0.83	5.63	1.62	-0.53**
Digits Span Backward	2.66	1.07	3.90	1.04	-0.57**
Corsi Span Forward	4.58	0.79	5.45	1.12	-0.38*
Corsi Span Backward	3.58	1.50	4.45	0.93	-0.20
Phonological Verbal Fluency – Letters (total)	15.33	7.24	19.81	7.92	-0.31*
Semantic Verbal Fluency – Fruits	8.55	2.4	12.4	2.83	-0.73**
Semantic Verbal Fluency – Animals	11.55	5.68	16.45	4.63	-0.61**
Cancellation task – Time of execution	101.18	37.38	176.1	76.69	-.76**
Cancellation task – Omissions	5.36	5.23	2	2.05	0.38*
General tendency on IGT	2.4	14.23	2.22	8.39	5.02

Note - * = Moderate; ** = High.
Note - * = Moderate 0.5>d<0.8** = High d>0.8.

Table 2. *Comparison between the ADHD group and control group for the CBCL measures using the Mann-Whitney test*

CBCL measures	Controls			ADHD				
	Q25	Q50	Q75	Q25	Q50	Q75	U	P
Anxiety	00.00	01.00	03.00	04.25	07.00	11.00	14.50	.00*
Withdrawn	00.00	00.00	01.00	01.50	04.50	06.50	12.50	.00*
Somatic complaints	00.00	00.00	01.00	03.00	05.00	06.00	08.50	.00*
Social problems	00.00	00.00	01.00	04.25	07.50	10.00	01.00	.00*
Thought problems	00.00	00.00	01.00	02.00	02.50	05.00	17.50	.00*
Attention problems	00.00	00.00	01.00	10.00	12.00	15.75	00.00	.00*
Rule-Breaking Behaviour	00.00	00.00	00.00	02.25	03.50	06.75	05.00	.00*
Aggressive behaviour	00.00	03.00	04.00	08.00	12.50	15.00	08.50	.00*

Note - * = Significant for p <0.01

Table 3. *Significant Spearman's correlations for neuropsychological measures and volume variables in the ADHD group*

Nº	CC	VM	FT	WMR	WML	WMT
Rey – Copy	-.53	.47	.70*	-.39	-.15	-.29
Rey – Memory	-.09	.68*	.78**	.30	.49	.38
Digits Span Forward	-.25	.30	.63*	-.13	.06	-.05
Phonological Verbal Fluency	-.53	.23	.24	-.64*	-.70*	-.64*
Cancellation – Time of execution	.70*	-.22	.00	.68*	.37	.51

Note - CC = Corpus Callosum; VM = Cerebellar Vermis; FT = Frontal Total; WMR = Total Right White Matter; WML = Total Left White Matter; WMT = Bilateral White Matter.
* = significant for p<0.05; **significant for p<0.01.

Behavioural results

With regard to the presence of behavioural problems, including those investigated using the CBCL, the comparisons between the groups indicated that the ADHD-i group showed a higher frequency of symptoms in all of the behaviour domains analysed. On a close examination of the behaviour problems in the ADHD-i group, it was found that 50% of the subjects had signs of social problems at clinical levels. Moreover, the results of the individual analyses indicated that 4 children had signs of generalised anxiety (30%), 4 had signs of attention problems, 2 had signs of withdrawal, 2 had signs of rule-breaking behaviour, and 2 had signs of aggressive behaviour.

Table 2 shows the results of the analyses of the behavioural problems evaluated with the CBCL in the ADHD-i group compared to the control group. The children with ADHD-i had significantly higher scores on the first, second and third quartiles for all behaviour problems, with a significance index greater than 99% (see **table 2**).

Correlations between morphometric and neuropsychological results for the ADHD-i group

When the performance on the neuropsychological tests was correlated with the data for the morphometric variables among the children with ADHD (see **table 3**), the findings indicated significant correlations between: a) the volume of the corpus callosum and the variable Time of execution of the Cancellation Task, showing a strong and positive correlation; b) the volume of the cerebellar vermis and the Rey Figure – Memory test, presenting a moderate and positive correlation; c) the total volume of the frontal lobe and the Digits Span Forward, revealing a moderate and positive correlation; d) the volume of the right white matter and the Time of execution - Cancellation task, revealing a moderate and positive correlation; e) the volume of the left white matter and the Phonological Verbal Fluency, showing a strong and inverse correlation; f) the volume of the right white matter and the Phonological Verbal Fluency, presenting a moderate and inverse correlation; and g) the volume of the total white matter (left and white) and the Phonological Verbal Fluency, revealing a moderate and inverse correlation. The other correlations can be seen in **table 4**.

Discussion

The findings of the present study allow a wider discussion of the neurobiological profile of the inattentive subtype of ADHD. Our results demonstrated that the participants with ADHD, in comparison to children with typical development, showed a worse performance on tasks involving attention, working memory and phonological fluency. Although all the participants with ADHD were children with the inattentive subtype, it was also possible to identify the presence of signs related to other behavioural problems. Nonetheless, the small number of participants and the intra-variability observed among individuals with ADHD may have made it more difficult to determine the occurrence of a specific subtype of comorbidity in association with ADHD. Furthermore, ADHD, as a multidimensional disorder, may manifest itself in different ways (subtypes) and with different intensities. The predominantly inattentive subtype, as it suggests, has a prevalence of symptoms of inattention, but it does not exclude the possibility of ADHD-i individuals have other behavioural problems in some level, such as aggressivity. Thus the inattentive subtype might involve some symptoms of aggressivity, but not to an extension that is inappropriate for developmental level, and it probably does not bring significant functional impairment in two or more settings.

Neuroimaging findings

Detection of morphological changes that escape subjective judgement is possible by quantitation, quantitative morphological methods can provide new and frequently essential insights in the neurobiological bases of disorders, such as ADHD. There are several methods for measuring brain volume. Region of interest (ROI) is a method for measuring brain structures with anatomical validity and it is still considered a gold standard method for brain measurement. However, it also has limitations, including but the time-consuming nature of manual ROI drawings, both in delineating a priori-defined regions and in the rigorous training needed to ensure rater reliability, which does not easily allow for comparison of many brain regions or large subject groups (Giuliani et al. 2005). Voxel-based morphometry is a fully automated user independent MR image analysis technique that permits voxel-wise statistical comparisons over the entire brain providing

Table 4. *Spearman's correlation among cognitive tasks and morphologic variables in the ADHD group*

Nº	13	14	15	16	17	18	19	20	21	22	23
1	-.53	.47	.10	.45	.47	.50	.70*	-.39	-.15	-.29	-.40
2	-.09	.68*	-.03	.29	.41	.41	.78**	.30	.49	.38	.09
3	-.25	.30	.29	.35	.38	.40	.63*	-.13	.06	-.05	-.09
4	-.08	.54	.11	.27	.37	.36	.58	-.34	-.40	-.43	.06
5	-.17	-.09	.09	.21	.04	.11	.17	-.37	-.05	-.24	-.43
6	-.03	.33	-.23	.12	.02	.12	.29	-.16	.06	-.08	-.46
7	-.53	.23	-.04	.07	.15	.12	.24	-.64*	-.70*	-.64*	-.54
8	-.57	-.19	.43	.53	.53	.53	.43	-.42	-.12	-.29	-.24
9	-.48	.40	-.22	.24	.33	.33	.60	-.41	-.10	-.20	-.54
10	.70	.70	-.35	.35	.35	.35	.35	.00	.35	.00	-.35
11	.70*	-.22	.28	-.12	-.09	-.07	.00	.68*	.37	.51	.45
12	.79	.95	-.40	-.38	-.22	-.29	-.31	.29	.10	.24	.42

Note = 1 - Rey – Copy; 2 - Rey – Memory; 3 - Digits Span Forward; 4 - Digits Span Backward; 5 - Corsi Span Forward; 6 - Corsi Span Backward; 7 – Phonological Verbal Fluency – Letters (total); 8 – Semantic Verbal Fluency – Fruits; 9 – Semantic Verbal Fluency – Animals; 10 – Trail Test – Time; 11 - Cancellation – Time of execution; 12 - Cancellation – Omissions; 13 - Morphology of Corpus Callosum; 14 - Morphology of Cerebellar Vermis; 15 – Morphology of Lateral Ventricles; 16 - Morphology of Frontal White Matter – Left; 17 – Morphology of White Matter - Right; 18 - Morphology of White Matter – Bilateral; 19 - Morphology of Frontal - Total; 20 - Morphology of White Matter – Total Right; 21 - Morphology of White Matter – Total Left; 22 - Morphology of White Matter - Bilateral Total; 23 - Morphology of Brain. * significant for $p<0.05$; **significant for $p<0.01$.

information about regional brain concentration or volume differences between groups (Keller and Roberts 2009, Mandarim-de-Lacerda et al. 2010). Although VBM is rapid and fully automated, it is not a replacement for manual ROI-based analyses. Both methods provide different types of information and offer complementary results when used in association.

Regarding the volumetric characterisation of the ADHD-i group analysed in this study, in comparison to the control subjects, the ADHD group presented differences according to voxel-based morphometric analysis. Differences related to the grey matter volume, the frontal and posterior cortical neural areas, and the subcortical regions were observed between the ADHD-i group and the controls. Some cortical regions such as frontal cingulate gyri and caudate are considered part of the neural frontal-striatal-cortical circuitry underlying selective attention (Shaw et al. 2007).

The results obtained by voxel-based morphometric analysis are consistent with previous studies and recent reviews, which have demonstrated that ADHD subjects present volume reductions in an inferior fronto-striato-cerebellar system. This system includes the frontal, striatal, parietotemporal and cerebellar regions, predominately in the right hemisphere (Rubia 2011, Pastura et al. 2011).

It is possible that biological modifications determine, to some degree, differences in the brain development of individuals with ADHD. Different hypothesis can be established to interpret these brain differences and due to our findings we decided to discuss the data by means the complex influence of maturational variables. There is considerable data suggesting that children with ADHD of the inattentive subtype show delayed brain maturation, mainly impacting the development of the cortico-subcortical system, and, subsequently, the neuropsychological functioning (Shaw et al. 2007). Therefore, the results obtained by volumetric analysis and by neuropsychological assessment may reflect both neuronal losses and white matter rearrangements in this developmental disorder.

Maturational deviation of the white matter in ADHD

The anatomical-functional results for the participants in the ADHD group mainly showed positive correlations between the right white matter areas and the corpus callosum with the Time of execution of the Cancellation Test, confirming the participation of those regions on the speed of information processing (Marco et al. 2012).

We also observed an anatomical-functional correlation between phonological processing and the volume of the bilateral white matter (moderate and inverse correlation).

The performance on the phonological fluency test involves two major subsystems of processing: a) neurocognitive areas of grey matter, which modulate the executive functions of the dorsolateral prefrontal cortex and b) functional integrity of the bilateral white fibres, which are associated with the speed performance of the test. A possible consideration would be that a deviation in the development of the white matter may explain the anatomical-functional correlations in some neurodevelopmental disorders, e.g., nonverbal learning disorder, velo-cardio-facial syndrome and Sotos syndrome (Rourke 1987, 1995). Similarly, ADHD might be associated with the abnormal neurodevelopment of white matter in brain circuits related to the attention network.

The explanation to this abnormal development may lie in the neural organisation of the brain areas composed of white matter. While short distance cortico-cortical connection fibres (arciform fibres or U fibres) predominate in the left hemisphere, there is a greater volume of long-distance cortico-cortical fibres in the right hemisphere (Rourke 1987, 1995). Injury or dysfunction of the white matter may therefore interfere with the functioning of the right hemisphere, which could explain a number of the functions that are impaired in ADHD and associated with this hemisphere, such as deficits in visual selective attention tasks (Rourke, 1987, 1995). This hypothesis is supported by other functional imaging and/or morphometric studies (Yeo et al. 2003, Fayed and Modrego 2005). For example, through morphometric analysis, Yeo et al. (2003) identified a significant reduction ($p = 0.003$) in the white matter volume on the right dorsolateral prefrontal cortex in individuals with ADHD.

Functional compensation and neuroplasticity

The results of Phonological Fluency test and the Cancellation test and their correlations with the white matter of the right and left hemisphere could be evidence of the role of the neuromodulatory mechanisms of cognitive functions in the process of hemispheric specialisation and regionalisation (Springer and Deutsch 2008). It is known that phonological fluency is associated with the left hemisphere (Alvarez-Linera et al. 2002), and when this region is damaged or its regionalisation is immature, the phonological fluency recruits compensatory regions of the contralateral hemisphere that are not regionalised to phonological processing.

As mentioned above, regions of the right hemisphere are formed by a substantial volume of long-distance cortico-cortical connecting fibres, and the recruitment of these regions for the execution of some tasks could therefore result in slower cognitive processing. It is important to consider that the regions responsible for the processing of some activities may also be susceptible to the mechanisms of inhibition of the non-dominant hemisphere (Sohlberg and Mateer 2009), but the requirement of compensation mechanisms from the non-dominant hemisphere can lead to a reduction of the functions related to the recruited hemisphere (overcrowding effect) due to an overload of their dominant cognitive processing systems. This process could be translated into conflicts of functional regionalisation, explaining the attentional deficits that have we observed, which were correlated with the right hemisphere and the main inter-hemispheric zone, the corpus callosum.

Neuropsychological profile in ADHD

As expected, the comparative analysis between the two groups revealed that the ADHD group showed worse performance on all measures considered to be associated with executive functions, i.e., semantic and phonological verbal fluency, digit span and corsi span. The ADHD subjects also had a greater number of omission errors and a presented a slower reaction time than the controls (CCPT). The correlation observed in the ADHD sample between the frontal lobe volume and the performance on one of working memory's components, i.e., temporary storage (Digits Span Forward - $\rho=0.63$, $p<0.05$) is an interesting finding that demonstrates the rule of executive functions in the cognitive modulation of ADHD. These results are consistent with other findings in the literature, which demonstrate the association between some components of the executive functions and the regions of the dorsolateral prefrontal cortex (Zelazo and Müller 2002).

The moderate and positive correlation between the volume of the cerebellar vermis and the Rey Memory test ($\rho=0.68$, $p<0.05$) corroborates the documented relationship between this area of the cerebellum and the brain's other association areas involved in higher mental functions, such as the prefrontal cortex. Some morphometric studies on ADHD have consistently shown smaller cerebellar volumes in these subjects when compared to healthy ones, especially with respect to the segments of the posterior-inferior cerebellar hemispheres and the vermis (Berquin et al. 1998, Seidman et al. 2005).

The participation of the cerebellum in cognitive functions was discussed by Schmahmann & Sherman (1998) in a study performed with adult patients with brain damage in the cerebellum resulting from several causes (mainly stroke in the cerebellar artery or postinfectious encephalitis). The authors found a constellation of impairments, including impairments in executive functions, such as planning, verbal fluency and working memory, as well as signs of inappropriate behaviour. Those findings led the authors to describe a *cerebellar cognitive affective syndrome,* in which the neural circuits that connect the cerebellum to the cortical and limbic structures are affected.

Conclusions

The evidence obtained in the present study suggests that the inattentive subtype of ADHD is associated with neuropsychological deficits, mainly in the attention and executive functions. This finding may be related to a delayed maturation of white matter fibres that connect different regions associated with attention networks. In other words, ADHD symptoms would be explained by impairment of the axonal myelination development in cortico-subcortical circuitry related to attention and executive functioning.

The limitations of this study involves as a small number of cases and greater dispersion in relation to age and IQ. Those limitations indicate the need for further studies with larger sample, with other subtypes of ADHD, and with or without comorbidities. Then the complex interrelationship between anatomic-functional data and the neuropsychological profile of ADHD could be better elucidated. Such studies will contribute to the diagnostic procedures and interventions used in clinical practice.

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