Journal of Attention Disorders
1–10

DOI: 10.1177/1087054719855683
journals.sagepub.com/home/jad
SAGE

Gray Matter Volume in Elderly adults With ADHD: Associations of Symptoms and Comorbidities With Brain Structures

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Abstract

Objective: To investigate total and selected region-of-interest-based gray matter volume (GMV) in older adults with ADHD. **Method:** Twenty-five elderly (≥65 years old) patients with ADHD and 34 healthy controls underwent 1.5-T magnetic resonance imaging (MRI). We used voxel-based morphometry to compare GMV between groups and performed a correlation analysis with ADHD symptoms and comorbidities. **Results:** Findings revealed a smaller total GMV in males with ADHD and a smaller GMV in the right medial frontal orbital area extending toward the medial frontal superior, the frontal superior, and the subgenual anterior cingulate cortex (ACC) besides correlations between inattentiveness and ACC (bilaterally) and left cerebellum, hyperactivity/impulsivity and the left frontal inferior orbital, depression and caudate (bilaterally), and the right inferior parietal lobule. **Conclusion:** Neural correlates in regions related to attention, executive control, and affective processing suggest that impairments in frontostriatal and frontoparietal-cerebellar areas observed in adults with ADHD persist into old age. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

ADHD, brain abnormalities, elderly, voxel-based morphometry, ADHD Impairment

Introduction

ADHD is a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity. It begins in childhood and may persist into adulthood. ADHD is associated with impairments in several areas such as professional, educational, social, and affective relationships (American Psychiatric Association [APA], 2013). In recent years, researchers have begun to investigate ADHD in elderly people and have observed its persistence in this age group (Das, Cherbuin, Easteal, & Anstey, 2014; Guldberg-Kjär & Johansson, 2009; Michielsen et al., 2012; Silva & Louza, 2008). Michielsen et al. (2012) reported an estimated prevalence rate of 2.8% for syndromic and 4.2% for symptomatic ADHD in older adults (55-85 years). These rates are close to the estimated rate of 3.3% reported by Guldberg-Kjär and Johansson (2009) in people aged 65 to 80 years. These initial studies began to delineate some characteristics of ADHD expression in this age group and they suggest that symptoms decrease with age and their relationships with the co-occurring mood disorders and cognitive performance also change. Gray matter volume (GMV) deficits are reported in younger patients with ADHD in regions involved mainly in attention and executive function and some reduction in the same regions are expected in normal aging (Fjell, McEvoy, Holland, Dale, & Walhovd, 2014; Tamnes et al., 2013). However, our knowledge of brain abnormalities in ADHD when overcoming aging is almost nonexistent.

The brain abnormalities most commonly found in children and adolescents with ADHD are related to a decrease in the volume of the whole and right cerebrum, prefrontal cortex, caudate (Frodl & Skokauskas, 2012; Valera, Faraone, Murray, & Seidman, 2007), right globus pallidus, putamen (Frodl & Skokauskas, 2012), and cerebellum (Stoodley, 2014; Valera et al., 2007). Shaw et al. (2007) found that children with ADHD exhibit a marked delay in cortical maturation, more prominently in prefrontal regions, but progressing similarly to the healthy control group.

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According to some authors, volumetric differences in subcortical structures in children with ADHD, such as the putamen and caudate, seem to disappear as they grow older (Frodl & Skokauskas, 2012). However, volume reductions in the caudate relative to healthy controls are found in adults with ADHD (Montes et al., 2010; Onnink et al., 2014; Seidman et al., 2011), while one study (Moreno-Alcázar et al., 2016) found an increase in caudate GMV. A recent cross-sectional meta-analysis (Hoogman et al., 2017) with participants with a median age of 14.0 (range = 4-63) years indicated that people with ADHD had significantly smaller volumes of the accumbens, amygdala, caudate, hippocampus, putamen, and intracranial volume. No difference was noted in the volumes of the pallidum or thalamus. The subcortical volume differences in ADHD are most prominent in children and nonexistent in adults when the case-control comparisons were stratified by age. In exploratory lifespan modeling, they also suggested a delay of maturation in the same subcortical regions in children (until 14 years) and a delay of degeneration in adults (21-63 years) beyond the fourth decade of life in ADHD (Hoogman et al., 2017).

Although brain abnormalities in children with ADHD are well established, in adults, the results are heterogeneous (Moreno-Alcázar et al., 2016). Besides the abnormalities in the caudate region (Montes et al., 2010; Moreno-Alcázar et al., 2016; Onnink et al., 2014; Seidman et al., 2011), studies using manually defined regions of interest (ROIs) and voxel-based morphometry (VBM) found abnormalities in the orbitofrontal cortex (Hesslinger et al., 2002), inferior frontal gyrus (Depue, Burgess, Bidwell, Willcutt, & Banich, 2010), dorsolateral prefrontal cortex (DLPFC; Moreno-Alcázar et al., 2016; Seidman et al., 2006), inferior parietal lobule (IPL; Seidman et al., 2011), anterior cingulate cortex (ACC; Amico, Stauber, Koutsouleris, & Frodl, 2011; Makris et al., 2010; Moreno-Alcázar et al., 2016; Seidman et al., 2006), putamen (Moreno-Alcázar et al., 2016), cerebellum (Makris et al., 2015) and supplementary motor area extending to superior frontal cortex (Moreno-Alcázar et al., 2016), total gray matter (GM; Ambrosino, De Zeeuw, Wierenga, Van Dijk, & Durston, 2017; Seidman et al., 2006), and global cerebral volume (Maier et al., 2016). Taken together, these studies show a predominance of volume reduction in brain regions implicated in ADHD.

ADHD patients share some similar clinical features with healthy aging as found in some brain structural changes. A reduction in cortical volume, especially in the frontal lobes (Fjell et al., 2014; Tamnes et al., 2013), but also parietal, temporal, and cerebellar regions has been reported in studies of healthy aging, so that regions that maturate later (such as the prefrontal cortex) during healthy brain development are the ones especially prone to atrophy earlier with aging (Tamnes et al., 2013).

Based on these neuroanatomical evidences, the aim of this study was to investigate whether and how ADHD and controls would differentiate in late life. We choose, initially, to carry out a whole-brain analysis to detect more robust regional abnormalities in GMV (Rubia, Alegría, & Brinson, 2014). Once cortical reductions are relatively global in normal aging (Fjell et al., 2014) and there are evidences of a total GM reduction in ADHD (Ambrosino et al., 2017; Seidman et al., 2006), we also compared total GMV between groups.

In addition, to identify more subtle structural abnormalities not evidenced in whole-brain analysis, we carried out an exploratory analysis choosing a priori ROIs more consistently reported in ADHD, related to fronto-parietal and fronto-striato-cerebellar circuits that sustain attention, inhibition, cognitive control, motivation, and emotion (Dickstein, Bannon, Castellanos, & Milham, 2006). We also included hippocampus and amygdala as ROIs. In healthy older adults, temporal areas undergo reductions over time of comparable magnitude as frontal areas (Fjell et al., 2014) and previous findings suggest that hippocampus enlargement and amygdala volume loss are not very stable across different samples of patients with ADHD (Hoogman et al., 2017; Perlov et al., 2008). Hippocampus is known to be involved in episodic memory (Fjell et al., 2014), attentional processes such as visuospatial working memory, and it modulates executive functions (Perlov et al., 2008). In various psychiatric disorders with affective symptoms, hippocampus and amygdala have been implicated; affective symptoms, emotional instability, and impulsivity frequently are present in ADHD (Perlov et al., 2008).

Our hypothesis is that elderly with ADHD will exhibit reduction in total GMV and/or continue to exhibit regional brain abnormalities in GMVs, regardless the symptoms decrease with increasing age (Das et al., 2014; Michielsen et al., 2012).

Method

Participants

All participants provided written informed consent to participate. The study was approved by the local Ethics Committee (Protocol No. 0598/11), and it was conducted at the Institute of Psychiatry of the University of São Paulo, Brazil. The inclusion criteria were as follows: male and female patients aged ≥65 years with the diagnosis of ADHD according to *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; APA, 1994), and at least with 4 years of schooling and matched healthy controls. Additional information from relatives (e.g., siblings, cousins, and aunts) and contemporary friends of the ADHD participants (47% of the ADHD sample) corroborated information concerning childhood symptoms. Exclusion criteria were age less than 65 years, other *DSM-IV* Axis-I disorders history of brain trauma or any abnormality on magnetic resonance imaging (MRI), current

or previous neurologic or psychiatric disease other than ADHD (except symptoms of mild depression and anxiety), diagnosis of dementia (or complaints of recent memory loss), substance or alcohol use disorder (abuse/dependence), uncorrected hearing and visual impairments, chronic lung disease, and clinically significant or decompensated cardiovascular disease. The sample was obtained by convenience. The research was widely publicized through the Institute of Psychiatry website and other websites for older people, in Facebook pages for people with ADHD, as well as posters and folders in clubs and recreational institutions for older people. We also contacted younger people with ADHD, who had already participated in previous research, aiming to identify parents and grandparents with symptoms that might suggest ADHD. There were no referrals from other clinics and the individuals selected for the research were those who identified themselves with lifetime symptoms of ADHD.

Assessment instruments. We used the following screening and scales to assess participants: Mini Mental State Examination (MMSE; Folstein, Folstein, & Mchugh, 1975); Adult ADHD Self-Report *Scale*–18 items *(ASRS-18;* Kessler et al., 2005) *was used for a* quantitative measure of clinical symptoms; the *semi-structured psychiatric interview* Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children/Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) was partially used in this study for the screening and investigation of ADHD symptoms in childhood and adolescence; the Structural Clinical Interview for *DSM-IV* (SCID; First, Spitzer, Gibbon, & Williams, 1997) was used to assess comorbidities; Geriatric Depression Scale (GDS-15; Yesavage et al., 1983); and the Beck Anxiety Inventory (BAI; Beck, Brown, Epstein, & Steer, 1988). We included estimates of intellectual quotient (IQ) verified from the matrix reasoning and vocabulary subtests of the Wechsler Adult Intelligence Scale–Third Edition (Wechsler, 1997).

Procedures

MRI acquisition and processing. All MRI scans were acquired using a 1.5-T Siemens Espree system (Siemens, Erlangen, Germany) at the Institute of Psychiatry.

Morphological data were acquired using a T1-weighted magnetization-prepared rapid gradient echo sequence (MPRAGE) using the following parameters: repetition time (TR) = 2,400 ms, echo time (TE) = 3·65 ms, number of excitations (NEX) = 1; field of view (FOV) = 240 mm; flip angle =8°; matrix = 192 × 192 pixels; slice thickness = 1.2 mm (no gap between slices); voxel size = 1.25 × 1.25 × 1.2 mm; resulting in 160 slices covering the whole brain.

The imaging protocol also included a T2-weighted turbo spin-echo transaxial sequence (24 slices, slice thickness = 5 mm, 1-mm gap) and a fluid attenuated inversion recovery (FLAIR) transaxial sequence (24 slices, slice thickness = 5 mm, 1-mm gap). Individual image inspection of the data sets of each participant was performed visually by an expert neuroradiologist to identify any silent gross brain lesions and artifacts that could interfere with image processing and analysis.

The data were processed using the current version of Statistical Parametric Mapping, Version 12 (SPM12, Wellcome Trust Centre for Neuroimaging, London, United Kingdom), implemented in MATLAB R2012a (MathWorks, Sherborn, MA). First, all anatomical images were reoriented; the mm coordinates of the anterior commissure were matched to the origin *x, y, z* (0, 0, 0), and the orientation approximated Montreal Neurological Institute (MNI 152) space. All images were then segmented and classified into GM, white matter, and cerebrospinal fluid using the unified segmentation method implemented in SPM12, which provides both the native space versions and diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) imported versions of the tissues (Ashburner & Friston, 2005). A customized template was created from participants using the DARTEL protocol (Matsuda et al., 2012). The deformation field was applied to the segmented images in sequence. Finally, the images created in the previous step were standardized to MNI 152 space, resliced to 2 × 2 × 2 mm voxels and smoothed using an 8-mm full-width-at-half-maximum (FWHM) Gaussian kernel. The total GM volumes were obtained from the modulated images.

Statistical Analysis

Demographic, intellectual functioning and clinical data. Statistical analysis was performed the *Statistical Package for the Social Sciences*—SPSS (Version 25) for Windows. Differences in demographic and clinical characteristics among the groups were examined using the chi-square test or the Fischer test for categorical variables and independent sample *t* tests for continuous variables. A significance level of 5% was used for all analyses.

VBM data. The total GMV was calculated using the MATLAB get_totals script (see http://www.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) implemented for statistical parametric maps (SPM) version 12 using the segmented images in the native space for each participant. Between-group differences in total GMV were tested using the general linear model (GLM) calculated with SAS® University Edition (version: university.cny.sas.com@sas:university-6p.2/6p.2.4d9732411a6d-1-1). Age and sex were included as covariates.

We performed an exploratory voxel-wise comparison of regional GMVs. The between-group whole-brain voxel-wise comparisons were performed using an analysis of covariance (ANCOVA) model in SPM, with age and sex as confounding

Table 1. Demographic and Clinical Characteristics.

Variables	ADHD ($n = 25$)	Controls ($n = 34$)	p value
Sex			.110[a]
Female, *n* (%)	16 (64)	28 (82)	
Male, *n* (%)	9 (36)	6 (18)	
Age, $M \pm SD$ (years)	66.9 ± 3.3	68.9 ± 4.1	.001[b]
Years of schooling, $M \pm SD$	13.6 ± 5.7	14.6± 3.8	.406[b]
Estimated IQ	113.88 ± 11.55	113.23 ± 10.34	.626[b]
MMSE (total), $M \pm SD$	28.0 ± 1.4	28.9 ± 0.9	.015[b]
GDS (current symptoms of depression), $M \pm SD$	6.6 ± 3.5	2.4 ± 3.7	<.001[c]
BAI (current symptoms of anxiety), $M \pm SD$	12.2 ± 6.6	4.0 ± 3.5	<.001[c]
ASRS–A total score (inattention), $M \pm SD$	26.7 ± 4.8	9.5 ± 5.2	<.001[c]
ASRS–B total score (hyperactivity/impulsivity), $M \pm SD$	22.2 ± 6·8	9.6 ± 5·5	<.001[c]

Note. *n* = number of participants; IQ = intellectual quotient; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; BAI = Beck Anxiety Inventory; ASRS = Adult ADHD Self-Rating Scale.
[a]Chi-square test.
[b]Mann–Whitney test.
[c]ANCOVA (adjusted for age, GDS, and BAI).

factors. The total GMV was also entered as an additional covariate. The threshold for the resulting statistics was set at $p < .001$ (uncorrected for multiple comparisons) level of significance ($Z = 3.09$) and displayed as SPMs in standard anatomical space. The findings in these exploratory analyses were considered to be significant if they survived family-wise error (FWE) correction for multiple comparisons over the whole brain ($p_{FWE} \leq .05$). These maps were then inspected for the presence of clusters of differences (increase/decrease). Only regions with a minimum of 10 voxels contiguous are reported.

Subsequently, the *small volume correction* (SVC) tool was applied in a priori brain regions based on previous studies of ADHD (Amico et al., 2011; Hesslinger et al., 2002; Hoogman et al., 2017; Makris et al., 2015; Montes et al., 2010; Moreno-Alcázar et al., 2016; Onnink et al., 2014; Seidman et al., 2011). This included the following ROIs: (a) DLPFC (superior and middle frontal gyrus, the *pars triangularis*, and the *pars opercularis* of the inferior frontal gyrus), (b) frontal orbital cortex (FOC; *pars orbitalis* of the inferior frontal orbital gyrus), (c) IPL (angular and supramarginal gyri), (d) basal ganglia (caudate, putamen, and pallidum), (e) ACC (anterior cingulated gyrus), (f) amygdala, (g) hippocampus, and (h) cerebellum. Each GM region was spatially delimited by applying masks onto the SPMs based on the anatomical volumes of interest that are available within the automatic anatomical labeling SPM toolbox (see http://www.gin.cnrs.fr/AAL). All anatomical masks were used separately in each hemisphere, and ROIs were investigated in both cerebral hemispheres. Findings for these hypothesis-driven, SVC-based analyses were reported as significant if they were relevant after FWE correction for multiple comparisons ($p_{FWE} \leq .05$) over the search volume of each ROI, with a minimum of 10 voxels.

Table 2. Means and *SD* by Group and Sex of the Total GMV.

Group	Sex	*n*	*M* GMV (ml)	*SD*
ADHD	Female	16	597.85	25.36
	Male*	9	628.08	55.03
Control	Female	28	595.57	45.47
	Male*	6	657.03	61.06

Note. GMV = gray matter volume.
*$p = .047$.

In addition, correlation analysis with ADHD (ASRS–Parts A and B), depression (GDS), and anxiety (BAI) symptoms were performed to investigate their influence on focal differences between the groups across the total GMV and in the ROIs.

Results

We included 25 patients with ADHD (16 women) and 34 healthy controls (28 women). There were no significant differences in sex, years of schooling, or estimated IQ between groups. The mean age was 66.9 ± 3.3 and 68.9 ± 4.1, respectively ($p = .001$). In the ADHD group, four individuals (14%) reported previous diagnosis of ADHD and noncontinuous use of methylphenidate. One of the participants used it between 1997 and 2004. Of the other three, one had been using it for 2 years, the other 3 years, and the third for 4 years. None of these individuals were on medication during the evaluations. Further demographic and clinical data are shown in the Table 1.

The mean sum of GM voxels (total GMV) in the segmented GM images led to a total volume of 608.74 ± 40.38 ml in the ADHD group and 606.42 ± 53.13 ml in the control group (*t* test, nonsignificant). There was a significant

Table 3. Correlations Between ADHD and Depressive Symptoms and Selected ROIs.

	ROIs	MNI[a] coordinates (*x*, *y*, *z*)	Voxels[b]	*T*[c]	*Z*[d]	p_{FWE}
ASRS-A (Inattention)	ACC (right) ↓	6, 28, −8	81	4.99	3.97	.008
		2, 24, 28	16	4.18	3.50	.037
	ACC (left) ↓	0, 36, 8	216	5.03	3.99	.009
		0, 24, 30	37	4.96	3.96	.010
	Cerebellum (Left Region IX) ↑	−6, −48, −32	30	5.67	4.33	.016
ASRS-B (hyperactivity/impulsivity)	Frontal inferior orbital (Left BA 47) ↓	−44, 42, −12	169	5.49	4.24	.004
GDS (depression)	Caudate (right) ↓	20, 10, 8	197	4.68	3.80	.025
	Caudate (left) ↓	−16, 12, 12	392	5.87	4.42	.003
	Supramarginal gyrus (Right BA 40) ↑	52, −38, 28	45	5.32	4.15	.012

Note. Statistical significance after family-wise error correction for multiple comparisons ($p < .05$, voxel level) within the respective volume of interest circumscribed using the small volume correction approach. ROI = regions of interest; MNI = Montreal Neurological Institute; ASRS = Adult ADHD Self-Rating Scale; ACC = anterior cingulate cortex; ↓ = negative correlation; ↑ = positive correlation; BA = Brodmann area; GDS = Geriatric Depression Scale.

[a]MNI coordinates = coordinates of the voxel with maximum statistical significance within each cluster, according to the Montreal Neurological Institute standard.

[b]Number of contiguous voxels that exceeded the initial threshold of $p < .001$ (corrected) in the statistical parametric map.

[c]*T* = voxel value of maximum statistical significance within each cluster.

[d]*Z* scores apply to the voxel of maximum statistical significance within each cluster.

sex-by-diagnosis interaction effect, $F(1, 54) = 4.14$; $p = .047$, males with ADHD showed a smaller GMV than male controls ($p = .038$). There was no GMV difference between female patients and controls (Table 2).

The whole-brain between-group exploratory analysis, using the SPM to compare regional GMVs, showed one smaller voxel cluster in the ADHD group with a peak statistical significance in the right medial frontal orbital area (Brodmann area [BA] = 10; 413 voxels; peak voxel at $x = 12$, $y = 44$, $z = -8$; $p_{FWE} = .014$ corrected for multiple comparisons), extending to medial frontal superior, the frontal superior and the subgenual ACC (Figure, Supplemental Material).

We further evaluated between-group regional GMVs in a priori-selected brain regions (ROIs) using the SVC approach, considering a minimum of 10 voxels contiguous. There were no significant differences between groups in GMV in the ROIs analyzed.

Correlation analysis found no significant correlations between inattention symptoms (ASRS–Part A), hyperactivity/impulsivity symptoms (ASRS–Part B), GDS, BAI, and the total GMV. However, in the analysis of ROIs, inattention (ASRS–Part A) showed a negative correlation with a cluster of GMV in the right and left ACC and a positive correlation with GMV in left cerebellum (Region IX of the posterior lobe). Hyperactivity/impulsivity (ASRS–Part B) was negatively correlated with GMV in the left FOC subregion corresponding to BA 47 (Table 3).

Scores of depression symptoms (GDS) were negatively correlated with GMV in the left and the right caudate and positively correlated with GMV in the right supramarginal gyrus (BA 40). No significant correlations were found between anxiety symptoms (BAI) and GMV.

Discussion

The aim of the present VBM study was to investigate whole-brain and regional GMV differences between elderly individuals with and without ADHD and our hypothesis was partially confirmed. Men with ADHD showed a smaller total GMV than men in healthy controls. This difference is congruent with previous studies with younger samples such as Seidman et al. (2006) and Ambrosino et al.(2017), even though there are studies that did not find any difference in total GMV between nonelderly adults with ADHD and healthy controls (Amico et al., 2011; Depue et al., 2010; Onnink et al., 2014). Contrary to ours, most studies that reported findings on ADHD population included samples that were predominantly male and the localization and progression of these abnormalities throughout life and the sex-based differences of these abnormalities are not well understood (Almeida Montes et al., 2012; Frodl & Skokauskas, 2012). Distinct regional neurobiological deficits underlying ADHD in the two sexes has been proposed by some researchers (Almeida Montes et al., 2012; Onnink et al., 2014). For example, Almeida Montes et al. (2012) compared whole-brain cortical thickness in both sexes in three age groups (children, adolescents and adults). They suggest a hypothesis of dysfunctional mechanisms involving neural pathway formation, axonal and dendritic arborization, and synaptogenesis in childhood followed by dysfunctional mechanisms of synaptic pruning and competitive elimination in adolescence to adulthood to explain a reduced cortical thickness in ADHD. Furthermore, a hormonal influence could explain the differences between the sexes. In their study, an increase in cortical thickness in female adolescents was verified and they suggest

that this may reflect the effect of estrogen inducing axonal sprouting and an increase in the number of synapses. In adulthood, the excess synapses were pruned, and reduction of cortical thickness was observed in both sexes; however, this was less pronounced in females (Almeida Montes et al., 2012).

We also found a significant smaller GMV in the right prefrontal cortex of the ADHD group. In an early meta-analysis performed by Dickstein et al. (2006), the medial frontal gyrus (BA 10) had significantly more likely activations in ADHD participants than in controls, when considering only studies that specifically examined response inhibition. Etkin, Egner, and Kalisch (2011) suggested that this region, together with the ACC, is also involved in appraisal and expression of negative emotion, beyond a regulatory role with respect to limbic regions involved in generating emotional responses. The smaller GMV in the right ACC in the ADHD group is also in line with many early studies (Amico et al., 2011; Makris et al., 2010; Moreno-Alcázar et al., 2016) although there is no consensus regarding the laterality. Our find about a negative correlation between inattention and ACC volume reinforce that it also plays key role in attention modulation beyond cognition/executive control such as decision making and working memory (Etkin et al., 2011).

Inattention was also positively correlated with left cerebellum (Lobule IX) volume. This finding is consistent with the meta-analysis performed by Stoodley (2014) that found significantly decreased GMV bilaterally in Lobule IX in patients with ADHD. The author considers these regions part of dorsal and ventral attention networks. Lower volume in other cerebellar regions, such as the tonsil and culmen, have been negatively correlated with inattention in adults with ADHD (Duan et al., 2018).

Hyperactivity/impulsivity was negatively correlated with the left inferior frontal orbital gyrus (*pars orbitalis*, BA 47) volume. The left BA 47 has been implicated in response inhibition tasks (Dickstein et al., 2006). On the contrary, Depue et al.(2010) in a sample of younger adults (with combined-subtype ADHD in childhood) found a negative correlation between response inhibition and the GMV in the *pars opercularis* of the right inferior FOC. This could suggest that distinct subregions of the inferior frontal cortex (and laterality) are involved in inhibiting motor actions and other behavioral responses related to hyperactivity and impulsivity. Moreover, the FOC connections with lateral prefrontal and dorsal ACC neurons are relevant in translating motivational information into actions. Deficits in these regions may result in failure to monitor conflicts resulting in impulsivity/hyperactivity and an inefficient modulation of cognitive control and allocation of attention (Makris et al., 2015). Differently in our finding, in a study performed by Onnink et al. (2014) with a younger sample, hyperactive/impulsive symptoms were correlated with the caudate volume; in addition, male patients exhibited a smaller right caudate volume than male controls.

Regarding comorbid symptoms verified in our sample, the groups differed with respect to their current depression and anxiety symptomatology, as verified through the GDS and BAI, with the ADHD group presenting more symptoms. However, the patient groups were in remission or with mild depressive symptomatology, as well as mild anxiety symptoms. Comorbidities, such as depressive and anxiety disorders, are common in adults with ADHD with an estimated prevalence of comorbid depression ranging from 9% to 50% of cases (McIntosh et al., 2009) and this comorbidity may persist into older age. In another study (Michielsen et al., 2013), depressive symptomatology was also verified in a group of elderly patients with ADHD. Although the scores reflect a clinical state of mild depression, we found a negative correlation with the left caudate and a positive correlation with the right IPL. Studies investigating the link between major depressive disorder and structural brain changes in ADHD are scarce and did not examine differences in or correlations with the basal ganglia or IPL, nor are conclusive about the involvement of other regions, such as the hippocampus and amygdale (Onnink et al., 2014). Abnormalities in the caudate region are common in children and are also found in adults with ADHD (Frodl & Skokauskas, 2012; Hoogman et al., 2017). However, the role of these abnormalities in emotional dysregulation in later life is not clear. Moreover, the IPL is part of a neural system which subserves attention and behavioral inhibition. Adults with ADHD report more frequently bad events and heightened intensity and instability of negative emotions in daily life, as well as showing equivocal or negative answers for positive emotions (Skirrow & Asherson, 2013). As there are strengthened connections between parietal and other regions (ACC and caudate) involved in attentional and inhibitory processes, one hypothesis is that the association between depressive symptoms and the IPL could reflect a distinct neural network, at least in patients in this age group with ADHD. Nonetheless, more studies investigating these and other regions in young and old patients with ADHD and comorbidities are necessary.

One study, conducted by van Tol et al. (2010), found that the reduced volume of the rostral–dorsal anterior cingulate gyrus is a nonspecific effect in depression and anxiety disorders, independent of illness severity, medication use, and sex. This region is implicated in ADHD and we also found a reduced volume in subgenual ACC in the ADHD group, however, without correlation with depression and/or anxiety symptoms. Other important observation is that, despite a possible influence of pharmacological treatment for ADHD on brain structures in our study, we considered it unlikely that they occurred, as only four participants took medication for a relatively short period of time and not continuously.

This is the first volumetric study of the brain only in elderly people with ADHD comparing with healthy elderly, and it is unclear whether our findings represent the outcome of abnormal neurodevelopment (as proposed by Almeida Montes et al., 2012) besides a neurodevelopmental delay in childhood, and how aging influences it (positively or negatively), once it is expected that the core symptoms of ADHD decrease with age (Guldberg-Kjär & Johansson, 2009; Michielsen et al., 2012). The time when the brain structures of people with ADHD reach the apex of their maturation before their decline, the balance between changes in white matter and GM and brain plasticity (Fjell et al., 2014; Reuter-Lorenz & Cappell, 2008; Westlye et al., 2010) throughout the whole process of development and normal aging have not yet been understood. As we mentioned earlier, in studies of normal aging, some authors suggest that some brain areas thought to develop later would also degenerate earlier in old age (Tamnes et al., 2013), while a study in ADHD (Hoogman et al., 2017) suggest a delay of maturation in subcortical regions in children and a later onset of degeneration in these same regions in adults with ADHD. Moreover, one follow-up (Proal et al., 2011) in adults (mean age 41 years old) with ADHD established in childhood tested whether anatomic differences would be associated with current ADHD diagnosis, including persistence versus remission. The authors found anatomic GM reductions in adults with childhood ADHD, regardless of current diagnosis and suggest that diagnostic remission may result from compensatory maturation of prefrontal, cerebellar, and thalamic circuitry (Proal et al., 2011), which could also partly explain why symptoms decrease with age despite older adults with ADHD maintain neuroanatomical differences when compared with the controls.

As our sample is composed of individuals that may represent people with less severe symptoms with fewer psychiatric and clinical comorbidities, we should consider other situations which could change the course and the clinical presentation of the ADHD in late life. An association between antecedent severe ADHD phenotype and dementia risk might be influenced by metabolic dysregulation. Environmental risk factors would be underlying brain neurochemistry to facilitate this link between metabolic dysregulation and the risk for Alzheimer and Lewy Body dementia (Fluegge & Fluegge, 2018).

Some limitations should be considered in our study. Our sample size is relatively small and included few men. Because of this, it was not possible to divide the sample for analyses by sex, nor by subtypes of presentation (inattentive, hyperactive/impulsive, or combined). It was not possible to divide the sample in relation to the presence or absence of comorbid symptoms of depression and/or anxiety. However, due to the high frequency of these comorbidities in adults with ADHD, it may be difficult to obtain elderly samples exclusively with the central ADHD symptoms. Further research is needed to replicate these conditions. It should also be considered, that the SPM-based technique compares neuroanatomical indices between groups. In particular, the VBM approach used herein provides GM measures that are restricted to volume estimates, whereas newer software that uses surface-based methods (such as FreeSurfer) decomposes cortical volume into thickness and area (Fischl, 2012). Future studies using such newer methods are warranted, given that cortical thickness and cortical area develop under different genetic influences (Blokland, De Zubicaray, McMahon, & Wright, 2012), undergo distinct patterns of aging-related changes (Hogstrom, Westlye, Walhovd, & Fjell, 2013), and may display different degrees and regional location of abnormalities in elderly ADHD samples compared with controls.

Despite these considerations, this study found neural correlates, such as smaller total GMV in elderly men with ADHD, and between-group differences in regions involved mainly with functions, such as attention, executive control, and affective processes, that have often been implicated in the pathophysiology of ADHD. Our findings suggest that biological characteristics, such as frontostriatal and frontoparietal-cerebellar models of ADHD, may persist into old age. More studies with larger samples and a longitudinal design are required to investigate modifying effects in brain structures such as sex, aging, comorbidities, and treatment in patients with ADHD.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The research was partially funded by Fundação de Apoio à Pesquisa do Estado de São Paulo (FAPESP) (nr.2012/03311-4). The authors received no financial support for the publication of this article and declare that they have no competing interests related to this study.

Supplemental Material

Supplemental material for this article is available online.

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