Cerebellar volume in patients with dementia

Volume cerebelar em pacientes com demência

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Abstract

Objective: The aim of this study was to examine the cerebellar volume of subjects at different stages of Alzheimer's disease and to investigate whether volume reductions in this structure are related to cognitive decline. **Method:** Ninety-six subjects from an epidemiological study were submitted to a magnetic resonance imaging scan and evaluated using the Mini-Mental State Examination and the Functional Activities Questionnaire. Subjects were divided into five groups according to the Clinical Dementia Rating scale. Twenty-six subjects from the original group who had no dementia diagnosis at baseline were re-evaluated for the onset of dementia after two years. **Results:** The volumes of the cerebellar hemispheres, posterior cerebellar lobe, vermis and temporal lobe were found to be reduced as a function of the severity of the disease. There were significant positive correlations between the volume of the temporal lobe and cerebellum and the language, attention, and total scores in the Mini-Mental State Examination and the Functional Activities Questionnaire. A logistic regression analysis demonstrated that reduced temporal lobe, posterior cerebellar lobe and vermal volume at baseline is a risk factor for the onset of dementia. **Conclusion:** This is the first study demonstrating that reduced cerebellar volume is already apparent at the predementia stage. The results of this study support the involvement of the cerebellum in the progression of dementia. Whereas the cerebellum might not be directly associated with the origin of Alzheimer's disease, it may provide useful information related to its prognosis.

Descriptors: Cerebellum; Epidemiological studies; Dementia; Alzheimer's disease; Disease progression

Resumo

Objetivo: *O objetivo deste estudo foi examinar o volume cerebelar em indivíduos em diferentes fases da doença de Alzheimer e investigar se sua redução estaria relacionada com o declínio cognitivo.* ***Método:*** *Noventa e seis indivíduos de um estudo epidemiológico foram submetidos à ressonância magnética e avaliados por meio do Mini Exame do Estado Mental e do Questionário de Atividades Funcionais. Os sujeitos foram divididos em cinco grupos de acordo com a Escala de Gravidade da Demência. Vinte e seis indivíduos do grupo original que não tinham o diagnóstico de demência no início do estudo foram reavaliados após dois anos para detectar o desenvolvimento da doença.* ***Resultados:*** *Os volumes dos hemisférios cerebelares, lobo cerebelar posterior, vermis e lobo temporal estavam diminuídos proporcionalmente à gravidade da doença. Houve correlações positivas e significativas entre o Questionário de Atividades Funcionais, Mini Exame do Estado Mental e seus respectivos subtestes para linguagem e atenção com os volumes dos lobos temporal e cerebelar. A análise de regressão logística demonstrou que o volume reduzido do lobo temporal, lobo cerebelar posterior e vermis pode ser um fator de risco para o futuro desenvolvimento de demência.* ***Conclusão:*** *Este é o primeiro estudo que demonstrou que o volume do cerebelo pode estar reduzido na fase pré-demência e reforça o papel dessa estrutura na progressão da doença de Alzheimer. Considerando que o cerebelo pode não estar diretamente associado com a origem da doença de Alzheimer, este achado tem valor para o prognóstico.*

Descritores: *Cerebelo; Estudos epidemiológicos; Demência; Doença de Alzheimer; Avanço da doença*

Introduction

The occurrence of dementia is rising substantially worldwide. There is currently no cure for dementia; therefore, extensive efforts for the prevention of the disease have mounted.[1] The proper identification of individuals at increased risk for dementia will allow for a more efficient implementation of preventive measures currently available.[1]

There is a growing interest in magnetic resonance imaging (MRI)-based measures and associated standard cognitive

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Submitted: February 22, 1010
Accepted: September 24, 2010

assessments as methods allowing for the optimal prediction of future clinical decline.[2] MRI is widely used as a noninvasive method to assess gray and white matter volumes, with highly reproducible results.[3] Gray and white matter volumes were shown to correlate with confirmed pathological neuronal loss and with the molecular hallmarks of Alzheimer's disease (AD).[4]

Recently, the possibility of an early diagnosis of AD has brought attention to the importance of neuroimaging investigations in predementia patients.[5] Several studies using region-of-interest (ROI) and voxel-based analyses have reported reduced volumes in the hippocampus, parahippocampal gyrus, cingulate and other brain regions in patients with mild cognitive impairment (MCI) and AD.[2,6-8] The spatial pattern of brain atrophy in MCI is complex and highly variable and does not always progress in a linear manner. Characterizing these inter-individual variations in the manifestation of these diseases through the development of biomarkers poses even greater challenges.[8,9]

There is strong evidence that the cerebellum not only modulates important motor functions, but also plays a significant role in the operation of cognitive functions, emotional processing, and behavior.[10,11] From this perspective, the cerebellum exerts a regulatory function that enhances and supplements other brain functions, throughout direct and indirect circuits.[10,11] In AD, diffuse plaques are commonly found in fibrillar and thioflavin-positive cells of the granular layer and Purkinje cells in the molecular layer of the cerebellar cortex.[12,13] It has been suggested that neuronal loss in the cerebellum, such as decreases in granule cell numbers and volumetric loss in the molecular layer, may be the result of primary pathologic changes in the cerebral cortex, a process called *diaschisis*.[14] *Diaschisis* is the mechanism suggested for cerebellar impairment in dementia.[10]

There is a lack of studies examining the cerebellar volume in patients with AD. In this study, we analyzed the volume of the cerebellum and its subregions in subjects with AD, MCI, and in healthy control subjects. We hypothesized that the cerebellar volume would be proportionally reduced at different stages of dementia. We also investigated whether cerebellar reductions are related to cognitive impairment including orientation, memory, attention, language, and executive functions.

Method

1. Database

All data used in this study were obtained from the Elderly Epidemiology Study (EPIDOSO) database. The EPIDOSO study was the first community-based cohort study examining the elderly in Brazil.[15] This epidemiological study evaluated 1,667 individuals aged 65 years and older living in an urban district of the city of São Paulo. The main goal of the EPIDOSO was to identify predictors of good health in the elderly.[15]

2. Subjects

We selected 96 subjects from the outpatient clinic of EPIDOSO with AD (n = 70) and cognitive impairment without dementia (n = 16), in addition to 10 subjects without cognitive complaints or functional impairment and with a Mini-Mental State Examination (MMSE) score of 30. All subjects were classified with the Clinical Dementia Rating scale (CDR).[15]

Subjects were divided into five groups according to dementia severity (CDR score) as follows: 0 = controls, 0.5 = questionable or very mild impairment, 1 = mild impairment, 2 = moderate impairment, and 3 = severe impairment. We classified all the subjects without cognitive complaints or functional impairment and with an MMSE equal to 30 as CDR = 0. The patients who met the diagnostic criteria proposed by Petersen et al. for MCI were included in the CDR = 0.5 group.[16]

Alzheimer's diagnosis was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[17] A clinical and socio-demographic questionnaire including questions about age, gender, education, neurological and psychiatric family history, previous psychiatric treatment, and drug treatment was administered to each patient. Subjects were excluded if they had any neurological, psychiatric or medical conditions that could potentially affect the central nervous system, such as substance abuse or dependence, atypical headache, head trauma with loss of consciousness, asymptomatic or symptomatic cerebral infarction detected on T2-weighted MRI, hypertension, chronic lung disease, kidney disease, chronic hepatic disease, cancer or diabetes mellitus. Subjects were also excluded if the cause of dementia was not AD (8 cases). We used the Structured Clinical Interview for DSM-IV (SCID)[18] to exclude psychiatric disorders as the cause of cognitive impairment.

The cognitive evaluation was performed with the MMSE[19] and adjusted for years of education based on information provided by Bruck et al.[20] Functionality was evaluated with the Functional Activities Questionnaire (FAQ).[21]

All participants signed informed consent forms before participation in this study, which was approved by the Institutional Review Board (IRB) of the Universidade Federal de São Paulo (CEP nº 0258/08).

3. Outcome

Twenty-six subjects without dementia at baseline (CDR = 0 and CDR = 0.5) were re-evaluated after two years. MR images were analyzed to evaluate whether cerebellar volume alterations at baseline could be related to future cognitive decline.

4. Image acquisition and analysis

MRI scans were performed immediately or up to 15 days after the neuropsychological evaluation. Images were collected using a GE Sigma 1.5T scanner (General Electric Medical Systems, Milwaukee, Wisconsin) with a coronal 3D SPGR acquisition sequence (TE = 5msec, TR = 33.3msec, flip angle = 45 degrees, acquisition matrix = 256x256, NEX = 1, FOV = 34cm, slice thickness = 1.3mm, 124 slices). Data were analyzed using the software Brains 2.[22] Two raters, blind in regard to the subjects' diagnoses, performed ROI analyses. All brain structures, except the cerebellar vermis, were measured using the Brains 2 semi-

automated method.[22] Brain segmentation was performed for all patients and manually checked and edited to ensure accuracy.[23,24] Volumes were output in cm^3. To evaluate whether cerebellar volume reductions were secondary to superior structure atrophy, the cerebral and temporal lobes were also segmented. All cerebral and cerebellar measurements were corrected for the total intracranial volume (TIV).

1) TIV, cerebral, and temporal lobe volumes

Total intracranial volumes were calculated by manually tracing the intracranial volume of each coronal slice after exclusion of the skull and dura, summing these areas across successive coronal slices including gray and white matter and CSF volumes, and multiplying the sum by the slice thickness. These measures included the frontal, parietal, temporal, and occipital cortices, subcortical structures, the cerebellum, and the brainstem.

The cerebral volume was obtained from T1-weighted volumetric imaging using a semi-automated, iterative 3D morphologic technique. This technique includes a consistent CSF-brain intensity threshold set at 60% of mean brain intensity. Every slice between the superior point of the cortex and the inferior limit of segmentation, set at the lowest point of the brain, was measured.[25]

The temporal lobes were segmented on cerebral images, which required detecting their boundaries as determined by the upper plane of the cerebellum, the Sylvian fissure, the upper plane of the medial temporal lobe, and the posterior plane of the temporal lobe. The posterior plane of the temporal lobe was determined manually. The posterior border was defined as the point at which the posterior horn of the lateral ventricle appeared.[26]

2) Cerebellar volumes

The cerebellar hemispheres and vermis volumes were calculated by summing up the areas of successive coronal slices after ROI tracing. Tracing of the cerebellum was also performed using the Brains 2 semi-automated model and manually corrected based on descriptions from previous studies.[23,24] The left and right cerebellar hemispheres and the vermis were manually traced using protocols described elsewhere (De Bellis and Kuchibhatla[27] and Luft[23]). The measurement of the cerebellum started as it appeared laterally to the pons. The tentorium cerebelli acted as the superior limit and the base of the cerebellum itself as the inferior limit. The cisterna magna and transverse sinus were excluded.[27] The last slice included was the one at which the cerebellum was no longer distinguishable from the transverse sinus or had disappeared. The measurement of the vermis began at the slice where the anterior and/or inferior posterior lobes appeared. Measurements were made until the vermis was no longer visible.[27]

3) Reproducibility

To evaluate the intra-rater reproducibility, the same rater repeated the TIV, brain, temporal lobe, and cerebellar measurements twice, at least a week apart, for 10 randomly selected subjects. Inter-rater reproducibility was assessed by two investigators, blinded in regard to the patient's details, who measured TIV and brain volumes for five randomly selected subjects. Inter- and intra-rater reliability tests were considered excellent (ICC > 0.96) for all regions.

5. Data analyses

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 15.0 for Windows.[28] Before analysis, the measures were examined for normality using the Shapiro-Wilk test. The level of significance was set at $p < 0.05$, 2-tailed.

A Chi-square test was used to assess gender differences, whereas age, years of education, MMSE scores, and FAQ differences between groups were assessed using analyses of variance (ANOVAs). To account for inter-individual differences in head size, cerebellar volumes were corrected by dividing them by each subject's intracranial volume and multiplying this ratio by 1000.

By employing the General Linear Model, analyses of covariance (ANCOVAs) were performed to investigate volume differences in the brain and cerebellar subregions across CDR groups, followed by Duncan's post hoc test. Age and years of education were used as covariates. We examined the relationship between the cerebellar volume, MMSE total score, MMSE sub-tests scores, and FAQ score by employing a multivariable regression model controlled for age, years of education, and cerebral and temporal lobe volumes.

Student's *t*-test was used to assess differences in cerebral, temporal lobe, and cerebellar volumes between patients that developed dementia and patients that did not develop dementia two years after baseline. Logistic regression analysis was used to calculate odds ratios (ORs) of association with 95% confidence intervals (CIs) of dementia onset with possible predictive variables. The left and right cerebellum and the vermis at baseline were used as main variables in each analysis and compared in a full multivariate model for potentially confounding effects of age, years of education, and left temporal lobe, right temporal lobe, and cerebral volume. Given the disproportionate stratified sampling, weighted analyses were performed. The level of alpha was set at $p < 0.10$.

Results

1. Demographic and clinical data

The general demographic characteristics of the groups are displayed in Table 1. No significant gender differences were observed between groups ($\chi^2 = 1.635$, $p = 0.802$), but there were significant differences in age ($F = 1.787$, $p = 0.138$) and years of education ($F = 1.733$, $p = 0.150$).

2. Brain and cerebellar measurements

Cerebellar hemispheres were progressively reduced in CDR groups 1, 2, and 3. The volume of the vermis, however, was found to be already reduced in the CDR 0.5 group, and this reduction trended progressively along with increasing CDR scores (see Table 2 for details).

There were significant correlations between all cerebellar regions and the MMSE total scores and sub-tests, and the FAQ. However, when controlling for brain and temporal lobe volumes, few correlations remained significant. MMSE total scores correlated positively with the volumes of the left temporal lobe ($\beta = 0.492$, $t = 1.876$, $p = 0.064$), right cerebellum ($\beta = 0.0543$, $t = 1.263$,

Table 1 - Clinical and demographic data

CDR	0	0.5	1	2	3	X^2/ F	p
N	10	16	28	24	18		
Gender: male (N, %)	5 (50.0%)	9 (52.9%)	13 (40.6%)	8 (36.4%)	5 (35.7%)	1.635	0.802
Age (Mean, SD)	77.8 (4.8)	79.6 (6.2)	75.7 (5.2)	78.0 (7.1)	79.9 (7.0)	1.787	0.138
Years of education (Mean, SD)	8.1 (3.3)	7.9 (4.3)	6.6 (3.3)	6.0 (3.7)	5.4 (2.8)	1.733	0.150
MMSE (Mean, SD)	30	28.3 (1.0)	20.5 (4.3)	13.0 (4.6)	6.1 (3.3)	112.066	< 0.001
FAQ (Mean, SD)	0	0	3.1 (0.6)	11.7 (1.0)	19.6 (1.4)	1760.058	< 0.001

$p < 0.080$), and posterior cerebellar lobe ($\beta = 0.0627$, $t = 1.774$, $p = 0.058$). The MMSE language sub-test correlated positively with the left temporal lobe ($\beta = 0.452$, $t = 1.642$, $p = 0.052$), right cerebellar hemisphere ($\beta = 0.442$, $t = 9.542$, $p < 0.020$), posterior cerebellar lobe ($\beta = 0.422$, $t = 1.284$, $p = 0.062$) and vermis ($\beta = 0.380$, $t = 4.520$, $p < 0.018$). Attention correlated positively with the posterior cerebellar lobe ($\beta = 0.365$, $t = 2.252$, $p = 0.044$) and vermis volumes ($\beta = 0.260$, $t = 2.747$, $p = 0.007$). FAQ scores correlated negatively with the left temporal lobe ($\beta = -0.666$, $t = -3.196$, $p = 0.002$), right cerebellum ($\beta = -0.111$, $t = -1.736$, $p = 0.086$) and vermis volumes ($\beta = -0.809$, $t = -2.884$, $p = 0.005$).

3. Outcome

Of the 26 subjects without dementia at baseline, 10 subjects (1 with CDR = 0 and 4 with CDR = 0.5) developed dementia after two years. There were no differences in intracranial volume, cerebral volume, temporal lobes, and right cerebellum between the two groups at baseline.

In a logistic regression analysis, reduced left temporal lobe (OR = 2.002, C.I.: 1.102-3.123, p = 0.058), posterior cerebellar lobe (OR = 1.402, C.I.: 1.004-2.903, p = 0.068), and vermal volume (OR = 1.480, C.I.: 1.024-2.803, p = 0.042) were related to future dementia onset.

Discussion

We determined the volumes of cerebellar substructures on MRI scans of healthy controls and subjects with cognitive impairment as classified with the CDR. Our study yielded three major findings: (1) the volumes of the cerebellum and its subregions were significantly smaller in subjects with cognitive impairment when compared to healthy controls; (2) the right cerebellar hemisphere, posterior cerebellar lobe, and vermis volumes were associated with poor cognitive performance as determined by the MMSE; and (3) the posterior cerebellar lobe and vermis volumes, together with the volume of the left temporal lobe, were associated with future dementia onset in the MCI group as compared to controls.

1. Cerebellar morphology in dementia

Dementias constitute a heterogeneous group of diseases that share a common cognitive impairment of organic etiology. Although several causes and pathophysiological mechanisms underlie the clinical presentation of different types of dementia, neuroimaging studies have confirmed some common findings such as atrophy of certain brain structures or even global brain atrophy and progressive impairment of different cognitive domains.[10] In AD, for example, temporal lobe volume reduction is observed even at early stages of the disease, and hippocampal reduction can be observed before the first symptoms manifest.[29]

Previous studies have reported cerebellar abnormalities in dementia.[13,30,31] In neuropathological studies, neuronal shrinkage and loss are well known changes that accompany AD and are most notable in the temporoparietal neocortex, limbic system, and some neuronal groups such as the locus coeruleus of the brain stem and the basal nucleus of Meynert in the basal forebrain.[30] Morphological studies, conversely, have focused on the traditional neuropathological hallmarks of AD, such as amyloid plaques, neurofibrillary tangles, and amyloid angiopathy,[30] and little has been reported on neuronal loss and other structural changes in AD.[13] There is only one structural MRI study that has previously demonstrated that the posterior cerebellar lobes are smaller in AD patients when compared to healthy controls, and that this atrophy is associated with poorer cognitive performance in AD subjects, but not in MCI patients.[31]

The most relevant pathological features of AD in the cerebellum are diffuse Aβ deposits and neurofibrillary tangles, but these are not associated with neuronal loss.[32] However, in many neurodegenerative diseases, when a relatively large central nervous system region is affected by neuronal loss, other regions are not always completely spared in terms of morphology due to their direct and indirect connections with the primarily affected region.[32] Therefore, in these 'secondarily' affected regions, despite the presence of mild atrophy, there is evidence that no relevant histopathological changes are visible under microscopic examination.[33]

Diaschisis is the cerebellar reduction related to the atrophy of superior structures and is commonly observed at late stages of dementia.[13] The main hypothesis suggesting the implication of the cerebellum in dementia invokes a possible role for *diaschisis,*[13,23,30] but our results show that cerebellar volume reductions can be observed even at early stages of the disease. Moreover, there are reports that secondarily affected regions could present mild atrophy and no histopathological changes,[33] and this is what we investigated here. Possible reasons for cerebellar volume reductions in dementia include vascular factors, toxins (e.g. alcoholic dementia),[13,23,30] and normal aging.[30]

In this study, we observed correlations between cerebellar volume reduction and cognitive decline in AD patients. Although the cerebellum is virtually free of neurofibrillary pathology, the

magnitude of cerebellar atrophy strongly correlates with the duration and stage of illness.[13,30] In previous studies, cerebellar atrophy was only evident at late stages of the disease,[13,30] and a correlation was observed between the loss of granule cells and the duration of AD.[13,30] Importantly, ascending fibers originating from the inferior olivary nucleus act as a powerful excitatory pathway on Purkinje cells in the cerebellar cortex that may play a substantial role in motor performance and learning of new motor skills.[34] Therefore, even cerebellar changes that are present due to superior structure atrophy can lead to the impairment of these connections and may have important consequences.

2. Cerebellum and cognitive impairment

In our study, cerebellar volume correlated with MMSE total scores and sub-scores for language and attention, in addition to having a negative correlation with the FAQ. In past studies, the cerebellum has only been implicated in movement, gait, posture, and balance.[10,11] However, recent studies suggest a possible involvement of the cerebellum in cognition, emotional processing, and behavior due to its connections with cortical areas and associated areas involved in superior mental functions.[10,11,35]

Some studies point to the involvement of the cerebellum in language control, and cerebellar lesions have been related to language impairments such as dysarthria, mutism, aggramatism, difficulty in naming and repetition tasks, verbal working memory, and impairment in verbal executive functions.[36-38] Apart from speech motor deficits, aphasic syndromes and isolated constellations of agrammatic speech have sporadically been observed in cerebellar dysfunctions.[38]

Hassid was the first to provide evidence that crossed cerebral *diaschisis* might also be associated with extensive constellations of disrupted verbal functions.[39] A recent report corroborates this idea and suggests that dysfunctional cortico-cerebellar connections could be related to deficient representations of temporal information and impaired sequencing of linguistic data.[40]

Even if cerebellar volume reductions were due to decreased temporal lobe and brain volume, to the best of our knowledge there are no studies demonstrating that vermis atrophy in dementia could be related to *diaschisis*. Although it is possible that reduced vermis volume could occur in conjunction with similar processes like cerebellar volume reduction, it may be best considered as a risk factor.

The possibility that the cerebellum might be a part of attentional networks was not seriously taken into consideration until the late 1980s and early 1990s. Since then, two lines of reasoning have been proposed to explain the role of the cerebellum in attention. It has become clear that the projections from the dentate nucleus (the largest and most phylogenetically recent of the cerebellar nuclei in humans and higher primates) to the primary motor cortex represent only a fraction of its output.[41] Kelly and Strick found that other portions of the dentate nucleus innervate oculomotor, prefrontal, and posterior parietal areas of the cerebral cortex, parts of the brain that are essential for cognitive functions including attentional control.[42] Activation has been observed in posterior parts of the cerebellum (including the hemispheres and vermis) when assessing spatial shifts in visual attention.[41]

Classically, the functions of the cerebellar vermis were thought to be related to the vestibular system and to be involved in balance, coordination, motor activity, tonus, and posture. But there is clear evidence of its involvement in such functions as speech, memory, visuomotor processing, attention, and emotion.[10,43] These functions are mediated by afferent connections of the vermis such as vestibulocerebellum fibers, reticulocerebellum fibers, and spinalcerebellum tracts, and by efferent connections with the pons, medulla oblonga and reticular formation.[11,44] Some studies reported connections between the cerebellar vermis and the flocculonodular lobe to the midbrain and the limbic system that have led to the idea of a 'limbic cerebellum'.[11,45]

The fact that visual information conveyed by the mossy and climbing fibers is integrated in Purkinje cells of the cerebellar vermis (lobules V, VI, VII) involved with oculomotor control has been firmly established from classical neurophysiological studies.[46,47] The flocculonodular lobe and the vermis modulate the position and velocity of the eyes with respect to the orientation of the head and the body, enabling the subject to fixate clearly on a new target, reposition the gaze in saccadic eye movements, and fixate on points while moving, besides being involved in the refinement of motor commands before they reach the eye muscles.[47] If the motor control of the eyes is impaired, the results of cognitive tests may also be impaired, because many cognitive tests like the MMSE require visual integrity.

3. Cerebellum and outcome

Based on these preliminary findings, reduced posterior cerebellar lobe and vermis volumes could be potential risk factors for future dementia onset, suggesting the possible involvement of the cerebellum in AD outcome. Although cerebellar changes accompany similar changes in the temporal lobe, they cannot be considered as an isolated factor. Our study evaluated volumes at one point in time, and we have hypothesized two possible ways in which cerebellar volume may change: (1) cerebellar volume reductions could be secondary to temporal lobe volume reductions, or; (2) cerebellar volume reductions could be evident prior to temporal lobe impairment and could be related to other factors not observed here. This suggests that cerebellar volume reductions can be considered as a risk factor later dementia onset.

Finally, a significant negative correlation between the volume of the vermis and functionality was observed. Previous studies have shown that the functioning of the vermis is related to the prognosis and mortality rates in dementia.[48] Since the cerebellum is also related to motor and executive functions, this finding indicates a new possibility to be explored in the context of dementia rehabilitation.

4. Limitations

The interpretation of our results is currently limited because we were not able to obtain detailed and extensive neuropsychological

Table 2 - TIV, cerebral and cerebellar volumes in cm^3 for each group*

CDR	0 Mean (SD)	0.5 Mean (SD)	1 Mean (SD)	2 Mean (SD)	3 Mean (SD)	X^2/ F	p	Duncan test (5%)
TIV	1722.19 (47.80)	1750.64 (99.12)	1728.96 (86.32)	1729.64 (78.39)	1747.19 (93.64)	0.334	0.854	0 = 0.5 = 1 = 2 = 3
Brain	596.09 (37.01); 1008.67 (95.30)	576.23 (42.24); 1034.39 (129.73)	536.44 (45.38); 1007.44 (114.49)	449.38 (87.39); 1019.38 (131.69)	418.91 (51.24); 1056.33 (66.36)	27.636	< 0.001	0 > 0.5 > 1 > 2 = 3
Left temporal lobe	71.86 (5.45), 120.41(8.12)	70.23 (4.67); 120.65 (8.95)	58.46 (4.32); 98.18 (5.67)	51.45 (4.48); 88.62 (4.58)	47.96 (3.79); 83.92 (4.23)	124.04 1	< 0.001	0 > 0.5 > 1 > 2 > 3
Right temporal lobe	70.89 (5.22); 117.77 (8.56)	70.77 (5.55); 117.44 (6.78)	55.03 (4.46); 94.96 (7.19)	51.06 (4.65); 87.99 (7.68)	49.22 (5.67); 83.45 (7.41)	19.389	< 0.001	0 = 0.5 > 1 > 2 = 3
Left cerebellum	30.40 (2.47); 53.21 (5.17)	28.86 (2.38); 49.70 (4.22)	26.90 (2.16); 46.43 (3.43)	24.04 (1.58); 41.54 (2.76)	20.69 (1.63); 36.04 (1.83)	53.976	< 0.001	0 > 0.5 > 1 > 2 > 3
Right cerebellum	30.15 (2.10); 51.95 (4.31)	31.40 (2.44); 55.00 (5.78)	24.90 (2.27); 44.41 (3.22)	23.46 (1.58); 40.54 (2.76)	20.12 (1.60); 35.04 (1.84)	80.858	< 0.001	0 = 0.5 > 1 > 2 > 3
Vermis	3.24 (0.48); 5.45 (0.82)	2.05 (0.31); 3.89 (0.54)	1.46 (1.84); 2.51 (0.33)	1.37 (0.29); 2.37 (0.50)	0.99 (0.27); 1.74 (0.50)	103.06 9	< 0.001	0 > 0.5 > 1 = 2 > 3
Cerebellar anterior lobe	9.08 (1.49); 15.25 (4.84)	9.06 (1.64); 15.75 (2.38)	8.11 (1.93); 13.84 (1.38)	8.15 (2.46); 13.99 (3.23)	6.56 (2.31); 10.57 (3.11)	2.097	0.088	0 = 0.5 > 1 = 2 > 3
Cerebellar posterior lobe	53.85 (3.82); 88.42 (5.23)	51.22 (2.36); 84.35 (3.44)	42.53 (2.18); 76.55 (4.21)	39.95 (2.95); 69.72 (3.33)	34.85 (1.88); 60.35 (2.12)	17.563	< 0.001	0 > 0.5 > 1 > 2 > 3

** First volume: corrected by TIV. Second volume: Absolute volume.*

data from our subjects, and were thus able to analyze only certain cognitive functions. Our control and MCI groups were very small, and we could not calculate ROC curves for cerebellar volumes and dementia onset. Our findings are correlational and thus cannot imply causality; whether cerebellar structural alterations and their relation to cognitive functioning are due to primary cerebellar impairment in the course of AD or secondary to destructive processes in other regions more typically associated with AD remains to be determined.

Conclusion

To the best of our knowledge, there are no studies evaluating cerebellar volume changes in patients with different levels of dementia and predementia. Our results support previous neuropathological findings of cerebellar involvement in cognition and AD. Moreover, they indicate that cognitive impairment may be at least partly related to structural changes in the cerebellum. Our findings and interpretations are preliminary and need to be confirmed and validated by future longitudinal studies. The cerebellum could be studied in MCI and AD cohorts to further examine the relationship between changes in the cerebellar morphology and cognitive impairment. The cerebellar roles in motor and non-motor functions could also be explored in studies on new therapeutics and rehabilitation for patients suffering from dementia.

Acknowledgements

This study was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil, and the Fundação de Apoio à Pesquisa do Estado de São Paulo (FAPESP), Brazil. AJ is funded by the Programa de Apoio a Projetos Institucionais com a Participação de Recém-Doutores - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (PRODOC-CAPES, 0151/08-4).

The funding sources had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Disclosures

Writing group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
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**Modest*
***Significant*
****Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

Note: UFT = Universidade Federal do Tocantins; UNIFESP = Universidade Federal de São Paulo; IIEP = Instituto Albert Einstein de Ensino e Pesquisa; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; PRODOC-CAPES = Programa de Apoio a Projetos Institucionais com a Participação de Recém-Doutores, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

For more information, see Instructions for Authors.

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