

Main effects and interactions of cerebral hemispheres, gender, and age in the calculation of volumes and asymmetries of selected structures of episodic memory

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Summary

The aim of this study was to clarify the influence of anatomical (cerebral hemisphere) and demographic (age and gender) variables on the gray matter (GM) volumes and volumetric asymmetry indices (VAIs) of selected structures involved in episodic memory.

A cross-sectional study was performed in 47 healthy volunteers. Neuropsychological evaluation revealed similar IQs across the sample. Using SPM-based software, brain segmentation, labeling and volume measurements of the hippocampus, amygdala, middle temporal gyrus and parahippocampal gyrus were performed in each cerebral hemisphere. A two-way between-groups multivariate analysis of covariance (MANCOVA) was applied to GM volumes and VAIs.

The main effects of gender and cerebral hemisphere on GM volumes were significant ($p < .001$), while there was no significant interaction effect between gender and cerebral hemisphere. VAI measurements showed a non-significant effect of gender, but a significant influence of age ($p = .015$). The linear model of interactions and main effects explained 33% of the variance influencing the GM volume quantification.

While cerebral hemisphere and gender were found to affect the volumes of brain structures involved in episodic memory, the calculation of VAIs was affected only by age. A comprehensive understanding of the main effects and interaction effects of cerebral hemisphere, gender and age on the volumes and asymmetries of structures related to episodic memory might help neurologists,

psychiatrists, geriatricians and other neuroscientists in the study of degenerative brain diseases.

KEY WORDS: *episodic memory, limbic system, magnetic resonance imaging, multivariate analysis, neuroanatomy.*

Introduction

Some normative brain volumes assessed with magnetic resonance imaging (MRI) can be used to distinguish between pathological changes and normal age-related changes (Matsumae et al., 1996). Advanced evaluation of mental status in elders includes magnetic resonance volumetry of selected structures of the limbic system and it is an approach that has been used to investigate the pathophysiology of Alzheimer's disease (AD) (Mouton et al., 1998; Du et al., 2001), memory disorders (Kopelman, 2002), schizophrenia (Gur et al., 2000; Kalus et al., 2005), brain trauma and temporal lobe epilepsy (Bigler et al., 2002). A common finding in some of these pathologies is a decrease in the volume of selected structures such as the hippocampus, amygdala and entorhinal cortex (Gonçalves-Pereira et al., 2006). These structures are involved in a subtype of long-term memory named episodic memory which is one of the earliest affected functions in patients with AD; in particular, the establishment of new episodic memories is impaired, whereas events dating back to more remote periods in the past are better preserved (Dickerson and Sperling, 2008; Sperling, 2010).

The importance of understanding the volumetric relationships between the hippocampal region, amygdala and entorhinal and parahippocampal cortices is indeed linked to their involvement in encoding and retrieving episodic memory (Squire, 2004). Although previous studies reported quantitative volume data obtained using quantitative brain MRI evaluations, they focused mainly on whole brain, gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes (Coffey et al., 1992; Courchesne et al., 2000). Other studies reported the volumes of specific gyri but did not assess the influence, on these measurements, of basic variables such as gender, age and cerebral hemisphere (Courchesne et al., 2000). To the best of our knowledge, available information about the influence of basic demographic (gender and age) and anatomical (cerebral hemisphere) variables in the calculation of the volumes and asymmetries of structures related to episodic memory remains limited. Greater understanding of these associations might help neurologists and radiologists in the early diagnosis of brain diseases whose initial

signs include decreases in selected brain volumes and sometimes atrophy (Trivedi et al., 2011). The aim of this study was to clarify the influence of anatomical and demographic variables on the GM volumes and asymmetries of selected structures involved in episodic memory. Adjusted marginal means of volumes and volumetric asymmetry indices (VAIs) of the hippocampus, amygdala, middle temporal gyrus and parahippocampal gyrus are here reported, together with their associations with the variables cerebral hemisphere, gender and age, in a sample of healthy young volunteers.

Materials and methods

A cross-sectional study was performed in 47 healthy volunteers who underwent brain MRI. Twenty-three participants were men (mean age \pm SD, 30.00 \pm 5.67 years; range, 20–40 years) and 24 were women (mean age \pm SD, 30.13 \pm 5.79 years; range, 20–40 years). The neuropsychological evaluation comprised: the Wechsler Adult Intelligence Scale III (Wechsler, 1997); a modified version of the Mini-Mental State Examination (Reyes-de-Beaman et al., 2004); and the Beck's Depression Inventory-II test (Beck et al., 1996). These tests revealed preserved mental status and IQs within the normal range, comparable across the sample. Exclusion criteria for MRI included the presence of a pacemaker or metallic implant, claustrophobia, and structural brain abnormalities on MRI scans.

Brain MRI

Conventional non-enhanced brain MRI was performed using a 3.0T GE Signa HDxt scanner (General Electric Healthcare, Milwaukee, WI). The protocol included three plane localizers, and all images were acquired with a high-resolution eight-channel brain array coil. The exami-

nation included standard clinical sequences: sagittal T1-weighted FLAIR (TE/TR/TI = 9.9/2500/625 ms) with a 5/3-mm slice thickness/gap and a field of view (FOV) of 24 x 24 cm (the parameters of this sequence served to increase the definition of the subarachnoid space and cistern boundaries); T1-weighted axial fast spoiled gradient echo (FSPGR) (TE/TR = 3.9/9.4 ms) with a 1.3/0-mm slice thickness/gap, a FOV of 24 x 24 cm, and a matrix of 256 x 256 (in-plane resolution of 1 mm); coronal T2-weighted fast spin-echo (FSE) (TE/TR = 164.1/2617 ms) with a 3/0-mm slice thickness/gap and a FOV of 22 x 16 cm; and axial FLAIR (TE/TR/TI = 115.8/11002/2750 ms) with a 5-mm/1-mm slice thickness/gap and a FOV of 22 x 22 cm.

Volumetric data analysis

MR imaging data from the T1-weighted axial FSPGR sequence were transferred to a workstation, after which, applying Individual Brain Atlases using Statistical Parametric Mapping (IBASPM) software (Alemán-Gómez et al., 2006), we calculated volume statistics (in mm³) of selected brain structures (Tae et al., 2008). The IBASPM software uses the spatial normalization and segmentation routines of the Statistical Parametric Mapping software version 2 (SPM2) (Friston et al., 2003). The steps involved in the calculation of brain volumes (Fig. 1) have been previously described elsewhere (Roldan-Valadez et al., 2013). Briefly, they are the following:

- normalization: the MR image is normalized to the International Consortium for Brain Mapping (ICBM) (based on volumetric parameters extracted from 152 normal MRI scans) T1-weighted template of the Montreal Neurological Institute (MNI) space to obtain the spatial transformation matrix. With the transformation matrix, the GM image is transformed to MNI space.
- segmentation: the MR image is segmented into GM, WM and CSF in native space.

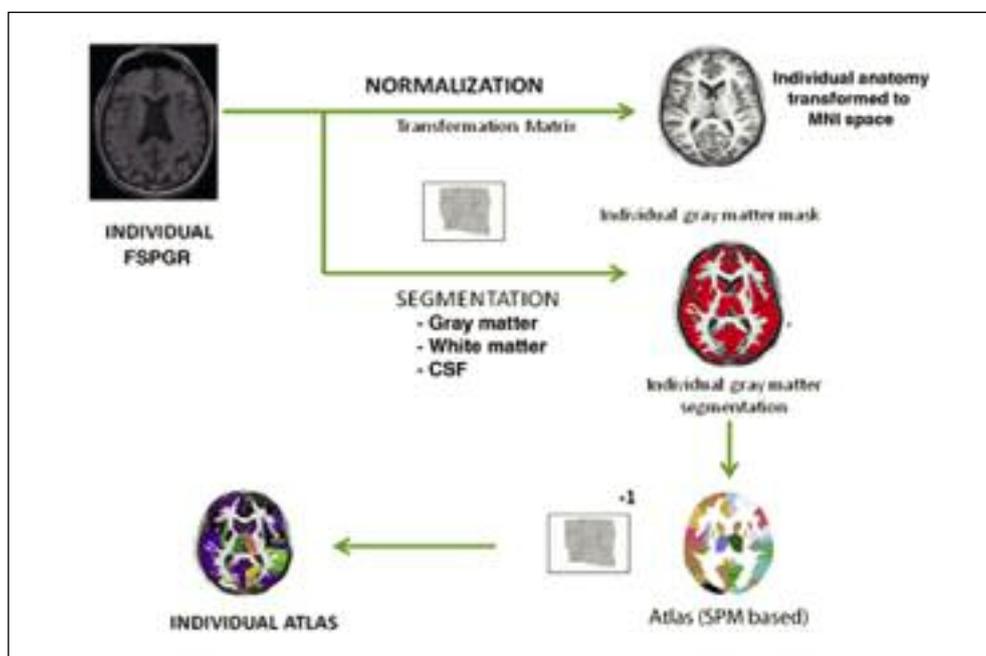


Figure 1 - Algorithm showing the post processing steps used by the IBASPM software in the calculation of brain volumes (Alemán-Gómez et al., 2006; Tae et al., 2008).

- automatic labeling: each normalized individual GM voxel is labeled based on an automatic anatomical labeling atlas comprising 116 predefined segmented structures (Tzourio-Mazoyer et al. 2002).

- atlasing: individual atlases are created from each subject's MR image. The individual atlases are reversely normalized, and the GM image in native space is masked using its individual 116 brain structures.

- volume statistics: for all individual atlases, the volumes of the 116 predefined brain structures are calculated. When the voxel values of the GM image exceed the voxel values of the WM and CSF images, the voxel is included for volume calculation.

Following this post-processing procedure, we selected only the volume measurements of the hippocampus, amygdala, middle temporal gyrus and parahippocampal gyrus. Figure 1 shows an algorithm of the steps followed by the IBASPM software. All images were coded so that researchers were blinded to each volunteer's identity, gender and age.

Selected brain structures involved in episodic memory

Anatomically related structures essential for declarative memory and episodic memory include the hippocampus (Squire et al., 2004), amygdala, middle temporal gyrus and parahippocampal gyrus (Squire, 2009). Figure 2 depicts the location of these selected brain structures involved in episodic memory.

Statistical analysis

A two-way between-groups multivariate analysis of covariance (MANCOVA) (Pallant, 2011) was performed to investigate the influence of gender and cerebral hemisphere differences in the volumetry of anatomical structures involved in episodic memory. Four dependent variables were

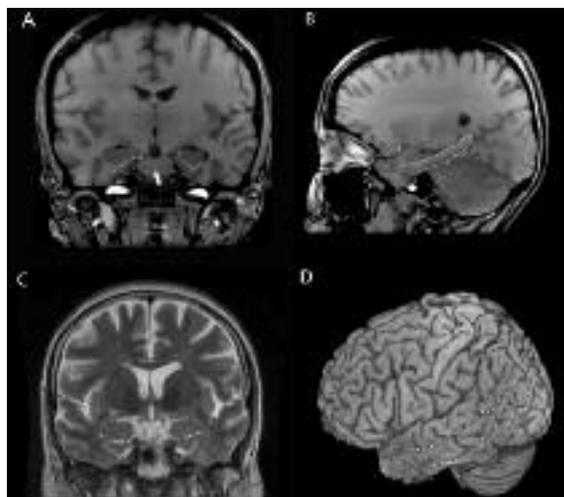


Figure 2 - Selected brain structures involved in episodic memory.

A, Coronal T1-weighted brain MRI, the dotted lines represent the parahippocampal gyrus; B, sagittal-oblique T1-weighted brain MRI, showing the hippocampal gyrus; C, coronal T2-weighted MRI, depicting the amygdala; and D, 3D reconstruction of the brain with dotted lines showing boundaries of the middle temporal gyrus.

re used, i.e. the measured GM volumes of the hippocampus, amygdala, middle temporal gyrus and parahippocampal gyrus. The independent variables were gender and cerebral hemisphere. Age was used as a covariate to control for individual differences. The effect size assessment (proportion of the variance in the dependent variable that can be explained by the independent variable) for each of the results was performed using the partial eta squared (η^2) proposed by Cohen (1988), where 0.01 to 0.06 = small effect; 0.06 to 0.14 = moderate effect, and a value greater than 0.14 = large effect.

A two-way between-groups MANCOVA was performed on the VAIs of the four selected structures; the VAI for each structure was defined as the absolute difference between the volumes (in mm^3) of a pair of symmetrical selected structures (one in each cerebral hemisphere) divided by their mean and multiplied by 100 (Wu et al., 2005). The only independent variable in this analysis was gender, and the covariate was age. Statistical significance was indicated by $p < 0.05$ (two-tailed).

All analyses were carried out using the IBM® SPSS® Statistics software (version 21.0.0.0, IBM Corporation, Armonk, NY); for the graphics, we used the STATISTICA data analysis software system (version 10.0; StatSoft, Inc., Tulsa, OK, USA).

Results

Descriptive statistics

The study was conducted in 23 men (mean age \pm SD; 30.00 ± 5.67 years; range, 20–40 years) and 24 women (mean age \pm SD; 30.13 ± 5.79 years; range, 20–40 years). Good quality segmentation was acquired in all brain images with volume quantification for the eight selected structures in each patient (in total, 376 volumes and 188 VAIs were included in the analyses). Variables were checked for normality, linearity, univariate and multivariate outliers, multicollinearity and homogeneity of variance-covariance matrices, and no serious violations were noted; the assumption of homogeneity of variance-covariance matrices was examined using Box's M test, which was not significant (Box's M value = 56.043, $F = 1.716$, $df (30, 22192.480)$, $p = .009$).

Interactions, effect sizes and main effects on GM volumes

After adjusting for age, there was no significant interaction effect between gender and brain hemisphere on GM volumes of selected areas: $F (4, 86) = 1.128$, $p = .349$; Wilks' Lambda .950; with a small effect size (partial $\eta^2 = .050$) and an observed power of .341. Instead there was a significant main effect of gender: $F (4, 86) = 11.629$, $p < .001$; Wilks' Lambda .649, with a large effect size (partial $\eta^2 = .351$); and also of cerebral hemisphere: $F (4, 86) = 178.839$, $p < .001$, Wilks' Lambda .107, again with a large effect size (partial $\eta^2 = .893$); both variables showed an observed power of 1.0. The covariate, age (years), was non-significantly related to GM volume quantification: $F (4, 86) = 1.672$, $p = .164$. Table 1 presents a summary of the multivariate assessment.

After a Bonferroni adjustment for multiple comparisons (new p -value = .0125), the MANCOVA showed, on the

one hand, a significant influence of gender on the volumes of three areas: amygdala, middle temporal gyrus, and hippocampus, but not on the hippocampus. On the other hand, there emerged a significant effect of cerebral hemisphere on the volumetry of the four structures. Table II shows the between-subject statistics of these independent variables.

Estimated marginal means

Mean scores indicated that the left hippocampus and the left middle temporal gyrus were larger than their counterparts in the right cerebral hemisphere. Also, there emerged significant differences in the volumetry of these structures between males and females, with male brains found to show larger volumes. The volumes of the amygdala and parahippocampal gyrus, on the other hand, were larger in the right cerebral hemisphere and, again, differences were found between males and females, with larger volumes in the males. Table III shows the estimated marginal means adjusted for cerebral hemisphere and gender and for the influence of age, controlled at the value of 30.06 years.

MANCOVA assessment of volumetric asymmetry indices

The assumption of homogeneity of variance-covariance matrices was interpreted as met since Box's M was not significant (Box's M value = 10.192, $F = .921$, $df (10, 9138.207)$, $p = .513$). There emerged a non-statistically significant main effect of gender in the calculation of VAIs: $F (4, 41) = .451$, $p = .771$; Wilks' Lambda .958, with a very small effect size (partial $\eta^2 = .042$) and an observed power of .145. However the covariate, age (years), was significantly related to the VAI quantification. $F (4, 41) = 3.501$, $p = .015$, with a large effect size (partial $\eta^2 = .255$) and an observed power of .820.

The between-subject analysis (Bonferroni adjustment of the p-value for multiple comparisons was .0125) showed a significant influence of age in the VAI calculation only for the middle temporal gyrus $p = .010$. The observed power was .744. However, there emerged no major influence for the other three selected structures: hippocampus, $p = .0304$; parahippocampal gyrus, $p = .028$ and amygdala, $p = .919$. Table IV shows the adjusted means (and standard errors, SEs) for the selected VAIs; Fig.s 3 and 4 depict a comparative graph of the VAIs of the selected structures.

Discussion

The clinical relevance of our study lies in the application of multivariate analyses to the measurement of GM volumes and VAIs. Although several studies have reported regional GM volumes, only a limited number of them have presented statistical evidence of the main effects and interactions of gender and cerebral hemisphere (Roldan-Valadez et al., 2015). To the best of our knowledge, none of them have analyzed their results focusing on the structures involved in episodic memory. An additional value of this study is that we present an adjusted means table giving SEs and confidence intervals (missing in other studies) for each selected structure, which may be a useful source of reference for comparison with ongoing protocols or selected populations in clinical research.

We found evidence that showed how GM volumes of structures involved in episodic memory vary according to gender and cerebral hemisphere. Additionally, the analysis of the VAIs showed a non-significant main effect of gender. Age instead did have a significant influence on VAI measurements. In our view, the absence of a significant influence of gender and cerebral hemisphere in the VAI calculations is due to the fact that the VAI value itself summarizes the volumetric data from both cerebral hemispheres. In general, males and females were coincident as regards the side of a cerebral hemisphere having the larger size; therefore, the significance of the variable age might be taken as evidence that even in young adulthood (20–40 years) there occur subtle changes in brain volumes that are unveiled only using multivariate analyses. We believe the finding of absence of an effect of age, as a covariate, on the GM volumes themselves was due to the relatively small age range of the sample (however, age was significant in the MANCOVA analysis for VAI calculations). Our linear model of interactions and main effects explained 33% of the variance influencing the volume quantification of selected brain structures involved in episodic memory. We consider it important to include moderator variables such as gender, cerebral hemisphere and age in a volumetric analysis of brain structures. They might help to explain why some researchers obtain statistically significant results while others do not and how such brain volumes change with age or gender. The adjusted means and SE values for left↔right cerebral hemispheres and male↔female brains of healthy young adults (20–40 years old) presented in this study were able to explain

Table I - Multivariate analyses showing the significance of the influence of selected variables (age, gender and cerebral hemisphere) on GM volumes.

Independent variable	Wilks' Lambda	F-test	p-value	Effect size (partial eta squared)	Observed power
Intercept	.133	139.766	< .001	.867	1.0
Age	.928	1.672	.164	.072	.494
Gender	.649	11.629	< .001	.351	1.0
Cerebral hemisphere	.107	178.839	< .001	.893	1.0
Gender * Cerebral hemisphere	.950	1.128	.349	.050	.341

There was no significant interaction between gender and cerebral hemisphere, therefore the model is explained by the significant main effects of each variable independently; the influence of age was not significant.

Table II - Between-subject effects (of gender and cerebral hemisphere) on GM volumes of selected structures involved in episodic memory.

Independent variable	Dependent variable	F-test	p-value	Effect size (partial eta squared)	Observed power
Gender	Hippocampus	4.131	.045	.044	.520
	Parahippocampal gyrus	31.916	< .001	.264	1.000
	Amygdala	44.125	< .001	.331	1.000
	Middle temporal gyrus	18.921	< .001	.175	.990
Cerebral hemisphere	Hippocampus	8.417	.005	.086	.819
	Parahippocampal gyrus	188.847	< .001	.680	1.000
	Amygdala	9.956	.002	.101	.877
	Middle temporal gyrus	81.588	< .001	.478	1.000

Bonferroni adjustment considered a p-value = .0125 as the required alpha level.

Table III - Adjusted means of the volumes (cm³) of selected structures involved in episodic memory.

Gender	Dependent variable	Right Hemisphere				Left Hemisphere			
		Mean	SE	95% CI		Mean	SE	95% CI	
				Lower bound	Upper bound			Lower bound	Upper bound
Female	Hippocampus	3.751	.102	3.548	3.954	4.030	.102	3.827	4.233
	Parahippocampal gyrus	4.577	.088	4.403	4.752	3.449	.088	3.274	3.623
	Amygdala	.973	.023	.926	1.019	.898	.023	.852	.945
	Middle temporal gyrus	15.446	.280	14.890	16.001	17.784	.280	17.229	18.340
Male	Hippocampus	3.940	.104	3.733	4.147	4.260	.104	4.053	4.467
	Parahippocampal gyrus	5.168	.090	4.990	5.347	3.860	.090	3.682	4.038
	Amygdala	1.129	.024	1.082	1.177	1.055	.024	1.008	1.102
	Middle temporal gyrus	16.460	.286	15.893	17.028	19.229	.286	18.662	19.797

Abbreviations: SE=standard error; 95% CI=95% confidence interval. Values are grouped by cerebral hemisphere and gender (means and SEs were adjusted for the influence of age, controlled at the value of 30.06 years).

Table IV - Volumetric asymmetry indices of selected structures involved in episodic memory.

VAIs	Female				Male			
	Mean	SE	95% CI		Mean	SE	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
Hippocampus	7.9	1.3	5.4	10.5	9.3	1.3	6.7	11.9
Parahippocampal gyrus	28.2	1.3	25.6	30.7	29.0	1.3	26.4	31.6
Amygdala	9.2	1.4	6.4	12.0	8.8	1.4	5.9	11.7
Middle temporal gyrus	14.1	1.1	11.9	16.3	15.8	1.1	13.6	18.1

Abbreviations: VAIs=volumetric asymmetry indices; SE=standard error; 95% CI=95% confidence interval. Values are grouped by gender (means and standard errors were adjusted for the influence of age, controlled at the value of 30.06 years).

the variability in the data model. However, model validation should be done in subsequent studies. The four specific structures analyzed in this study are principal components in the integration of long-term memory (Fig. 5). The hippocampus has been considered one of the most important structures in episodic memory; it shows atrophy along the lifespan and its volume has been seen to decrease in patients with AD (Chiang et al., 2010). However, previous studies did not look into cerebral hemisphere differences. Unlike previous authors (Watson et al., 1992; Gonçalves Pereira et al., 2005), we, in our study, showed a larger volume of the left hippocampus. Our results may have differed from theirs because they did not apply the multivariate analysis approach.

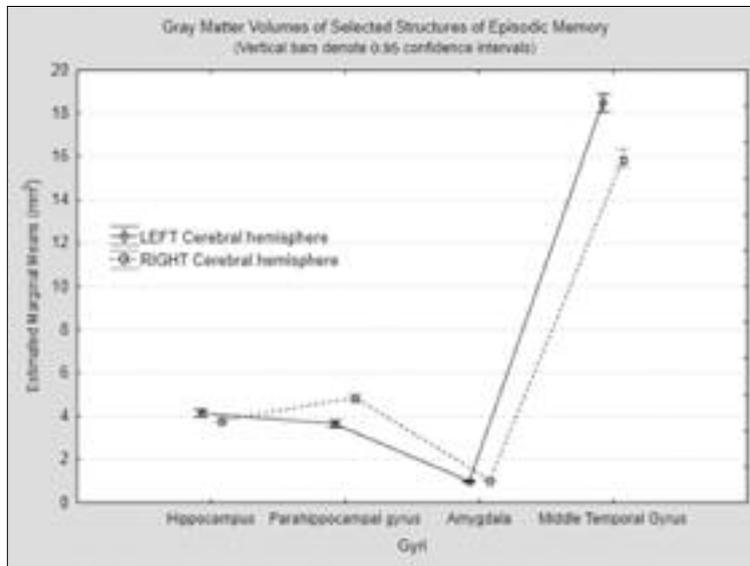


Figure 3 - Line graph showing estimated marginal mean volumes of selected structures involved in episodic memory.

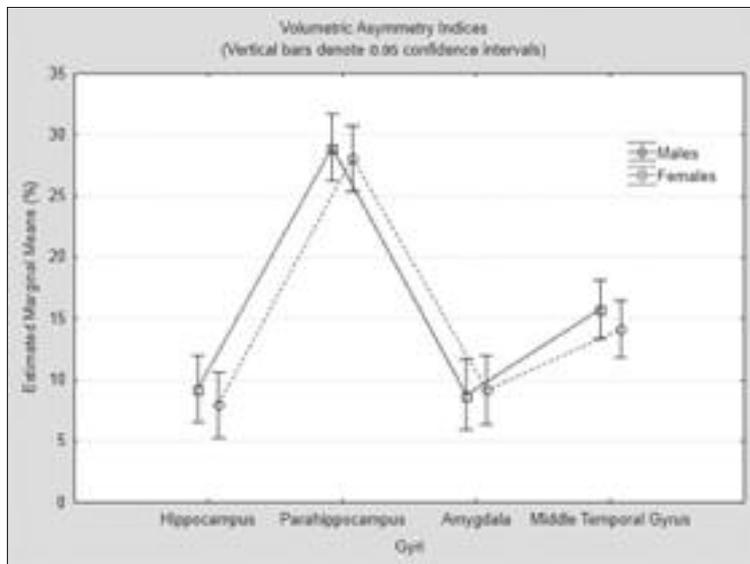


Figure 4 - Line graph depicting estimated marginal means of VAIs of selected structures involved in episodic memory.

The parahippocampal gyrus was larger in the right cerebral hemisphere. Previous authors have associated this finding with a larger volume of the right entorhinal cortex (Kovalev et al., 2003). Additionally, we found larger measurements in males. The previous literature failed to clarify the clinical significance of these findings (Hänggi et al., 2011; Insausti et al., 1998; Gonçalves-Pereira et al., 2006; Yokum et al., 2012).

The middle temporal gyrus volume was found to be smaller in the right hemisphere in both males and females; in general, the gyrus volumes and VAI values were also greater in males. This asymmetry has previously been associated with healthy aging, as well as mild cognitive impairment and AD (Hänggi et al., 2011). As regards the amygdala, our results showed larger volume measurements in the right hemisphere for both genders, which is in agreement with previous studies (Bernasconi et al., 2003; Gonçalves-Pereira et al., 2006; Gonçalves Pereira et al., 2005), the amygdala was larger in males than females. The finding of a higher VAI for the female amygdala has been associated with integrative sensory and emotional functions. This structure is a cornerstone of self-relevant biological and social appraisals of the environment and also of the processing of autobiographical events. It also participates in the integration of emotion, perception and cognition (including memory for past autobiographical events), and “forges the establishment and maintenance of an integrated self” (Markowitsch and Staniloiu, 2011).

Some limitations of this study need to be addressed: we consider this research an initial stage in a line of research seeking to shed light on the MR morphometric associations between brain structures that might support the diagnosis of degenerative brain diseases, such as mild cognitive impairment and AD. We are aware that other interesting interactions exist between other GM volumes, however, it was not our aim to include them in this study (Joshi et al., 2010). Although some normative databases have been proposed for some brain structures (e.g. Gonçalves-Pereira et al., 2006), a worldwide consensus is still missing; our findings rely on the adjusted means for cerebral hemisphere and gender, with the corresponding confidence intervals for these data. Although commonly used segmentation techniques have been reported to convey potential left-right asymmetric biases, which can raise doubts about the reliability of measurements (Maltbie et al., 2012), SPM-based segmentation and automatic labeling are processes currently accepted and used by the neuroimag-

ing community around the world. Validation of other methods, however, might be useful to support findings in future studies. The generalizability of our findings is directly related to the clinical applicability of normative values of specific brain structures.

A comprehensive knowledge of brain volumes is useful not only in the diagnosis of longitudinal changes in elderly brains, but also for the detection of alterations of limbic system structures in young adulthood related to recreational drug abuse (cocaine) (Barrós-Loscertales et al., 2011) and obesity (even in females younger than 18 years) (Yokum et al., 2012). These are only two examples of the vast wealth of evidence in the medical literature.

In conclusion, understanding the influence of the cerebral hemispheres, gender and age in GM volume measurements and VAs should be a first step in understanding the modern pathophysiology of the human brain. Radiologists, anatomists and imaging neuroscientists can help in the measurement of normative brain volumes, providing useful data for clinicians in the areas of neurology, psychiatry, geriatrics, neuropsychology and other fields of the neurosciences; this information might support our understanding of the brain system.

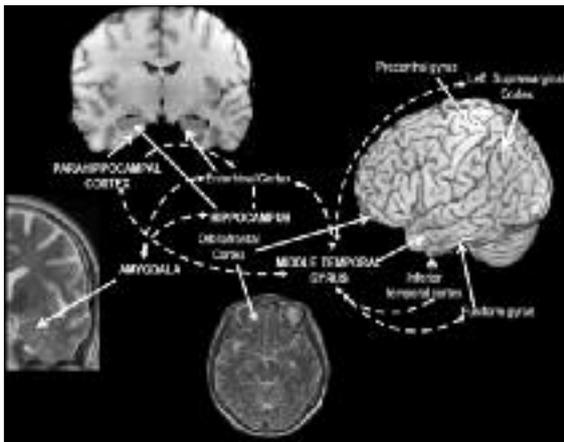


Figure 5 - Axial and coronal brain MR images and volumetric brain reconstruction showing reported associations (white arrows) between the selected structures considered in this study.

Dashed white arrows depict interconnections between brain structures involved in the episodic memory circuit (Joshi et al., 2010); some of them were not included in our assessment.

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