International Journal of Medical Science and Clinical Invention 10(10): 6932-6944, 2023
DOI:10.18535/ijmsci/v10i10.05
https://valleyinternational.net/index.php/ijmsci

Original Article,

Depressive symptoms associated with brain morphometry in Mild Cognitive Impairment stage due to Alzheimer's and Parkinson's disease

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Abstract:

Objectives: Although there are studies linking depressive symptoms with psychiatric diseases, and then, with brain morphometry, scarce is the literature examining the association between depressive symptoms and brain morphometry in the prodromal stage of neurodegenerative disorders. In the current analysis, we used a fair sample of Mild Cognitive Impairment (MCI) stage due to Alzheimer's disease (AD) and Parkinson's disease (PD) patients, to examine the association between different depressive symptoms and a large variety of brain morphometric factors.
Methods/ Design: Our sample consisted of 352 patients. The Geriatric Depression Scale (GDS) was used for the association with brain measurements. Principal Components Analysis (PCA) and regression models were used for the analyses. Age, sex, years of education, Addenbrooke's cognitive examination revised (ACE-R), and estimated total intracranial volume were used as covariates.
Results: Factor3 was significantly and positively correlated with GDS total, Dysthymia, Anxiety and Hopelessness. r_factor1, r_factor2 and r_factor5 were significantly and positively correlated with Anxiety, while r_factor5 was also correlated with GDS total. Concerning volumes, v_factor3 was found to be correlated with GDS total, Dysthymia, Anxiety and Hopelessness.
Conclusions: The association between depressive symptoms and upcoming neurodegenerative disorders is reflected in human brain structural alterations, suggesting specific modifications in network-like patterns and neuronal connectivity. Characterizing differences in the morphometry of brain regions among MCI patients with depressive symptoms may aid the early diagnosis and treatment of these symptoms.

Keywords: Geriatric Depression Scale, Mild Cognitive Impairment, brain morphometry.

Introduction :

Neurodegenerative diseases are commonly accompanied by depressive symptoms, especially depression and anxiety [1]. The presence of depressive symptoms in Alzheimer's dementia (AD) and Parkinson's disease (PD) has a negative

impact on the quality of life of both patients and their caregivers [2] and has been also linked with accelerated progression of disability, earlier institutionalization and mortality[3, 4].Depressive symptoms of different diseases have been also associated with brain morphometry [5]. In general, regarding depression and anxiety disorders, reduced volume of the rostral-dorsal anterior cingulate gyrus appears as a generic effect [6]. Although there are studies linking depressive symptoms with psychiatric diseases, and then, with brain morphometry, scarce is the literature examining the association between depressive symptoms and brain morphometry in the context of neurodegenerative disorders.

During depressive symptoms, neuroplastic stress-related processes occur in the hippocampus, cingulum, left amygdala, and right dorsomedial prefrontal cortex [7]. Depressive symptoms have been also associated with regional cortical metabolism in AD patients, suggesting that these symptoms are fundamental expressions of the cortical dysfunction of the disease [8]. However, reports are not quite linear, with a different study suggesting no association between atrophy of the amygdala and depressive symptoms in AD [9]. In a group of anxiety mild PD patients, psychiatric symptom severity was associated with decreased grey matter volume [10], indicating that the precuneus and the anterior cingulate cortex may play a significant role in the pathogenesis of anxiety in PD. By using the Geriatric Depression Scale (GDS), depressive symptoms have also been associated with brain morphometry in PD, and more precisely, with left hippocampal volume, and right parahippocampal gyrus volume [11]. However, a different study found no association between apathy and frontotemporal atrophy, in a small group of PD patients; raising questions about which symptom is associated with brain morphometry in this specific neurodegenerative disorder. A different study of patients with essential tremor suggests that symptoms of depression and anxiety could be linked to specific structural brain changes [12]. The discrepancy of these results may be explained by the complexity of brain circuits, highlighting the importance of an holistic assessment of brain structure with the stratification of many morphological features.

Existing literature points towards a context-specific association between specific depressive symptoms and brain morphometry measures in neurodegenerative disorders. However, most of the studies examine either AD or PD independently, or in the stage of Mild Cognitive Impairment (MCI), or using a unique brain morphometric factor that cannot provide an accurate delineation of the morphological brain network. Further, most of the studies include quite a small sample size. In the current analysis, we used a fair sample of patients with MCI due to upcoming early AD or PD to examine the association between different depressive symptoms and a large variety of brain morphometric factors.

Methods :

Participants were patients of the Third Age Day-care Center IASIS (http://www.iasis-amke.gr/kentro-imeras.html), and all signed an informed consent prior to the evaluation. The diagnosis of the clinical as well as cognitive status of each participant was reached through diagnostic consensus meetings of all the researchers and main investigators, both neurologists and neuropsychologists, with the use of a score higher than 23 in the Mini Mental State Examination (MMSE) as a cutoff, based on existing optimal diagnostic cutoff points [13]. Thus, individuals with MCI stage based on AD or PD diagnosis were included in the study. The diagnosis of AD or PD was based on the well-established diagnostic criteria [14, 15]. In both groups, individuals had 11 mean years of education, and mean age of 75 years (see Table 1). All participants answered the Geriatric Depression Scale (GDS), regarding how they felt over the past week of the examination, which is a self-reported measures of depression in older adults, consisted of 30 questions [16]. We further created scores reflecting five subscale categories of depression, identified by Adams et al.: dysthymia, withdrawal apathy, anxiety, cognitive concern, and hopelessness[17]. All participants were also evaluated on the Addenbrooke's cognitive examination (ACE-R), a test which was designed for dementia screening[18]. No further psychiatric evaluation was performed.

All patients underwent a magnetic resonance imaging (MRI) exam within a period of two months from the time of assessment. A clinical brain MRI protocol was employed, which included a three-dimensional (3D), high spatial

resolution T1-weighted (3D HR-T1) gradient echo pulse sequence for the acquisition of detailed anatomical images. MRI scans were performed in three different diagnostic imaging centers equipped with 6 different MR scanners. Therefore, acquisition parameters varied depending on the MR scanner used. All imaging data were screened by an experienced neuroradiologist (P.T.) for the detection of abnormalities or pathologies and the presence of image artifacts (e.g., due to gross motion).Volumetric segmentation and cortical reconstruction were performed with the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu) (v.6.1)[19-21]. This was followed by parcellation of the cerebral cortex into units based on gyral and sulca structure, as described at the Destrieux cortical atlas[22]. One hundred forty-eight measures (74 from each hemisphere) and 41 regional volumes were generated. We used a PC (i7) Windows 11 for processing the images under NeuroDebian 8.0 cell and Oracle VirualBox 6.1.

Statistical analysis:

Quantitative variables are presented with mean and standard deviation (SD). Qualitative variables are presented with absolute and relative frequencies. For the comparison of proportions chi-square test was used. For the comparison of mean values between study Student's t-test was performed. Odds Ratio (95% Confidence Interval) adjusted for sex, age, years of education, ACE-R and estimated total intracranial volume (eTIV) were used to evaluate the difference of GDS scores between the two study groups. Principal component analysis (PCA) with Varimax rotation was performed in order to reduce variables associated with MRI volumes. The cut-off point for factor loadings was 0.40 and for eigenvalues it was 1.00. Cronbach's a was used to test internal consistency reliability of the factors. Partial correlation coefficients that are based on linear regression analysis were used to explore the association of GDS scores with MRI - - components as produced from factor analyses and after controlling for age, educational years, ACE-R and eTIV. All reported *p* values are two-tailed. Statistical significance was set at $p<0.05$ and analyses were conducted using SPSS statistical software (version 24.0).

Table 1. Demographic and clinical characteristics by study group

	AD (N=281; 69.9%)	PD (N=71; 17.7%)	P
Sex, N(%)			
Males	117 (41.6)	37 (52.1)	0.111+
Females	164 (58.4)	34 (47.9)	
Age (years), mean (SD)	75.6 (6.4)	75.0 (6.2)	0.444++
Years of education, mean (SD)	11.8 (5.8)	11.2 (4.6)	0.437++
MMSE, mean (SD)	26.0 (1.9)	26.5 (2.1)	0.038++
ACER, mean (SD)	72.9 (9.3)	75.8 (11.4)	0.030++
eTIV, mean (SD)	1468178.3 (166712.8)	1499159.6 (194204.4)	0.178++

+Pearson's chi square test; ++ Student's t-test

Table 2. GDS scores by study group

	AD	**PD**	**P+ PD vs AD**
	Mean (SD)	Mean (SD)	
GDS total	7.49 (6.22)	12.35 (6.94)	<0.001
Dysthymia	1.99 (2.14)	3.54 (2.58)	<0.001
Withdrawal apathy	1.59 (1.43)	2.99 (1.68)	<0.001

Anxiety	1.04 (1.20)	1.46 (1.14)	0.014
Cognitiveconcern	0.96 (1.00)	1.28 (1.03)	0.043
Hopelessness	0.64 (0.98)	1.31 (1.29)	<0.001

+Student's t-test

Table 3. Odds Ratio for the difference of GDS scores between study groups

	PD vs AD	
	OR (95% CI)	P
GDS total	1.12 (1.07 – 1.17)	<0.001
Dysthymia	1.34 (1.19 – 1.50)	<0.001
Withdrawal apathy	1.83 (1.52 – 2.21)	<0.001
Anxiety	1.35 (1.08 – 1.68)	0.008
Cognitive concern	1.35 (1.04 – 1.75)	0.023
Hopelessness	1.68 (1.33 – 2.13)	<0.001

*Odds Ratio (95% Confidence Interval) adjusted for sex, age, years of education, ACE-R and eTIV

Table 4. Factor loadings from Principal component analysis for MRI components of left hemisphere. Names of structures were derived from the study of Destrieux et al [22]

MRI components of left hemisphere		Factor					
Short Name	**Description**	**1**	**2**	**3**	**4**	**5**	**6**
LGV_G_and_S_frontomargin	Fronto-marginal gyrus and sulcus						
LGV_G_and_S_occipital_inf	Inferior occipital gyrus and sulcus						0.49
LGV_G_and_S_paracentral	Paracentral lobule and sulcus				0.59		
LGV_G_and_S_subcentral	Subcentral gyrus and sulci		0.44				
LGV_G_and_S_transv_ frontopol	Transverse frontopolar gyri and sulci					0.62	
LGV_G_and_S_cingul_Ant	Anterior part of the cingulate gyrus and sulcus	0.49					
LGV_G_and_S_cingul_Mid _Ant	Middle-anterior part of the cingulate gyrus and sulcus	0.49					
LGV_G_and_S_cingul_Mid _Post	Middle-posterior part of the cingulate gyrus and sulcus		0.6				
LGV_G_cingul_Post_dorsal	Posterior-dorsal part of the cingulate gyrus		0.61				
LGV_G_cingul_Post_ventral	Posterior-ventral part of the cingulate gyrus		0.52				
LGV_G_cuneus	Cuneus		0.56				
LGV_G_front_inf_Opercular	Opercular part of the inferior frontal gyrus	0.45					
LGV_G_front_inf_Orbital	Orbital part of the inferior frontal gyrus					0.44	
LGV_G_front_in_Triangul	Triangular part of the inferior frontal gyrus					0.55	
LGV_G_front_middle	Middle frontal gyrus				0.6		
LGV_G_front_sup	Superior frontal gyrus				0.59		
LGV_G_Ins_lg_and_S_ cent_ins	Long insular gyrus and central sulcus of the insula		0.62				
LGV_G_insular_short	Short insular gyri		0.58				
LGV_G_occipital_middle	Middle occipital gyrus						0.43
LGV_G_occipital_sup	Superior occipital gyrus						0.49
LGV_G_oc_temp_lat_fusifor	Lateral occipito-temporal gyrus		0.47				

LGV_G_oc_temp_med_Lingual	Ligual part of the medial occipito-temporal gyrus		0.61				
LGV_G_oc_temp_med_Parahip	Parahippocampal part of the medial occipito-temporal gyrus			0.52			
LGV_G_orbital	Orbital gyri	0.54					
LGV_G_pariet_inf_Angular	Angular gyrus				0.55		
LGV_G_pariet_inf_Supramar	Supramarginal gyrus				0.6		
LGV_G_parietal_sup	Superior parietal lobule				0.65		
LGV_G_postcentral	Postcentral gyrus				0.78		
LGV_G_precentral	Precentral gyrus				0.81		
LGV_G_precuneus	Precuneus		0.57				
LGV_G_rectus	Straight gyrus, Gyrus rectus	0.53					
LGV_G_subcallosal	Subcallosal area, subcallosal gyrus			0.55			
LGV_G_temp_sup_G_T_transv	Anterior transverse temporal gyrus	0.53					
LGV_G_temp_sup_Lateral	Lateral aspect of the superior temporal gyrus	0.48					
LGV_G_temp_sup_Plan_polar	Planum polare of the superior temporal gyrus			0.67			
LGV_G_temp_sup_Plan_tempo	Planum temporale of the superior temporal gyrus	0.45					
LGV_G_temporal_inf	Inferior temporal gyrus			0.54			
LGV_G_temporal_middle	Middle temporal gyrus	0.56					
LGV_Lat_Fis_ant_Horizont	Horizontal ramus of the anterior segment of the lateral sulcus	0.53					
LGV_Lat_Fis_ant_Vertical	Vertical ramus of the anterior segment of the lateral sulcus						
LGV_Lat_Fis_post	Posterior ramus of the lateral sulcus	0.74					
LGV_Pole_occipital	Occipital pole						0.66
LGV_Pole_temporal	Temporal pole						
LGV_S_calcarine	Calcarine sulcus		0.64				
LVG_S_central	Central sulcus		0.58				
LGV_S_cingul_Marginalis	Marginal branch of the cingulate sulcus	0.55					
LGV_S_circular_insula_ant	Anterior segment of the circular sulcus of the insula	0.57					
LGV_S_circular_insula_inf	Inferior segment of the circular sulcus of the insula	0.68					
LGV_S_circular_insula_sup	Superior segment of the circular sulcus of the insula	0.77					
LGV_S_collat_transv_ant	Anterior transverse collateral sulcus			0.56			
LGV_S_collat_transv_post	Posterior transverse collateral sulcus		0.47				
LGV_S_front_inf	Inferior frontal sulcus	0.56					
LGV_S_front_middle	Middle frontal sulcus	0.54					
LGV_S_front_sup	Superior frontal sulcus		0.41				
LGV_S_interm_prim_Jensen	Sulcus intermedius primus						
LGV_S_intrapariet_and_P_trans	Intraparietal sulcus and transverse parietal sulci	0.57					
LGV_S_oc_middle_and_Lunatus	Middle occipital sulcus and lunatus sulcus						0.4
LGV_S_oc_sup_and_transversal	Superior occipital sulcus and transverse occipital sulcus		0.5				
LGV_S_occipital_ant	Anterior occipital sulcus and						

	preoccipital notch						
LGV_S_oc_temp_lat	Lateral occipito-temporal sulcus			0.4			
LGV_S_oc_temp_med_and_ Lingual	Medial occipito-temporal sulcus and lingual sulcus			0.46			
LGV_S_orbital_lateral	Lateral orbital sulcus	0.56					
LGV_S_orbital_med_olfact	Medial orbital sulcus	0.73					
LGV_S_orbital_H_Shaped	Orbital sulci			0.55			
LGV_S_parieto_occipital	Parieto-occipital sulcus		0.58				
LGV_S_pericallosal	Pericallosal sulcus	0.59					
LGV_S_postcentral	Postcentral sulcus		0.47				
LGV_S_precentral_inf_part	Inferior part of the precentral sulcus	0.42					
LGV_S_precentral_sup_part	Superior part of the precentral sulcus		0.5				
LGV_S_suborbital	Suborbital sulcus		0.47				
LGV_S_subparietal	Subparietal sulcus	0.59					
LGV_S_temporal_inf	Inferior temporal sulcus			0.72			
LGV_S_temporal_sup	Superior temporal sulcus	0.43		0.56			
LGV_S_temporal_transverse	Transverse temporal sulcus						
% variance explained		15.12	12.19	8.67	7.99	4.06	3.57
Cronbach's a		0.91	0.92	0.78	0.84	0.6	0.7

Table 5. Factor loadings from Principal component analysis for MRI components of left hemisphere. Names of structures were derived from the study of Destrieux et al [22]

MRI components of right hemisphere		Factor					
Short Name	**Description**	**1**	**2**	**3**	**4**	**5**	**6**
RGV_G_and_S_frontomargin	Fronto-marginal gyrus and sulcus			0.44			
RGV_G_and_S_occipital_inf	Inferior occipital gyrus and sulcus		0.59				
RGV_G_and_S_paracentral	Paracentral lobule and sulcus			0.5			
RGV_G_and_S_subcentral	Subcentral gyrus and sulci				0.49		
RGV_G_and_S_transv_frontopol	Transverse frontopolar gyri and sulci				0.55		
RGV_G_and_S_cingul_Ant	Anterior part of the cingulate gyrus and sulcus				0.52		
RGV_G_and_S_cingul_Mid_Ant	Middle-anterior part of the cingulate gyrus and sulcus	0.53					
RGV_G_and_S_cingul_Mid_Post	Middle-posterior part of the cingulate gyrus and sulcus						0.58
RGV_G_cingul_Post_dorsal	Posterior-dorsal part of the cingulate gyrus		0.47				
RGV_G_cingul_Post_ventral	Posterior-ventral part of the cingulate gyrus		0.6				
RGV_G_cuneus	Cuneus		0.59				
RGV_G_front_inf_Opercular	Opercular part of the inferior frontal gyrus				0.52		
RGV_G_front_inf_Orbital	Orbital part of the inferior frontal gyrus				0.54		
RGV_G_front_in_Triangul	Triangular part of the inferior frontal gyrus	0.48					
RGV_G_front_middle	Middle frontal gyrus			0.58			
RGV_G_front_sup	Superior frontal gyrus			0.66			

RGV_G_Ins_lg_and_S_cent_ins	Long insular gyrus and central sulcus of the insula		*0.43*		0.52		
RGV_G_insular_short	Short insular gyri				0.49		
RGV_G_occipital_middle	Middle occipital gyrus		0.56				
RGV_G_occipital_sup	Superior occipital gyrus			0.45			
RGV_G_oc_temp_lat_fusifor	Lateral occipito-temporal gyrus		0.55				
RGV_G_oc_temp_med_Lingual	Ligual part of the medial occipito-temporal gyrus		0.61				
RGV_G_oc_temp_med_Parahip	Parahippocampal part of the medial occipito-temporal gyrus					0.62	
RGV_G_orbital	Orbital gyri				0.52		
RGV_G_pariet_inf_Angular	Angular gyrus			0.56			
RGV_G_pariet_inf_Supramar	Supramarginal gyrus			0.53			
RGV_G_parietal_sup	Superior parietal lobule			0.75			
RGV_G_postcentral	Postcentral gyrus			0.79			
RGV_G_precentral	Precentral gyrus			0.8			
RGV_G_precuneus	Precuneus	0.42					
RGV_G_rectus	Straight gyrus, Gyrus rectus				0.67		
RGV_G_subcallosal	Subcallosal area, subcallosal gyrus					0.41	
RGV_G_temp_sup_G_T_transv	Anterior transverse temporal gyrus	0.4					
RGV_G_temp_sup_Lateral	Lateral aspect of the superior temporal gyrus	0.44					
RGV_G_temp_sup_Plan_polar	Planum polare of the superior temporal gyrus					0.65	
RGV_G_temp_sup_Plan_tempo	Planum temporale of the superior temporal gyrus				0.51		
RGV_G_temporal_inf	Inferior temporal gyrus					0.69	
RGV_G_temporal_middle	Middle temporal gyrus	0.43					
RGV_Lat_Fis_ant_Horizont	Horizontal ramus of the anterior segment of the lateral sulcus	0.58					
RGV_Lat_Fis_ant_Vertical	Vertical ramus of the anterior segment of the lateral sulcus						
RGV_Lat_Fis_post	Posterior ramus of the lateral sulcus	0.67					
RGV_Pole_occipital	Occipital pole		0.59				
RGV_Pole_temporal	Temporal pole					0.52	
RGV_S_calcarine	Calcarine sulcus		0.61				
RGV_S_central	Central sulcus						0.44
RGV_S_cingul_Marginalis	Marginal branch of the cingulate sulcus	0.51					
RGV_S_circular_insula_ant	Anterior segment of the circular sulcus of the insula	0.59					
RGV_S_circular_insula_inf	Inferior segment of the circular sulcus of the insula	0.65					
RGV_S_circular_insula_sup	Superior segment of the circular sulcus of the insula	0.62					
RGV_S_collat_transv_ant	Anterior transverse collateral sulcus					0.64	
RGV_S_collat_transv_post	Posterior transverse collateral sulcus	0.47					

RGV_S_front_inf	Inferior frontal sulcus	0.47					
RGV_S_front_middle	Middle frontal sulcus						0.47
RGV_S_front_sup	Superior frontal sulcus						0.64
RGV_S_interm_prim_Jensen	Sulcus intermedius primus						
RGV_S_intrapariet_and_P_trans	Intraparietal sulcus and transverse parietal sulci		0.4				
RGV_S_oc_middle_and_Lunatus	Middle occipital sulcus and lunatus sulcus	0.42					
RGV_S_oc_sup_and_transversal	Superior occipital sulcus and transverse occipital sulcus	0.49					
RGV_S_occipital_ant	Anterior occipital sulcus and preoccipital notch						
RGV_S_oc_temp_lat	Lateral occipito-temporal sulcus					0.43	
RGV_S_oc_temp_med_and_Lingual	Medial occipito-temporal sulcus and lingual sulcus		0.43				
RGV_S_orbital_lateral	Lateral orbital sulcus						
RGV_S_orbital_med_olfact	Medial orbital sulcus	0.58					
RGV_S_orbital_H_Shaped	Orbital sulci					0.48	
RGV_S_parieto_occipital	Parieto-occipital sulcus		0.46				
RGV_S_pericallosal	Pericallosal sulcus	0.68					
RGV_S_postcentral	Postcentral sulcus		0.47				
RGV_S_precentral_inf_part	Inferior part of the precentral sulcus	0.42					
RGV_S_precentral_sup_part	Superior part of the precentral sulcus						0.55
RGV_S_suborbital	Suborbital sulcus						
RGV_S_subparietal	Subparietal sulcus	0.4					
RGV_S_temporal_inf	Inferior temporal sulcus					0.7	
RGV_S_temporal_sup	Superior temporal sulcus	0.52					
RGV_S_temporal_transverse	Transverse temporal sulcus	0.47					
% variance explained		11.45	9.4	8.93	8.08	7.39	6.28
Cronbach's a		0.87	0.88	0.83	0.84	0.78	0.8

Results:

Our sample consisted of 352 subjects, with a mean age of 74.3 years old (SD=7.4). Demographic and clinical characteristics by study group are shown in Table 1. PD group exhibited significantly higher score in MMSE (p=0.038) and ACE-R (p=0.03) compared to AD group.

GDS scores by study group and comparison with normal subjects are shown in Table 2. After adjustment for sex, age, years of education, ACE-R and eTIV, all GDS dimensions appeared to be significantly higher in PD cases compared to AD patients (p<0.05). PD cases were associated with higher odds of being depressed or exhibiting subscale symptoms of depression compared to AD cases, in the fully adjusted model (see Table 3).

PCA -generated 6 factors for the right and left hemispheres that explained 51.6% and 51.53% of the total variance, respectively -. MRI components with loadings exceeding 0.4 are provided in Table 4 and Table 5. Among all MRI components of both right and left hemispheres, segments of the circular sulcus of the insula (LGV_S_circular_insula anterior, inferior and superior) as well as the area of Posterior ramus of the lateral sulcus (LGV_Lat_Fis_post) had the highest factor loadings (0.57-0.77), suggesting that differences in these brain regions exert thelargest effect on GDS scores (Table 5,6). Regarding brain volumes, 5 factors were identified from PCA that explained 74% of the variance (see Table 6). Cronbach's alpha for all

factors was higher than 0.7, indicating an acceptable level of reliability.

Next, we tested correlations between the MRIs factors for the left and right hemisphere, generated by PCA, with GDS total and sub-scale scores (dysthymia, withdrawal apathy, anxiety, cognitive concern, and hopelessness). Multiple significant correlations were observed between factors and GDS scores even - after adjustment for sex, age, years of education, ACE-R and eTIV. Results are presented in Tables 7 to 9. Specifically, the third factor (l_factor3) of left hemisphere was positively associated with GDS total scores (p=0.004), Dysthymia (p=0.014), Anxiety (p<0.001), and Hopelessness (p=0.015) (see Table 7). When we examined the right hemisphere, we observed a positive correlation between anxiety symptoms and, the first - (p=0.013), -second (p=0.045), and - fifth factor (p=0.006) (see Table 8). Moreover, the fifth factor (r factor5) of the right hemisphere was marginally associated with GDS total scores (p=0.05).

Further, we investigated the association between total and subscale GDS scores with factors of MRI volumes. The analysis revealed a positive association of the second factor (v factor2) and GDS total score (p=0.023), Dysthymia (p=0.022), Anxiety (p=0.005), and Hopelessness (p=0.004) (see Table 9) Moreover, the third factor (v factor3) of MRI volumes was marginally and positevely associated with Anxiety score (p=0.049).

Table 6. Factor loadings from Principal component analysis for MRI volumes

	Factor				
	1	**2**	**3**	**4**	**5**
VOL_Left_Cerebellum_Cortex					**0.91**
VOL_Left_Thalamus_Proper			**0.82**		
VOL_Left_Caudate				**0.85**	
VOL_Left_Putamen				**0.63**	
VOL_Left_Pallidum	**0.57**				
VOL_Brain_Stem					**0.64**
VOL_Left_Hippocampus		**0.72**			
VOL_Left_Amygdala		**0.73**			
VOL_Left_Accumbens_area		**0.64**			
VOL_Left_VentralDC			**0.54**		
VOL_Right_Cerebellum_F49Cortex					**0.91**
VOL_Right_Thalamus_Proper			**0.73**		
VOL_Right_Caudate				**0.86**	
VOL_Right_Putamen				**0.62**	
VOL_Right_Pallidum	**0.66**				
VOL_Right_Hippocampus		**0.77**			
VOL_Right_Amygdala		**0.79**			
VOL_Right_Accumbens_area		**0.68**			
VOL_Right_VentralDC			**0.44**		
VOL_CC_Posterior	**0.76**				
VOL_CC_Mid_Posterior	**0.89**				
VOL_CC_Central	**0.85**				
VOL_CC_Mid_Anterior	**0.82**				
VOL_CC_Anterior	**0.78**				
Variance explained (%)	20.0	17.6	12.6	12.2	11.5
Cronbach's a	0.88	0.81	0.87	0.84	0.87

Table 7.Partial correlation coefficients of GDS scores with MRI components of left hemisphere after adjusting for sex, age, years of education,disease, ACE-R and eTIV

Left		GDS total	Dysthymia	Withdrawal apathy	Anxiety	Cognitive concern	Hopelessness
l_factor1	r	0.04	0.04	-0.06	0.09	0.02	0.03
	P	0.496	0.516	0.300	0.084	0.648	0.611

l_factor2	r	0.01	-0.01	-0.05	0.09	-0.03	0.02
	P	0.910	0.820	0.314	0.083	0.523	0.753
l_factor3	r	0.15	0.13	0.06	0.22	0.01	0.13
	P	**0.004**	**0.014**	0.305	**<0.001**	0.823	**0.015**
l_factor4	r	-0.03	-0.03	0.00	0.02	-0.05	0.02
	P	0.541	0.539	0.985	0.669	0.325	0.752
l_factor5	r	0.04	0.04	0.07	0.03	-0.01	0.10
	P	0.494	0.505	0.195	0.530	0.852	0.075
l_factor6	r	0.02	0.02	-0.03	0.07	0.06	0.04
	P	0.716	0.664	0.553	0.195	0.280	0.455

Table 8.Partial correlation coefficients of GDS scores with MRI components of right hemisphere after adjusting for sex, age, years of education, disease, ACE-R and eTIV (continued)

Right		GDS total	Dysthymia	Withdrawal apathy	Anxiety	Cognitive concern	Hopelessness
r_factor1	r	0.06	0.05	-0.02	0.13	0.03	0.02
	P	0.280	0.322	0.740	**0.013**	0.585	0.755
r_factor2	r	0.03	0.03	-0.04	0.11	0.00	0.04
	P	0.541	0.547	0.413	**0.045**	0.928	0.410
r_factor3	r	-0.02	-0.03	0.02	0.01	-0.04	0.03
	P	0.681	0.636	0.710	0.886	0.492	0.577
r_factor4	r	-0.01	-0.02	-0.03	0.06	-0.04	0.04
	P	0.861	0.688	0.541	0.272	0.510	0.473
r_factor5	r	0.11	0.10	0.04	0.15	-0.02	0.09
	P	**0.050**	0.071	0.516	**0.006**	0.718	0.100
r_factor6	r	-0.07	-0.10	-0.08	0.01	0.00	-0.06
	P	0.192	0.064	0.133	0.784	0.947	0.255

Table 9.Partial correlation coefficients of GDS scores with MRI components after adjusting for sex, age, years of education, disease, ACE-R and eTIV (continued)

Volume		GDS total	Dysthymia	Withdrawal apathy	Anxiety	Cognitive concern	Hopelessness
v_factor1	r	0.04	0.01	0.06	0.08	-0.04	0.08
	P	0.428	0.906	0.301	0.130	0.455	0.118
v_factor2	r	0.12	0.12	0.05	0.15	0.03	0.15
	P	**0.023**	**0.022**	0.313	**0.005**	0.627	**0.004**
v_factor3	r	0.07	0.08	-0.02	0.11	0.02	0.05
	P	0.179	0.136	0.695	**0.049**	0.673	0.331
v_factor4	r	0.04	0.01	0.00	0.02	0.01	0.05
	P	0.462	0.887	0.972	0.665	0.807	0.330
v_factor5	r	0.05	0.03	0.03	0.09	0.07	-0.04
	P	0.406	0.520	0.571	0.099	0.189	0.485

Discussion:

In the present study, we integrated information from multiple domains of MRI data to examine if -depressive symptoms - among MCI patients were associated with brain morphometry patterns. Regarding depressive symptoms, dysthymia, anxiety, and hopelessness were associated with features of left-brain morphometry, while, anxiety, apart from the association with the left hemisphere, was further associated with features of right brain morphometry, irrespectively of demographic and clinical factors. The current study provides evidence for the context-dependent association of morphometric brain structures with depressive symptoms that are prevalent in MCI patients.

To analyze the large MRI data and to. uncover associations between specific brain regions with

depressive symptoms, we leveraged the method of PCA [23]. PCA allowed us to reduce the multidimensional and interrelated MRI data into uncorrelated variables, named as factors or principal components, that explain the maximum variance of depression symptoms. Each factor is comprised of different and uncorrelated MRI components. The factor loading of each MRI component reflects the correlation coefficient with the given factor, with items having the highest factor loading values to be associated stronger with the factor. Thus, this method allowed us to reduce the dimension of MRI data and identify which brain features are the most discriminating for depressive symptoms among MCI patients. Our findings suggest that differences in the brain regions of the circular sulcus of the insula and the area of posterior ramus of the lateral sulcus, of both hemispheres, explain most of the variability observed in GDS scores of MCI patients. Patients with major depression disorder (MDD) have been found to exhibit abnormal activity and connectivity of insula primary regions suggesting that this distinct brain area may play an important role in the pathogenesis of depression [24]. Thus, our findings are in line with those of previous research, supporting that insula area is affected in patients with depression symptoms. To our knowledge, no other studies until now have associated lateral sulcus regions with depression but given the anatomical adjacency of the two regions; i.e. insula is located deep inside the lateral sulcus [25], one could hypothesize that the functional network of this area is also altered.

Based on our findings, anxiety seems to be the only psychiatric symptom being associated with both left and right hemisphere. A wealth of neuroimaging studies have been conducted so far to determine structural and functional brain characteristics for anxiety disorders [26]. For instance, a study conducted in children with generalized anxiety disorder reported a higher ratio of gray matter to white matter in the upper temporal lobe of this cohort compared to control [27]; while different effects of distinct brain regions and lateralization in different anxiety disorders are mentioned on a different investigation [26]. Such results suggest that anxiety disorders are caused to a certain extent by differential activity in certain prefrontal cortex areas, paving the way to the inclusion of neuroimaging techniques in the diagnostic process of anxiety disorders [26]. In the field of neurodegenerative disorders, anxiety has been associated with depression, irritability, aggression, and mania among AD patients, and these aspects have been linked to frontal and prefrontal brain regions of both hemispheres [28]. In the current study anxiety was associated with regions of both sides of the brain in accordance with existing literature, indicating the prevailing role of anxiety in neurodegenerative disorders.

There is a high prevalence of dysthymia and major depression among patients with AD [29]. Although some studies suggest that dysthymia might be an emotional reaction to the progressive cognitive decline, and depression might be highly associated with biological factors [29-32], our results provide evidence that these symptoms can be reflected in brain regions differences among patients with neurodegenerative disorders. This is extremely prominent considering that early detection of depression onset in these patients can facilitate the prompt application of a treatment plan that may delay disease progression. Furthermore, our results are in accordance to previous reports and significantly contribute to a better understanding of psychopathology and the interaction between depressive symptoms and neurodegenerative disorders as illustrated by neuroimaging data [33].

The present study is the first to our knowledge which examines a large number of brain measurements in association with both global GDS and specific neuro-depressive symptoms in the MCI stage due to both AD and PD cases. On the other hand, the fact that the depressive symptoms 'evaluation was based on the GDS questionnaire as the only instrument is the main limitation of the study.

Depressive symptoms are not just associated with upcoming neurodegenerative disorders; there is now a link with specific brain measurements in MCI due to AD and PD diseases. It remains to be seen if the observed brain alterations are a consequence or a cause of neurodegeneration. Future longitudinal analyses should shed more light on the directionality of the results. Nevertheless, the current study significantly contributes to the field of the clinical application of neuroimaging in the diagnosis of psychiatric disorders that impact MCI patients. Such results could help on the patients 'treatment; probably

aiding on further relief of the multiple symptoms of these neurodegenerative disorders.

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