RESEARCH ARTICLE

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Factors associated with brain volume in major depression in older adults without dementia: results from a large autopsy study

Paula Villela Nunes[1], Claudia Kimie Suemoto[1], Renata Elaine Paraizo Leite[1], Renata Eloah de Lucena Ferretti-Rebustini[1], Carlos Augusto Pasqualucci[1], Ricardo Nitrini[1], Jose Marcelo Farfel[1], Katia Cristina de Oliveira[1], Lea Tenenholz Grinberg[1,2], Nicole Rezende da Costa[3], Camila Fernandes Nascimento[1], Faraz Salmasi[4], Helena Kyunghee Kim[4], Lionel Trevor Young[4], Wilson Jacob-Filho[1] and Beny Lafer[1]

[1]University of São Paulo Medical School, Sao Paulo, Brazil
[2]Memory and Aging Center University of California, San Francisco, CA, USA
[3]Faculdade de Medicina de Jundiai, Jundiai, Brazil
[4]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada
Correspondence to: P. V. Nunes, University of São Paulo Medical School, Sao Paulo, Brazil. E-mail: paula@formato.com.br

Objective: We examined brain volume and atrophy in individuals with major depressive disorder (MDD) without dementia that were referred to a large autopsy service. We also examined potential risk factors for brain atrophy, including demographics and clinical variables.

Methods: In this study, 1373 participants (787 male) aged 50 years or older who died from natural causes were included. Participants with no reliable informant, with cognitive impairment or dementia, with a medical history of severe chronic disease, or with prolonged agonal state were excluded. Presence of MDD at least once in their lifetime was defined according to the Structured Clinical Interview for DSM. Brain volume was measured immediately after removal from the skull.

Results: Mean age at death was 68.6 ± 11.6, and MDD was present in 185 (14%) individuals. Smaller brain volume was associated with older age ($p < 0.001$), lower education (years; $p < 0.001$), hypertension ($p = 0.001$), diabetes ($p = 0.006$), and female gender ($p < 0.001$). In the multivariate analysis adjusted for sociodemographics and cardiovascular risk factors, smaller brain volume was not associated with major depression ($\beta = -0.86$, 95% CI $= -26.50$ to 24.77, $p = 0.95$).

Conclusions: In this large autopsy study of older adults, MDD was not associated with smaller brain volumes. Regardless of the presence of MDD, in this sample of older adults without dementia, we found that smaller brain volumes were associated with risk factors for brain neurodegeneration such as older age, diabetes, hypertension, and lower education. Copyright © 2017 John Wiley & Sons, Ltd.

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Introduction

Despite intensive research aimed at identifying neurobiological substrates of depression in the last decade, our understanding of the pathophysiological mechanisms underlying depression remains limited (Schmaal *et al.*, 2015). With a lifetime prevalence of mood disorders ranging from 7% (Moussavi *et al.*, 2007) to as high as 20% worldwide (Kessler *et al.*, 2007) and treatment resistance contributing significantly to the burden of disease, there is substantial need for a better understanding of the underlying pathophysiology as well as a better characterization of the structural and functional neural correlates of depressive symptoms (Sacher *et al.*, 2012). Trauma, stress, psychological, and social factors undoubtedly play a role in the

etiology of depression. Furthermore, neuroimaging, neuropathological, and familial studies also point to a role played by structural biological factors (Bora *et al.*, 2012). However, we still lack information concerning the extent to which structural and functional changes co-occur in the brain of a depressed subject, especially in specific populations such as older adults.

Several neurobiological models have been proposed to account for mood disorders' pathogenesis. While some consistent findings have been reported, individual studies have also varied with respect to the primary brain regions affected by the illness and how these abnormalities are related to patients' clinical characteristics (Bora *et al.*, 2012; Arnone *et al.*, 2012). Despite the growing number of studies in this field, the relationship between structural changes in human brains and depression in older adults is still controversial (Jellinger, 2013). Initial structural reviews and meta-analyses pointed to a global atrophy being present in major depressive disorder (MDD) (Elkis *et al.*, 1995; Grieve *et al.*, 2013). Widely available structural magnetic resonance imaging has led to hypotheses of paralimbic circuits being involved in mood disorders, but still, the exact pattern of structural brain alterations associated with mood disorders remains unsolved, perhaps because of small sample sizes resulting in limited statistical power, disease heterogeneity, and the complex interactions between clinical characteristics, treatments, and brain morphology (Schmaal *et al.*, 2015; Bora *et al.*, 2012; Arnone *et al.*, 2012). Moreover, biological variables such as age (Miller and Corsellis, 1977) and dementia might influence the results. For example, older age can be associated with an increasing excess of white matter lesions in MDD (Arnone *et al.*, 2012). Therefore, morphological changes observed in depression seem to be regional rather than global (Schmaal *et al.*, 2015; Arnone *et al.*, 2012; Koolschijn *et al.*, 2009; Lorenzetti *et al.*, 2009), but the presence of a more global atrophy remains a possibility to some authors (Elkis *et al.*, 1995; Grieve *et al.*, 2013).

Interestingly, depression is also commonly found in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Huntington's disease, leading to the speculation that depression may be closely related to neurodegeneration, and may share similar neuropathological mechanisms (Burgut *et al.*, 2006). Molecular and cellular alterations, such as increased apoptosis, lower levels of neurotrophic factors, and lower number of neurons and glial cells, were observed in patients with major depression in postmortem studies (Kim *et al.*, 2016). Yet, the published findings are not consistent and are often complicated by comorbid conditions. Furthermore, there has been limited success in demonstrating a clear causal relationship between many of the reported pathological alterations in older adults with MDD (Jellinger, 2013).

There is a small number of postmortem studies or structural studies that examined brain volume in older adults with MDD (Schmaal *et al.*, 2015). Moreover, many studies do not make corrections for previous brain size and were made in small groups of patients. Therefore, the purpose of this study was to investigate volume in a large population of older adults with a history of MDD and without dementia. As an additional exploratory analysis, we examined potential risk factors for smaller brain volume among these participants.

Methods

A cross-sectional study was conducted in deceased subjects submitted to autopsy at the Sao Paulo Autopsy Service (SPAS) between 2004 and 2014. In Brazil, autopsy is mandatory for all individuals whose cause of death was not identified before death. SPAS is a community-based general autopsy service responsible for issuing death certificates in such cases within the city of Sao Paulo, Brazil, which has a population of 12 million residents. The SPAS performs around 13,000 autopsies per year.

Participants

Subjects were members of the Brain Bank of the Brazilian Aging Brain Study Group (BBBABSG). The local ethics committee approved the research protocol. Methodological procedures of the BBBABSG have been described elsewhere (Grinberg *et al.*, 2013; Suemoto *et al.*, 2013; Ferretti-Rebustini *et al.*, 2015).

Subjects with major cerebral lesions, including stroke and cerebral tumors, were excluded from the BBBABSG cohort because immediate brain examination is required to confirm the cause of death. Nurses with expertise in gerontology invited a knowledgeable informant to participate in the study. A knowledgeable informant was a close family member or caregiver that had at least one weekly contact with the deceased in the last 6 months prior to death and was able to recount and provide details of the deceased's health information. Subjects were included after the study procedures had been explained to the family members, and they had agreed to participate by signing an informed consent form. Inclusion criteria were as

follows: subjects 50 years and older and natural cause of death (non-traumatic). Cases with no reliable informant, medical history of advanced chronic disease, or prolonged agonal state were excluded. This study used information collected from 2004 to 2014 about 1632 individuals with complete clinical and morphometric records.

Clinical postmortem evaluation

Clinical evaluation consisted of assessment of the deceased's clinical and functional status in the 3 months prior to death. Information was obtained from the knowledgeable informant. A validated semi-structured clinical interview (Ferretti *et al.*, 2010) assessed demographics (age, gender, and formal educational attainment named schooling), conditions related to death, medical history (clinical and surgical), treatments, smoking habits, alcohol consumption, physical activity, functional status, neuropsychiatric symptoms, and cognitive performance. Neuropsychiatric symptoms and cognitive performance in the 3 months prior to death were further accessed with the Neuropsychiatric Inventory (Cummings *et al.*, 1994), the Informant Questionnaire on Cognitive Decline in the Elderly (Jorm, 1994), and the informant part of the Clinical Dementia Rating (CDR) scale (Morris, 1993) validated for postmortem use (Ferretti *et al.*, 2010). Clinical medical history was assessed in detail during the interview with the informant, including history of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, heart failure, and stroke, among other clinical data. During clinical evaluation, the interviewer continuously checked for data consistency and exclusion criteria, in order to detect any conditions that might lead to the exclusion of the case at hand. Cases with cognitive impairment and dementia (CDR $>$ 0) were later excluded for the purposes of the present study.

Depressive symptom evaluation

The presence of depressive symptoms was defined by occurrence of an episode of MDD during life, assessed by the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) (Spitzer *et al.*, 1995), according to information provided by the informant. The SCID is based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Depression was diagnosed when, in the most pronounced episode in life, at least one of these two main depressive symptoms was present: depressed mood and markedly decreased interest or pleasure in activities, along with at least four of the following symptoms for at least 2 weeks: alterations in weight, sleep, psychomotor activity, decreased energy, concentration and reasoning problems, feelings of worthlessness or guilt, and recurrent thoughts of death or suicide. Participants in the control group did not have any of the two core depressive symptoms.

Morphometric measurements

Brain volume (milliliter) was obtained calculating the volume of displaced liquid when immersing the brain in water, according to Archimedes' Principle, which is considered a reliable procedure for measuring volume of body regions (Tie *et al.*, 2012).

Statistical analysis

Participants were divided into two groups according to the presence or absence of MDD in life assessed by the SCID. To compare participants with and without MDD, we used chi-square tests for categorical variables and unpaired *t*-test for quantitative variables. Simple linear regression models were used to determine the association of brain volume with sociodemographics and clinical variables.

Multivariate linear regression was adjusted initially for age, gender, and education, and then further adjusted for hypertension, diabetes, stroke, physical inactivity, smoking, and alcohol use.

The level of significance was set at 0.05 in two-tailed tests. The software STATA 12.0 (College Station, TX: StataCorp LP) was used to perform the statistical analyses.

Results

From 2004 to 2014, we collected data from 1632 individuals; 259 participants who had cognitive impairment or dementia (CDR $>$ 0) were excluded. The final sample consisted of 1373 individuals. Mean age was 68.6 ($\pm$11.7) years; 45% were female and had 4.9 ($\pm$3.9) years of formal education. Informant Questionnaire on Cognitive Decline in the Elderly score was 3.01 ($\pm$0.04); mean brain volume was 1181 ($\pm$161) mL. MDD during life was present in 185 (14%) individuals, and 21 of those (11% of cases with MDD) had recurrent depression. Depressive symptoms in the 3 months prior to death assessed through the Neuropsychiatric Inventory were present in 17% of individuals. Among clinical variables,

hypertension was present in 66% of the sample, diabetes in 31%, physical inactivity in 53%, and current smoking in 33%.

When comparing individuals with MDD and without MDD, age, education, hypertension, diabetes, stroke, physical inactivity, and current alcohol use were similar between groups. In the MDD group, there were more women ($p < 0.001$) and current smokers ($p = 0.01$) as seen in Table 1.

To investigate the correlation between MDD and brain volume, we first tested factors related to smaller brain volume in the entire sample as seen in Table 2. All demographic and clinical risk factors, except physical inactivity, were related to brain volume. When correcting for the gender differences in the sample, differences in volume for current smokers and drinkers disappear.

In the multivariate analysis adjusted for sociodemographics and cardiovascular risk factors, smaller brain volume was not associated with MDD ($\beta = -0.86$, 95% CI = −26.50 to 24.77, $p = 0.95$) (Table 3).

As for the remaining sample, we also did not find smaller brain volumes in the cases with recurrent MDD ($n = 21$), positive answers in the SCID for previous suicidal ideation ($n = 88$), functional change ($n = 108$), cognitive complaints ($n = 86$), feelings of guilt ($n = 106$), energy loss ($n = 135$), psychomotor change ($n = 148$), sleep change ($n = 155$), weight change ($n = 169$), loss of interest ($n = 188$), or depressive mood ($n = 199$).

Table 2 Correlation of cerebral brain volume with demographic and clinical variables ($n = 1373$)

	β (95% CI)	*p*
Age (years)	−0.395 (−4.655 to −3.248)	<0.0001
Education (years)	6.654 (4.465 to 8.844)	<0.0001
Male	98.89 (82.49 to 115.29)	<0.0001
Hypertension	−30.05 (−48.14 to −11.96)	0.001
Diabetes	−25.97 (−44.58 to −7.36)	0.006
Stroke	−36.10 (−63.75 to −8.44)	0.01
Physical inactivity	−8.40 (−30.56 to 13.75)	0.46
Current smoking	25.23 (2.53 to 47.94)	0.03
Current alcohol use	26.29 (−0.33 to 52.91)	0.05

Simple linear regression.

Table 3 Association between cerebral volume and depression ($n = 1373$)

	β	95% CI	*p*
Crude	4.89	−20.02 to 29.79	0.70
Model 1[a]	15.98	−7.05 to 39.01	0.17
Model 2[b]	−0.86	−26.50 to 24.77	0.95

Reference: group without depression.
[a]adjusted for age, sex, education.
[b]adjusted for age, sex, education, hypertension, diabetes, stroke, physical inactivity, smoking, and alcohol use.

Discussion

Findings from our study, which is a large autopsy study with direct measures of brain volume, suggest that MDD is not associated with smaller brain volumes. These results are in accordance with previous studies demonstrating that morphological changes, if present in depression, are regional rather than global in adult patients (Schmaal *et al.*, 2015; Arnone *et al.*, 2012; Koolschijn *et al.*, 2009; Lorenzetti *et al.*, 2009; Kempton *et al.*, 2011), or in late life depression (Du *et al.*, 2014; Boccia *et al.*, 2015). Global volumetric brain measures used in the literature include intracranial volumes, total cerebral volume, whole brain, and whole brain gray/white matter. One

Table 1 Study population characteristics according to the presence of major depression ($n = 1373$)

	No major depression	Major depression	
	($n = 1188$)	($n = 185$)	*p*
Brain volume (mL), mean (SD)[a]	1181 (161)	1186 (157)	0.70
Age (years), mean (SD)[a]	68.8 (11.7)	68.6 (11.2)	0.80
Male, *n* (%)[b]	703 (59.3)	84 (45.4)	<0.001
Education (years), mean (SD)[a]	4.9 (3.9)	4.8 (3.7)	0.88
Hypertension, *n* (%)[b]	768 (66.3)	117 (64.3)	0.60
Diabetes, *n* (%)[b]	365 (31.5)	46 (25.3)	0.09
Stroke, *n* (%)[b]	122 (10.5)	23 (12.7)	0.38
Physical inactivity, *n* (%)[b]	356 (52.4)	98 (57.3)	0.25
Current smoking, *n* (%)[b]	222 (31.4)	75 (41.2)	0.01
Current alcohol use, *n* (%)[b]	143 (20.2)	38 (21.0)	0.81

[a]Multivariate analysis adjusted for age, sex, education.
[b]Multivariate analysis adjusted for age, sex, education, hypertension, diabetes, stroke, 83 physical inactivity, smoking, and alcohol use.

should also be attentive to publication bias against nonsignificant results. Therefore, in brain scans of patients with MDD, we did not expect to see general brain atrophy, which is usually the case in clinical practice. It is interesting to note that it has been reported that even treatment resistant depression is not associated with global brain atrophy (Maller *et al.*, 2012). Findings from the present study suggest that age itself may not be an aggravating factor for brain damage caused by MDD.

Regardless of the presence of MDD, we found that older age was associated with smaller brain volumes even in this sample of patients without dementia. This might be due to incipient neurodegenerative pathology that can result from the adding effects of conditions such as hypertension or diabetes mellitus and also neuronal loss associated to age (Oliveira-Pinto *et al.*, 2016). Indeed, even neurologically asymptomatic older people prospectively followed for 6 years show brain volume reduction with time, and moreover, the older the age, the greater the volume decline that can be observed (Enzinger *et al.*, 2005). But one should also consider that there is evidence to support that there has been an increase in height and head size of the world population in the last decade (Ferretti-Rebustini *et al.*, 2015) as well as in brain volume (Miller and Corsellis, 1977). In our study, we also found greater brain volume in males. We can speculate many reasons for that, such as selective mortality (Luy and Gast, 2014), differences in brain size, cognitive reserve, among others. In previous structural studies, interesting gender differences were found in brain aging (Coffey *et al.*, 1998; Oliveira-Pinto *et al.*, 2016). Factors influencing the asymmetric effect that gender has on brain development may help us understand how and why male and female brains differ in their predisposition or resilience to such conditions (Ruigrok *et al.*, 2014). In structural studies of estimation of intracranial volume, differences can also be found when comparing genders (Hshieh *et al.*, 2016). Because these studies have only been published recently, we should wait for more studies examining different populations to be published in order to better interpret these results.

Other risk factors for neurodegenerative disorders such as hypertension, diabetes, smoking, and alcohol use as well as lower education (Beydoun *et al.*, 2014; Cooper *et al.*, 2015) were also associated with atrophy in our sample. This is in accordance with a 6-year prospective study of brain volume of neurologically asymptomatic older people that found a higher rate of brain atrophy in those with higher glycated hemoglobin and higher alcohol intake (Enzinger *et al.*, 2005). The importance of diabetes mellitus types 1 and type 2 for macrovascular and microvascular complications and brain atrophy was robustly confirmed by a meta-analysis (Moulton *et al.*, 2015) with similar results for hypertension (Beauchet *et al.*, 2013). The correlation of lower education with smaller brain volume might involve diverse pathological processes. It is well known that a percentage of undernourished babies and children might have smaller brains when they become adults (Spurr *et al.*, 1983; Ivanovic *et al.*, 2004). This may be associated with poverty, health problems, and precarious access to education, among other explanations. On the other hand, smaller brains in some conditions can also be correlated to neurodevelopmental problems as well as to lessened intelligence in some tests (Ivanovic *et al.*, 2004; Witelson *et al.*, 2006); therefore, people under these conditions can have difficulty in completing their education. Previous clinical–pathological studies suggest that although education is not directly correlated with the development of neuropathological lesions, it seems to reduce the impact of such lesions on the development of dementia, thereby increasing cognitive reserve. Interestingly, even a few years of formal education contributes to cognitive reserve, decreasing the likelihood of developing cognitive impairment (Farfel *et al.*, 2013).

The influence of drug treatment on brain volume should also be taken into consideration. There are reports of the use of antidepressants being associated to normalization of hippocampal volume (Kempton *et al.*, 2011). One possible explanation is the promotion of neurogenesis, as antidepressants can increase levels of brain-derived neurotrophic factor (Shimizu *et al.*, 2003). Unfortunately, for many of our cases, complete information on current and previous treatments for depression and on the exact number of episodes and duration of each episode was not available. While our study did not find smaller brain volumes in older patients with MDD, it is still important to explore regional morphological alterations in the brains of this patient group, which can be either very small or limited to some regions (Schmaal *et al.*, 2015).

The prevalence of MDD during life (14%) or depressive symptoms in the 3 months prior to death (17%) in our sample of older adults is in accordance with other Brazilian epidemiologic studies (Viana and Andrade, 2012) and with the literature, in addition to our finding of a greater percentage of women and smokers in the group with depression (Kessler *et al.*, 2003). Strengths of our study include a large sample size and a diverse population in terms of ethnicity and educational background. The BBBABSG is linked to a general autopsy service in

the city of Sao Paulo and has access to a large and unique sample of brains. Differently from other collections, most participants from the BBBABSG had normal cognition during life (Grinberg *et al.*, 2007). While in recent years, we have enjoyed advancements in temporal, spatial, and neurochemical resolution of *in vivo* neuroimaging techniques (Lewis, 2002); here we evaluated the brain itself without sources of bias that can be present in structural studies with magnetic resonance imaging, especially those that use less time-consuming automated methods. The direct study of the postmortem human brain provides several essential elements in the study of psychiatric disorders at the level of populations of neurons and the specific neural circuits that they form (Lewis, 2002). The diagnosis of depression was based on the DSM-IV criteria verified through the application of a structured interview with a close informant of the deceased. Our study also has several limitations. We only evaluated the whole brain and not specific areas. Samples were often heterogeneous in terms of clinical variables, although our analysis was adjusted for these variables. Our study is a subsample selected from individuals that were referred for autopsy because we did not collect cases 24 h a day, 7 days a week. In addition, the cross-sectional and observational nature of the study does not permit confirmation of exact causal relations. A longitudinal clinical and neuroimaging study would further increase our knowledge of the influence of various types of depression on brain volume. In addition, the use of informant-reported data is a concern, as informants can be unaware of some treatments and disorders of the deceased and we did not get reliable information on the duration of MDD in this sample. The CDR used in this study is a screening tool for assessing cognitive function, so it presents substantial restrictions when cognitive function is assessed clinically. Similar limitations can be applicable to the SCID used for the diagnosis of major depression.

Future research would benefit from careful and inclusive reporting of clinical variables such as medication use and substance abuse, as well as the exact age of depression onset (Almeida *et al.*, 2016). However, it should be noted that there are studies involving adult patients in their first depressive episode without medication that found no global volumetric brain changes (Han *et al.*, 2014). The use of longitudinal designs to clarify the contribution of illness or its treatment on brain regions may also bring important contributions. This type of analysis is more time consuming and costly and could be included in future studies of our group. However, even in patients with treatment-resistant MDD, no differences were found in cranial and brain volumes and in the mean intracranial volume (Maller *et al.*, 2012).

Conclusion

The main finding of our study, in which we directly measured brain volume in a large population of older adults without dementia, is that depression is not associated with smaller brain volumes. Regardless of the presence of MDD, in this sample, we found that smaller brain volumes were associated with risk factors for brain neurodegeneration such as older age, diabetes, hypertension, and lower education. This study can be complemented by a prospective evaluation of the effects of depression using *in vivo* brain imaging techniques.

Conflict of interest

None declared.

Key points

- Major depressive disorder in older adults was not associated with smaller brain volume even when correcting for confounding factors.
- Smaller brain volume, regardless of the presence of depression, was associated with older age, hypertension, and diabetes.

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