British Journal of Medicine & Medical Research
14(4): 1-10, 2016, Article no.BJMMR.24034
ISSN: 2231-0614, NLM ID: 101570965

SCIENCEDOMAIN *international*
www.sciencedomain.org

Structural Correlates of Depressive Symptoms in Prodromal Alzheimer's Disease

Javier Olazarán[1,2*], Pablo García-Polo[1], Daniel García-Frank[1], Alicia Quirós[1], Juan Antonio Hernández-Tamames[1], Carmen Acedo[3], Juan Álvarez-Linera[1] and Ana Frank[3]

[1]Alzheimer Disease Research Unit, Alzheimer Center Reina Sofía Foundation - CIEN Foundation, Carlos III Institute of Health, Madrid, Spain.
[2]Gregorio Marañón University Hospital, Madrid, Spain.
[3]La Paz University Hospital, Madrid, Spain.

Authors' contributions

This work was carried out in collaboration between all authors. Author JO designed the study and wrote the first draft of the manuscript. Authors PG-P, DG-F and JAH-T contributed to the study design, conducted the MRI post-processing and reviewed the manuscript. Author AQ contributed to the study design, conducted the statistical analysis and reviewed the manuscript. Author CA provided logistic support and reviewed the manuscript. Author JA-L designed the MRI protocol of the ELMO study and reviewed the manuscript. Author AF was the principal investigator of the ELMO study and reviewed the manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/24034
Editor(s):
(1) Xin-an Liu, Neuroscience Department, the Scripps Research Institute, Scripps, Florida, USA.
(2) Jingli Xu, College of Pharmacy, University of New Mexico, USA.
Reviewers:
(1) Hazem Mohammed Ebraheem Shaheen, Damanhour University, Egypt.
(2) D. Sivaraman, Sathyabama University, Tamilnadu, India.
Complete Peer review History: http://sciencedomain.org/review-history/13594

Original Research Article

Received 1st January 2016
Accepted 20th February 2016
Published 8th March 2016

ABSTRACT

Background/Aims: We conducted a cross-sectional study to investigate the structural magnetic resonance imaging correlates of depressive symptoms at the initial clinical stages of Alzheimer's disease (AD).
Methods: Subjects aged 65 or more were categorized as prodromal AD (n=18), mild AD (n=35), or normal cognition (n=76). Depressive symptoms were measured by means of the 15-item abridged version of the Geriatric Depression Scale. Potential gray matter correlates of depressive symptoms

**Corresponding author: E-mail: javier@mariawolff.es, francisocojavier.olazaran@salud.madrid.org;*

were analyzed using the Statistical Parametric Mapping software package.
Results: Significant results were obtained in the prodromal AD group only. In that group, depressive symptoms were related to atrophy in the left precentral gyrus (Brodmann area 6) ($p \leq 0.01$, FWE corrected).
Conclusion: Our results, added to the existing literature, suggest that dysfunction in left-sided, cognitively and functionally salient, cortical regions along with relative preservation of deficit awareness, provided by the right hemisphere, explain depressive symptoms in the initial clinical stages of AD.

Keywords: Alzheimer's disease; depression; magnetic resonance imaging; structural correlates.

1. INTRODUCTION

Depressive symptoms are frequently reported in Alzheimer's disease (AD) [1,2], particularly at the initial clinical stages of the disease process [3,4]. Those symptoms, which often compromise the patient's and the caregiver's quality of life [4], pose important challenges in terms of physiopathology and treatment. Although several mechanisms have been proposed to explain the presence of depression in AD, the nature of this association remains controversial [5]. Usually interpreted as a symptom of, or a psychological reaction to, AD [6], depression has also been regarded as a trigger that lowers the threshold for dementia symptoms [7] and even as a hypothetical source of toxicity for the hippocampal neurons, thus increasing the risk of dementia [8,9]. Given that complexity of potential mechanisms, one may find discrepancies amongst results in clinical and epidemiological studies of AD and depression [5].

Structural studies can enlighten the mechanisms of depression in AD. In previous seminal research, Zubenko and collaborators reported selective damage in the locus coeruleus and the substantia nigra of patients with dementia who had also suffered from depression [10], which was accompanied by selective deficits in norepinephrine and serotonine [11]. However, those post-mortem studies were conducted in patients with major depression, hence not necessarily explaining the typically less severe depressive symptoms of the initial clinical stages of AD [12,13]. In a recent magnetic resonance imaging (MRI) study, which included patients with mild to moderate AD dementia, depression was related to atrophy in the left inferior temporal gyrus [14]. In other study, cortical thinning in the left parietal and temporal regions was observed in two independent cohorts of patients with AD and depression and a possible mediation of tau pathology was described [15]. In a ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) study, depressive symptoms of AD patients were associated with an increase in choline/creatine peak in the left dorsolateral prefrontal cortex, possibly indicating a neuronal membrane breakdown in that specific region [16].

We conducted a cross-sectional study to investigate the anatomical correlates of depressive symptoms in subjects with normal cognition, prodromal AD, or mild AD. The present investigation was performed in the context of a longitudinal collaborative project, which will also be presented in this paper.

2. MATERIALS AND METHODS

2.1 Setting and Subject Characteristics

The Observational Multicenter Longitudinal Study (ELMO, as from the Spanish initials) was envisioned, designed, and conducted by the Dementia Group of the Autonomous Community of Madrid (DEMCAM) to describe and analyze the clinical, biochemical, and MRI features of the initial stages of AD. Subjects aged 65 or more from 13 memory clinics of the Autonomous Community of Madrid (Spain) were invited to sign a consent form and participate in the survey (see the ELMO centers and investigators in the Acknowledgement section). Subjects were recruited from December 2008 to March 2012. The ELMO was approved by the Ethics Committee of the La Paz University Hospital.

A stringent set of exclusion criteria was utilized for enrolment of subjects. Patients with non-controlled medical diseases and those with poor expected survival or study compliance (e.g., patients with disseminated cancer, liver cirrhosis, lung fibrosis with severe respiratory insufficiency), were not included in the study. Potential psychiatric diseases were detected by means of patient and caregiver interview and medical records review, following the Diagnostic and Statistical Manual of Mental Diseases (DSM-

IV-TR) [17]. Past major depressive or anxiety disorders were permitted, but (either past or present) psychotic, bipolar, or substance-related/addictive disorders were cause of exclusion. Tremor at rest of any severity and moderate or severe rigidity, bradykinesia, or instability, as defined by the Unified Parkinson's Disease Rating Scale [18], were not permitted. Additional exclusion criteria were as follows: a) illiteracy; b) important neurosensory defect; c) subject unable to attend the study visits; d) lack of informant (with the exception of subjects with normal cognition); e) less than six months of symptom duration (in case of cognitive deterioration); f) clinically atypical AD [19]; g) cerebrovascular disease, either clinically recorded or observed as significant vascular lesions in neuroimaging study (i.e., cortical or strategic infarction or severe leukoaraiosis); h) any circumstance that could interfere with, or advice against, performance of MRI study, and i) presence of any systemic or neurological disorder, apart from AD, that could be responsible for the observed cognitive deficit.

2.2 Medical and Neurological Variables

A structured medical and neurological evaluation was conducted by the ELMO physicians (neurologists or geriatricians), who also reviewed all the available information from medical records and ancillary studies. The ELMO protocol included questions or items related to disease duration, memory symptoms, behavioural and psychological symptoms of dementia, motor symptoms, concomitant diseases and medications, physical exam (blood pressure, heart rate, height, weight, abdominal perimeter), neurological exam, and Hachinski score [20].

2.3 Neuropsychological Evaluation

The following tests and scales were conducted by neuropsychologists:

- Mini-mental State Examination (MMSE). This is the most widely used brief test of general cognition in dementia. The score ranges from 0 (worst) to 30 (best cognition) [21].
- Blessed Dementia Scale. This informant-based instrument measures dependency in instrumental activities of daily living (ADL) (from 0 to 8), dependency in basic ADL (from 0 to 9), and behavioural disturbance (from 0 to 11) [22].
- Seven Minute Test. This test measures free and cued verbal learning (from 0 to 16), time orientation (from 0 to 113), verbal category fluency (number of animals named in one minute), and construction ability (clock drawing, score from 0 to 7) [23].
- Trail-making Test. In this paper and pencil test, the patient is requested to link, alternatively, letters and numbers in ascending order. Hence, it is a measure of executive functions. Forms A and B were administered and both time and number of errors were recorded [24].
- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). The IQCODE is a structured interview that includes 26 questions regarding changes in the domains of cognitive function, other instrumental and advanced ADL, personality, and behaviour during the last 5 years. It is scored from 26 (very improved) to 130 (very worsened) [25].
- Functional Activities Questionnaire (FAQ). The FAQ is a questionnaire of instrumental ADL, which is administered to an informant. It comprises 11 items and is scored from 0 (total independence) to 33 (total dependence) [26].
- Geriatric Depression Scale (GDS). The 15-item abridged version of the GDS was used to analyze the potential structural correlates of depression in the present investigation. This instrument measures depressive symptoms by means of direct interview with the subject. A score from 0 (best) to 15 (worst affective status) is obtained [27].
- Clinical Dementia Rating (CDR). This instrument assesses three cognitive and three functional domains using a semi-structured interview with an informant and also some interview and mental status exam with the patient. A final score of 0 (no dementia), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), or 3 (severe dementia) is obtained [28].

2.4 ELMO Groups

After neurological and neuropsychological evaluation, the ELMO participants were classified into the following clinical groups:

a) Normal cognition (NC). These subjects may or may not have had memory complaints, but performed within normality (i.e., above 1.5 standard deviation [SD]) in

age- and education-adjusted neuropsychological tests.

b) Mild cognitive impairment (MCI). These subjects performed below normality (i.e., 1.5 SD) in at least one score of episodic memory (amnesic type, aMCI) and could also perform below normality in some other neuropsychological domain (multidomain type, mMCI). General cognition and functional capacities were essentially preserved and dementia diagnosis was absent [29]. Subjects from this group received a Clinical Dementia Rating (CDR) score of 0.5 [28]. Only those MCI subjects who had developed AD dementia at the last available follow-up visit will be presented and analyzed in the present paper (prodromal AD group).

c) Mild AD. These patients received a diagnosis of probable AD according to the NINCDS-ADRDA criteria, i.e., they suffered from deterioration in memory and at least one other neuropsychological domain, which significantly interfered with some instrumental ADL [19]. Subjects from this group received a CDR score of 1 [28].

2.5 Blood Sample

Complete blood count and determinations of glucose, ions, B12, folate, kidney, liver, and thyroid function were conducted in all the ELMO participants. Apolipoprotein E gen (*APOE*) haplotype was also determined in a subset of participants. In addition, blood samples were kept for potential future biological determinations.

2.6 MRI Study

The MRI study of the ELMO was acquired in a GE Healthcare 3T HDx scanner at the Neuroimaging Department of the Alzheimer Center Reina Sofía Foundation (ACRSF). The scanner was equipped with an eight-channel phased array receive coil and a gradient system capable of producing a gradient strength of 40mT/m. A comprehensive, 50-minute magnetic resonance acquisition protocol which included volumetric, perfusion, diffusion tensor imaging (DTI), echo-planar, fluid attenuated inversion recovery (FLAIR), and spectroscopical series was conducted. In the present paper, only the acquisition and post-processing procedures of the volumetric study will be described and analyzed.

A 3D-T1-weighted gradient echo volume was acquired for each subject. The 3D-T1-weighted acquisition parameters were as follows: TE = 4.152 ms, TR = 9.4 ms, TI = 650 ms, flip-angle = 12°, slice thickness =1 mm (with no gap between slices), acquisition voxel size = 0.83 × 0.83 × 1 mm, FOV = 240 mm, and sagittal acquisition with whole brain coverage. The statistical parametric mapping (SPM) technique and the diffeomorphic anatomical registration through exponentiated lie (DARTEL) algebra method [30] were used to perform voxel-based morphometry (VBM) analyses. Segmentation of the T1 weighted images in grey matter, white matter and cerebrospinal fluid [31] was followed by the elaboration of a grey matter template of an old-age, cognitively normal control group, which was created using the DARTEL procedure. The normalized volumetry maps were averaged and smoothed using a [8 mm, 8 mm, 8 mm] full width at half maximum (FWHM) isotropic Gaussian kernel. Smoothing of the normalized maps is known to reduce sensitivity, but it is required to minimize normalization errors as the anatomy between individuals is highly variable. By smoothing, we achieve more overlapping between subjects for a given cluster. Furthermore, data smoothing prepares the data to fit the SPM Gaussian random field theory working frame. The drawback will be some loss of spatial precision. All native maps were normalized to the template using the Montreal Neurological Institute (MNI) coordinates. The MNI normalization option was chosen in order to locate significant regions in a well defined space.

2.7 Statistical Analyses

The demographic and clinical variables of the three study groups at the time of the ELMO inclusion were presented and compared by means of descriptive statistics, Chi-square test, and one-way analysis of variance. As mentioned above, MRI data processing was performed using the SPM version 8 (SPM8) software package, which computes statistical parametric maps for localizing significant differences between two or more experimental groups and also allows for correlation assessment between the images and the potentially explanatory variables, using the general linear model. For the present investigation, the significant correlations in brain structures according to the GDS score were searched, firstly for the whole sample and secondly for each study group, using NC group as the reference. The design matrix was defined as multiple regression with one covariate of interest (i.e., GDS) and three confounding variables (i.e., total brain gray matter volume

[32], gender, and age). Gray matter rather than intracranial volume was utilized because regional, instead of generalized, atrophy should be expected in the initial stages of AD [33]. Cluster-level, family-wise (FWE), statistical corrections for multiple comparisons were applied and the threshold for statistical significance was set at $p<0.05$ (two-sided, FWE corrected).

3. RESULTS

The general disposition of the ELMO participants and the subjects who were included in the present study are depicted in Fig. 1. From a total of 201 participants that signed the consent form, 72 subjects had to be excluded due to: a) MCI that did not develop into AD dementia at the last available follow-up visit (49 subjects), b) subject did not have a usable MRI for the present study (15 subjects), and c) other reasons (8 subjects). Thus, 129 subjects were analyzed for the present paper. The mean age was 73.4 (SD 6.1, range 65 to 90), there was predominance of women (63.3%), and mean time of education was 10.7 years (SD 6.1, range 0 to 25).

The main clinical variables across the three study groups are presented in Table 1. Subjects with mild AD were older and had less educational achievement than subjects with NC. As expected, there were differences in cognitive performance, particularly regarding memory tests, and in functional status across the three study groups. Moreover, a higher frequency of *APOE* ε4 allele was observed in both AD groups. The severity of depressive symptoms according to the GDS was mild (mean score 1.9, SD 2.2, range 0 to 10) and comparable across the three study groups. Only eight subjects (6.2%) surpassed the GDS cut score for clinical depression (5/6).

No statistically significant results were found in the regression analysis of the structural correlates of depression when the total sample was analyzed (all p-values >0.05, data not shown). However, in the separate analyses of the study groups, significant negative correlations emerged in the group of prodromal AD. In that group, depressive symptoms were related to atrophy in the left precentral gyrus (Brodmann area [BA] 6) (Table 2, Fig. 2). In addition, a very small region of atrophy was detected, related to depressive symptoms, in the right postcentral gyrus (BA 2).

4. DISCUSSION

We conducted a cross-sectional study to determine the potential gray matter correlates of depressive symptoms in the initial clinical stages of AD. The research context was not a large but highly restrictive multicenter longitudinal study that conducted extensive clinical assessment and 3T structural MRI study. As expected, the participants displayed good physical health, with low frequency of vascular features, and virtual absence of clinical depression (Table 1). This restrictive research context, albeit compromising the generalizability of results, offered the opportunity to sensitively investigate the structural underpinnings of mild/subsyndromal depressive symptoms at AD clinical inception.

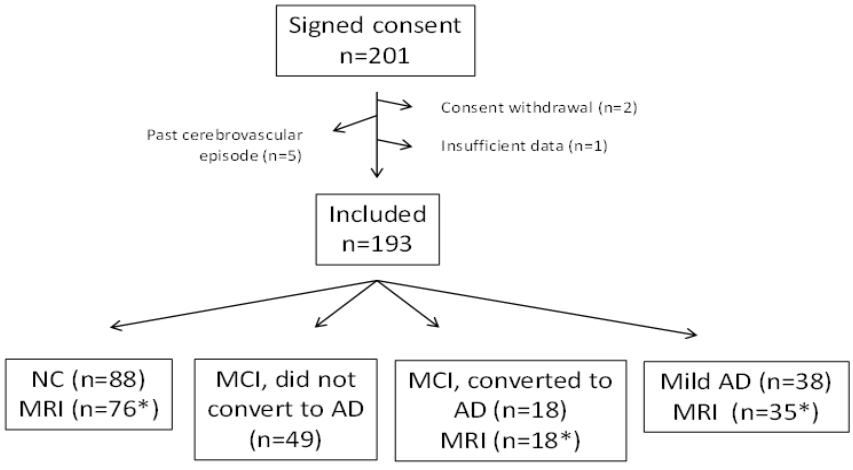

Fig. 1. General disposition of the ELMO participants

**Subjects selected for the present investigation, NC: normal cognition; MRI: magnetic resonance imaging; MCI: mild cognitive impairment; AD: Alzheimer's disease; ELMO: Observational Multicenter Longitudinal Study*

Table 1. Clinical variables in the three study groups

	NC (n = 76)	Prodromal AD (n = 18)	Mild AD (n = 35)	p
Age	71.4 (5.5)[1]	74.7 (4.6)	77.1 (6.0)[1]	0.000
Sex (% female)	60.5	50.0	77.1	0.197
Education (years)	12.7 (5.9)[1]	9.5 (6.6)	7.0 (4.1)[1]	0.000
Duration of cognitive symptoms (years)[3]	2.6 (2.8)	3.8 (2.2)	4.0 (2.9)	0.044
Hachinski score	0.8 (1.1)	1.4 (1.8)	1.2 (1.3)	0.151
Medications (n)[4]	3.7 (2.2)	4.2 (2.1)	3.5 (2..4)	0.466
Antidepressants (%)	23.5	27.3	42.9	0.122
MMSE	29.1 (1.2)[1]	26.3 (2.7)[1]	22.1 (4.4)[1]	0.000
7MT				
Orientation	112.8 (0.6)[1]	105.1 (15.1)[2]	78.3 (35.6)[1,2]	0.000
Immediate memory	15.8 (0.6)[1,2]	14.3 (2.5)[1]	13.6 (2.4)[2]	0.000
Delayed recall, free	10.0 (1.8)[1]	6.2 (2.9)[1]	4.6 (2.1)[1]	0.000
Delayed recall, cued	15.7 (0.6)[1]	12.9 (3.4)[1]	10.1 (2.8)[1]	0.000
Clock drawing	6.9 (0.3)[1]	6.2 (1.6)[2]	3.6 (2.5)[1,2]	0.000
Total score	73.6 (10.8)[1]	45.6 (16.2)[1]	16.8 (19.1)[1]	0.000
TMT				
TMT-A, time (seconds)	56.0 (20.3)[1]	94.2 (41.9)[1]	150.2 (99.1)[1]	0.000
TMT-A, number of errors	0.1 (0.5)[1,2]	1.1 (3.1)[1]	1.5 (1.8)[2]	0.000
TMT-B, time (seconds)[5]	126.5 (61.5)[1,2]	222.7 (73.3)[1]	249.9 (89.3)[2]	0.000
TMT-B, number of errors[6]	1.0 (3.4)[1]	0.9 (2.1)[2]	6.3 (4.9)[1,2]	0.000
FAQ	0.5 (1.0)[1]	6.2 (3.9)[1]	14.8 (6.3)[1]	0.000
CDR				
Gobal score	0.0 (0.1)[1]	0.5 (0.0)[1]	1.1 (0.4)[1]	0.000
Sum of boxes	0.1 (0.2)[1]	2.6 (0.9)[1]	5.5 (1.7)[1]	0.000
Family history of dementia (%)	57.3	54.5	62.9	0.796
APOE (% ε4)[7]	27.8	57.1	80.8	0.002
GDS	1.9 (2.5)	1.9 (2.0)	1.7 (1.8)	0.834

Data are expressed as mean (SD, range) unless % is indicated.

[1,2]Significant differences between groups with the same superscript number (p<0.05, Scheffé test); [3]n=56 in the NC group; [4]cholinesterase inhibitors and memantine were not included; [5]n=100; [6]n=90; [7]n=58.

AD: Alzheimer's disease; APOE: apolipoprotein E gene; FAQ: Functional Activites Questionnaire; GDS: Geriatric Depression Scale (15-item abridged version); 7MT: Seven Minutes Test; MMSE: Mini-mental State Examination; NC: normal cognition; TMT-A: Trail Making Test, part A; TMT-B: Trail Making Test, part B; y: years

Table 2. Brain regions that were inversely related to depressive symptoms in prodromal AD (n=18)*

Anatomical region	Coordinates (x,y,z) (MNI)	Cluster size	T value	p value
Left frontal lobe, precentral gyrus (BA 6)	(-60, 2, 16)	20	5.23	0.006
Right parietal lobe, Postcentral gyrus (BA 2)	(44, -32, 58)	7	5.26	0.018

**Only those regions with a FWE-corrected p<0.05 are represented. BA: Brodmann area; MNI: Montreal Neurological Institute*

A significant correlate between gray matter atrophy and depressive symptoms was found in the left premotor cortex (BA 6) for the prodromal AD group (Table 2, Fig. 2). To the authors' knowledge, this finding was not reported before. Brodmann area 6 participates in verbal working memory [34] (i.e., the human capacity of temporarily holding information and having that information rapidly accessible) [35] and was proposed as the substrate of neural transitions from motor to cognitive functions [36]. Several structural [14-16,37] and functional [38-40] imaging studies demonstrated associations between depressive symptoms and gray and white matter atrophy or hypoperfusion in patients with AD and depression, particularly in the left prefrontal cortex [38-40].

Hence, it is unlikely that our results disclosed the genuine or critical region for depressive

symptoms in the initial clinical stages of AD. By contrast, consistently with the previous studies, we propose a pattern of 'asymmetrical', predominantly left-sided, brain dysfunction that may be determinant to elicit a situation of cognitive and functional difficulties, with relatively well-preserved consciousness of deficits, leading to depressive symptoms and, if other psychological and biological factors concur, to clinical depression (Fig. 3). This explanation is supported by the observation of those GDS items related to cognition and activities of daily living (ADL) performance (i.e., 'have you dropped many of your activities and interests?', 'do you feel you have more problems with memory than most?', 'it is hard for you to get started on new projects?'), which were the most frequently endorsed by subjects from the prodromal AD group (*post-hoc* observations, data not shown). Giving further support to the proposed model, a previous longitudinal study of MCI subjects found that atrophy within left perisylvian areas was associated with naming and fluency decline, whereas left frontal atrophy was associated with decline in executive functions [41]. Moreover, left and right hemispheres have been associated with the processing of, respectively, positively and negatively valenced stimuli [42]. A situation of predominantly left damage could produce a selective processing of the emotionally negative stimuli, further contributing to depression.

Asymmetrical cerebral dysfunction is frequently observed in clinical practice at the beginnings of AD and is supported by neuropsychological, positron-emission tomography (PET), and pathological studies of AD [43]. To what extent this asymmetrical pattern of brain dysfunction contributes to depression in AD should be a matter of future research. Evolution towards widespread, less asymmetrical, brain damage in AD, along with the loss of deficit awareness, would explain the absence of significant results in our mild AD group, thus supporting the proposed model for depressive symptoms at the initial clinical stages of AD (Fig. 3). Beyond AD, this model could also be applied to other brain conditions. In fact, depression after stroke was more frequently reported in patients with left-sided lesions [44,45].

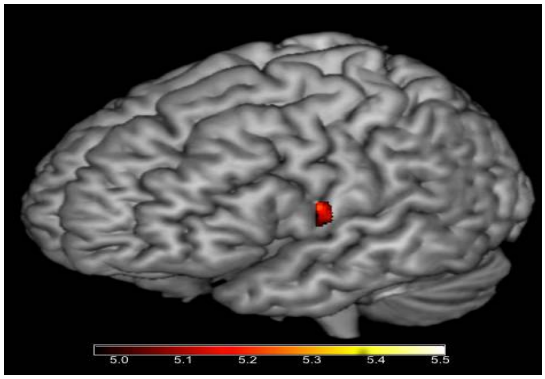

Fig. 2. Inverse structural correlate of depressive symptoms in prodromal AD (n=18). Depression was associated with atrophy in the left precentral gyrus (p<0.01, FWE corrected)

AD: Alzheimer's disease; FWE: family-wise error

The present research is novel in the sense that 3T MRI equipment was utilized, and within-group regression analysis was conducted, thus increasing the sensitivity and specificity to capturing valid results. In fact, after a rigorous control of multiple comparisons, we could identify a new region related to depressive symptoms in prodromal AD. However, the present study has important limitations. First, subjects with major depression were excluded from the study and the depressive symptoms were, in most cases, of questionable clinical relevance. Hence, although some of the results and proposed mechanisms could be contributing, our results cannot be

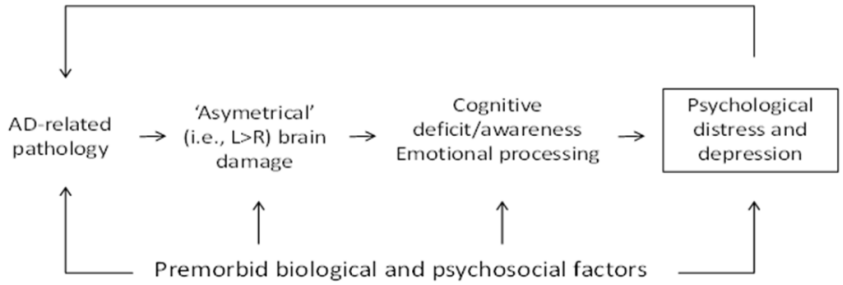

Fig. 3. Proposed model of factors leading to depression in the initial clinical stages of AD

AD: Alzheimer's disease; L: left; R: right

extrapolated to patients with AD and fully developed depression. Second, structural correlates of depression were found only in the group of prodromal AD. Then, it should be assumed that depression is different or has different determinants in patients with AD and more advanced cognitive deterioration. Third, subjects with subjective cognitive impairment (SCI), a transitional stage between NC and MCI, which is usually associated with depression [46], were not specifically analyzed. Future studies involving SCI subjects that present depressive symptoms and are positive for AD biomarkers should be particularly useful to confirm the model of genesis of depressive symptoms proposed herein (Fig. 3). Fourth, the midbrain monoaminergic nuclei [10] could not be specifically investigated, since those small nuclei fall out of 3T MRI resolution. And fifth, a potential role of non-AD specific factors (e.g., sex, personality, genetic factors, vascular lesions) could not be adequately analyzed, due to small sample size [47] or lack of vascular pathology [48].

5. CONCLUSION

The relationship between AD and depression is complex and, probably, bidirectional. In the initial clinical stages of the disease, mild depressive symptoms are explained by dysfunction in left cortical regions along with relative preservation of deficit awareness, provided by the right hemisphere. This model of genesis of depressive symptoms may contribute to more severe depression when other genetic and social circumstances concur and is also applicable in other neurological conditions, different from AD.

FUNDING

The ELMO and the DEMCAM received support from the Spanish Ministry of Health and from the Reina Sofía Foundation.

ACKNOWLEDGMENTS

List of participant centers (and investigators) of the ELMO: Hospital Universitario La Paz (Ana Frank García, Meritxell Valentí Soler, María Ascensión Zea Sevilla, Rocío García Cobos, Ángel Hernanz Macías, Clarissa Vincent Lázaro, Raquel Gonzalo Barbas, Nuria Jiménez Perdices, Arturo Sampedro Andrada, Genny Lubrini, Carmen Acedo Jiménez, Carolina Sáenz Lafourcade, Ana Simón Gozalbo), Centro Alzheimer Fundación Reina Sofía – Fundación CIEN (Belén Frades Payo, Juan Álvarez Linera, Ana Ramos González, Daniel García Frank, Juan Antonio Hernández Tamames), Hospital de Cantoblanco (Jesús López Arrieta, Pilar Bartolomé), Hospital General Universitario Gregorio Marañón (Eloísa Navarro Merino, Isabel Cruz Orduña, Javier Olazarán Rodríguez), Centro de Prevención del Deterioro Cognitivo – Ayuntamiento de Madrid (Marcos Llanero Luque, José María Ruiz Sánchez de León), Hospital de la Cruz Roja (Ángel Berbel García, Antonio Ortiz Pascual), Hospital de Getafe (Lorenzo Morlán Gracia, María Dolores Torrecillas Narváez), Hospital Rúber Internacional (Adolfo Jiménez Huete), Hospital Infanta Elena (Cristina Prieto Jurczynska), Hospital Infanta Cristina (David Pérez Martínez), Fundación Hospital de Alcorcón (José Luis Dobato Ayuso), Hospital Severo Ochoa (María de Toledo Heras), Hospital Clínico San Carlos (María Sagrario Manzano Palomo), Facultad de Psicología – Universidad Nacional de Educación a Distancia (Beatriz García Rodríguez), Facultad de Psicología – Universidad Complutense de Madrid (Sara Fernández Guinea, Diana Oviedo Céspedes), and Centro de Biología Molecular Severo Ochoa (María Jesús Bullido Gómez-Heras).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Hope T, Keene J, Fairburn CG, et al. Natural history of behavioural changes and psychiatric symptoms in Alzheimer's disease: A longitudinal study. British Journal of Psychiatry. 1999;174:39-44.
2. Li XL, Hu N, Tan MS, Yu JT, Tan L. Behavioral and psychological symptoms in Alzheimer's disease. Biomed Research International. 2014;927804.
3. Holtzer R, Scarmeas N, Wegesin DJ, et al. Depressive symptoms in Alzheimer's disease: Natural course and temporal relation to function and cognitive status. Journal of the American Geriatrics Society. 2005;53(12):2083-2089.
4. Winter Y, Korchounov A, Zhukova TV, Bertschi NE. Depression in elderly patients with Alzheimer dementia or vascular dementia and its influence on their quality of life. Journal of Neuroscience and Rural Practice. 2011;2(1):27-32.
5. Mintzer J, O'Neill C. Depression in Alzheimer's disease: Consequence or

contributing factor? Expert Reviews in Neurotherapies. 2011;11(11):1501-1503.
6. Chen P, Ganguli M, Mulsant BH, DeKosky ST. The temporal relationship between depressive symptoms and dementia: A community-based prospective study. Archives of General Psychiatry. 1999;(56)3:261-266.
7. Jorm AF. History of depression as a risk factor for dementia: An updated review. Australian and New Zeland Journal of Psychiatry. 2001;35(6):776-781.
8. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Archives of General Psychiatry. 2000;57(10):925-935.
9. Byers AL, Yaffe K. Depression and dementias among military veterans. Alzheimer's and Dementia. 2014;13(suppl. 3):S166-173.
10. Zubenko GS, Moossy J. Major depression in primary dementia: Clinical and neuropathologic correlates. Archives of Neurology. 1988;45(11):1182-1186.
11. Zubenko GS, Moossy J, Kopp U. "Neurochemical correlates of major depression in primary dementia. Archives of Neurology. 1990;47(2):209-214.
12. Royall DR, Palmer RF. Alzheimer's disease pathology does not mediate theassociation between depressive symptoms and subsequent cognitive decline. Alzheimer's & Dementia. 2013;9(3):318-325.
13. Wilson RS, Capuano AW, Boyle PA, et al. Clinical-pathologic study of depressive symptoms and cognitive decline in old age. Neurology. 2014;83(8):702-709.
14. Son JH, Han DH, Min KJ, Kee BS. Correlation between gray matter volume in the temporal lobe and depressive symptoms in patients with Alzheimer's disease. Neuroscience Letter. 2013; (548)26:15-20.
15. Lebedeva A, Westman E, Lebedev AV, et al. Structural brain changes associated with depressive symptoms in the elderly with Alzheimer's disease. Journal of Neurology Neurosurgery and Psychiatry. 2014;85(8):930-935.
16. Tsai CF, Hung CW, Lirng JF, et al. Differences in brain metabolism associated with agitation and depression in Alzheimer's disease. East Asian Archives of Psychiatry. 2013;23(3)86-90.
17. American Psychiatry Association. Diagnostic and statistical manual of mental disorders, Text Revision (DSM-IV-TR). American Psychiatric Association; Washington DC; 2000.
18. Fahn S, Elton RL. In recent developments in parkinson's disease. Macmillan Health Care Information, Florham Park, NJ. 1987;2:153-164.
19. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology. 1984;34(7):939-944.
20. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. Archives of Neurology. 1975;32(9):632-637.
21. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;12(3):189-198.
22. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile changes in the cerebral gray matter of elderly subjects. British Journal of Psychiatry. 1968;114,512:797-811.
23. Solomon PR, Hirschoff A, Kelly B, et al. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer´s disease. Archives of Neurology. 1998;55(3):349-355.
24. Partington J, Leiter R. Partington's pathways test. Psychological Service Center Bulletin. 1949;1:11-20.
25. Jorm A, Korten A. Assessment of cognitive decline in the elderly by informant interview. British Journal of Psychiatry. 1988;152:209-213.
26. Pfeffer RI, Kurosaki TT, Harrah CH, et al. Measurement of functional activities in older adults in the community. Journal of Gerontology. 1982;37(3):323-329.
27. Burns A, Lawlor B, Craig S (editors). Assessment scales in old age psychiatry. London, Martin Dunitz. 1999;2-3.
28. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. British Journal of Psychiatry. 1982;140:566-572.
29. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: Clinical characterization and outcome. Archives of Neurology. 1999;56(3):303-308.

30. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage. 2007;38(1):95-113.
31. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005;26(3): 839-851.
32. Pernet C, Andersson J, Paulesu E, Demonet JF. When all hypotheses are right: A multifocal account of dyslexia. Human Brain Mapping. 2009;30(7):2278-2292.
33. Lacalle-Aurioles M, Mateos-Pérez JM, Guzmán de Villoria JA, et al. Cerebral blood flow is an earlier indicator of perfusion abnormalities than cerebral blood volume in Alzheimer's disease. Journal of Cerebral Blood Flow & Metabolism. 2014;34(4):654-659.
34. Smith EE, Jonides J, Koeppe RA. Dissociating verbal and spatial working memory using PET. Cerebral Cortex. 1996;6(1):11-20.
35. Baddeley AD. Essentials of human memory. Hove, Psychology Press; 1999.
36. Hanakawa T, Honda M, Sawamoto N, et al. The role of rostral Brodmann area 6 in mental-operation tasks: An integrative neuroimaging approach. Cerebral Cortex. 2002;12(11):1157-1170.
37. Lee GJ, Lu PH, Hua X, et al. Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. Biological Psychiatry. 2012;71(9):814-821.
38. Akiyama H, Hashimoto H, Kawabe J, et al. The relationship between depressive symptoms and prefrontal hypoperfusion demonstrated by eZIS in patients with DAT. Neuroscience Letter. 2008;441(3): 328-331.
39. Honda H, Terada S, Sato S, et al. Subjective depressive mood and regional cerebral blood flow in mild Alzheimer's disease. International Psychogeriatrics. 2014;26(5):817-823.
40. Terada S, Oshima E, Sato S, et al. Depressive symptoms and regional cerebral blood flow in Alzheimer's disease. Psychiatry Research. 2014;221(1):86-91.
41. McDonald CR, Gharapetian L, McEvoy LK, et al. Relationship between regional atrophy rates and cognitive decline in mild cognitive impairment. Neurobiology of Aging. 2012;33(2):242-253.
42. Alfano KM, Cimino CR. Alteration of expected hemispheric asymmetries: Valence and arousal effects in neuropsychological models of emotion. Brain and Cognition. 2008;66(3):213-220.
43. Lam B, Masellis M, Freedman M, et al. Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. Alzheimer's Research & Therapy. 2013;5(1)1.
44. Robinson RG, Kubos KL, Starr LB, et al. Mood disorders in stroke patients: Importance of location of lesion. Brain. 1984;107(1):81-93.
45. Rajashekaran P, Pai K, Thunga R, Unnikrishnan B. Post-stroke depression and lesion location: A hospital based cross-sectional study. Indian Journal of Psychiatry. 2013;55(4):343-348.
46. Reisberg B, Prichep L, Mosconi L, et al. The pre-mild cognitive impairment, subjective cognitive impairment stage of Alzheimer's disease. Alzheimer's & Dementia. 2008;4(1)[Suppl 1]:S98-S108.
47. Leentjens AF, Moonen AJ, Dujardin K, et al. Modeling depression in Parkinson disease: Disease-specific and nonspecific risk factors. Neurology. 2013;81(12):1036-1043.
48. Starkstein SE, Mizrahi R, Capizzano AA, et al. Neuroimaging correlates of apathy and depression in Alzheimer's disease. Journal of Neuropsychiatry & Clinical Neurosciences. 2009;21(3):259-265.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/13594