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Amyloid and anatomical correlates of executive functioning in middle-aged offspring of patients with late-onset Alzheimer's disease.

Bárbara Duarte-Abritta [a,b], Stella-Maris Sánchez [a,b,c], Carolina Abulafia [a,b,d], Deborah R. Gustafson [e], Silvia Vázquez [f], Gustavo Sevlever [g], Mariana N. Castro [a,b,i,j], Leticia Fiorentini [a,b,j], Mirta F. Villarreal [a,b,c], Salvador M. Guinjoan [a,b,h,i,k,l,*]

[a] Grupo de Investigación en Neurociencias Aplicadas a las Alteraciones de la Conducta, Instituto de Neurociencias FLENI-CONICET, Buenos Aires, Argentina
[b] Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina
[c] Departamento de Física, Facultad de Cs. Exactas y Naturales, Universidad de Buenos Aires, Argentina
[d] Institute for Biomedical Research (BIOMED), Pontifical Catholic University of Argentina, Buenos Aires, Argentina
[e] Department of Neurology, State University of New York University Downstate Health Sciences University, United States
[f] Centro de imágenes moleculares (CIM), Fundación FLENI, Argentina
[g] Departamento de Neuropatología y Biología Molecular, Fundación FLENI, Buenos Aires, Argentina
[h] Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, Argentina
[i] Departamento de Salud Mental, Facultad de Medicina, Universidad de Buenos Aires, Argentina
[j] Servicio de Psiquiatría, Fundación FLENI, Buenos Aires, Argentina
[k] Neurofisiología I, Facultad de Psicología, Universidad de Buenos Aires, Argentina
[l] Laureate Institute for Brain Research, OK, United States

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ABSTRACT

A traditional hallmark of cognitive impairment associated with late-onset Alzheimer's disease (LOAD) is episodic memory impairment. However, early alterations have been identified in brain regions associated with executive function in asymptomatic, middle-age offspring of patients with LOAD (O-LOAD) compared to those with no family history. We hypothesized that executive function among O-LOAD would correlate with structural and amyloid brain imaging differently from those without a family history of LOAD (control subjects, CS). Executive function, cortical thickness, and in-vivo Aβ deposits were quantified in 30 O-LOAD and 25 CS. Associations were observed among O-LOAD only. Cortical thickness in the left lateral orbitofrontal cortex was positively associated with Design Fluency. The Stroop Color and Word Test, correlated positively with right rostral mid-frontal cortex thickness. Trails Making Test-B was inversely related to left medial orbitofrontal thickness. Tower of London total time was positively associated with β-amyloid deposition in the right precuneus. These results support previous evidence that early executive dysfunction might reflect subtle, early changes in persons at risk of LOAD and suggests that executive function alterations deserve further exploration in the LOAD literature.

Abbreviations

AD: Alzheimer's disease;
BDI-II: Beck's Depression Inventory, second version;
CS: Control subjects;
DF: Design Fluency;
EF: Executive functions;
LOAD: Late-onset Alzheimer's disease;
O-LOAD: Asymptomatic, middle-age offspring of patients with late-onset Alzheimer's disease;
PVC: Partial Volume Correction;
TMT-B: Trail Making Test, part B;
TOL: Tower of London Dx, total time

1. Introduction

The neuropathological changes in late-onset Alzheimer's disease (LOAD) precede the clinical symptoms by several decades (Braak and Braak, 1991; Braak and Del Tredici, 2011; Buchhave et al., 2012; Hubbard et al., 1990). In early stages of the disease, the brain can

* Corresponding author.
E-mail address: SGuinjoan@laureateinstitute.org (S.M. Guinjoan).

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compensate for these changes until cognitive decline becomes obvious and disrupts daily functioning, which is when clinical diagnosis of LOAD can be made. However, prior to clinical symptom onset, individuals exhibit very mild changes in cognition and present subtle yet measurable brain changes, which has been defined as the "preclinical" stage of LOAD (Sperling et al., 2011). Therefore, a fundamental objective of current biomedical research is to identify biomarkers of LOAD during the preclinical stage, which in the future will allow for an early diagnosis and intervention (Márquez and Yassa, 2019), as well as device of secondary prevention strategies (Hsu and A Marshall, 2017). Advances in the field of LOAD biomarkers in the last decade have provided the necessary tools for the development of more accurate and complete models about in-vivo biomarker progression, culminating in Jack and Holztman`s prospective longitudinal model based almost entirely on neuroimaging biomarkers (Jack and Holtzman, 2013). The authors propose several time-dependent LOAD models of disease staging based on neuroimaging biomarkers (structural MRI, PET PiB and PET FDG), contemplating variable ages of onset and comorbid conditions.

One of the main risk factors associated with LOAD is family history (Green et al., 2002); individuals with a first-degree relative diagnosed with LOAD have around 2–5 times the lifetime risk of developing the disease than people with no family history (Loy et al., 2014). Consequently, greater number of first-degree relatives with LOAD translates into an even higher risk of LOAD (Lautenschlager et al., 1996 2515). This increased risk would be influenced not only by heredity (genetics) but also by the presence of shared environmental and lifestyle factors. In a recent study, Wolters found that having a parent with dementia increases LOAD risk independently of known genetic risk factors such as APOE-e4 (Wolters et al., 2017), and another publication reported that parental family history might explain more variance in preclinical brain changes than APOE-e4 (Okonkwo et al., 2012). In light of this information, offspring of LOAD patients seems to be a promising population to explore early, preclinical neuroimaging biomarkers of LOAD (Jarvik et al., 2008). In a previous study of our group, we compared structural, amyloid and metabolic neuroimaging in healthy, middle-aged offspring of LOAD with increased risk of developing LOAD (O-LOAD) with matched control subjects (CS). In this work, we observed that O-LOAD displayed decreased cortical thickness, abnormal cerebral metabolism, and differences in amyloid deposition in precunei, posterior cingulate, and prefrontal and temporal areas (Duarte-Abritta et al., 2018). These neuroimaging measures refer to brain circuits potentially associated with executive function (EF) rather than episodic memory.

EF is an umbrella term that encompasses higher order cognitive processes critical for complex thought and behavior, such as planning, set-shifting, updating and monitoring of information, and inhibitory control, among others (Jurado and Rosselli, 2007). Several EF processes underlie adequate performance of multiple cognitive domains, including memory (Baudic et al., 2006), which has been historically considered the earliest cognitive function to become impaired in LOAD progression. However, some researchers propose that early executive dysfunction precedes and is responsible for subsequent memory deficits (Reinvang et al., 2012; Storandt, 2008). Indeed, many authors advocate for a link between memory and executive impairment even in prodromal stages of LOAD (Hazlett et al., 2015). It has been reported that patients with amnestic mild cognitive impairment (MCI) display worse performance on EF tasks (Johns et al., 2012; Zheng et al., 2012).

Studies aimed at the identification of structural correlates in LOAD associate executive dysfunction with changes in dorsolateral prefrontal regions (McDonald et al., 2012) and with posterior cortical areas, which reflects EF functioning through fronto-parietal networks (Dickerson et al., 2011; Vasconcelos et al., 2014). Another area of special interest is the entorhinal cortex, which, besides its better-known link to the hippocampus and memory processes (Solodkin et al., 2014), is also associated with prefrontal regions (Schott et al., 2011) – key areas involved in executive functioning (Jurado and Rosselli, 2007) that are also associated with early tau-related injury in LOAD (Braak and Braak, 1991). The presence of executive deterioration in mild and moderate LOAD is well-established (Albert, 1996; Blanco Martin et al., 2016; Kirova et al., 2015; Swanberg et al., 2004), but less is known about prodromal stages. Some neuroimaging studies reporting increased prefrontal brain response and hypometabolism in groups with increased risk of developing LOAD highlight the relevance of EF research as a possible preclinical marker of AD (Houston et al., 2005; Woo et al., 2010). One study explored preclinical AD, mild cognitive impairment (MCI), and LOAD samples in order to assess the whole AD continuum and observed multiple correlations between cortical thinning in frontal, parietal and subcortical regions and lower performance in EF (Kang et al., 2019b).

Our group, which focuses on changes in population at risk of developing LOAD, reported that the same O-LOAD assessed in the aforementioned Duarte-Abritta et al. (2018) exhibited lower EF performance compared to CS, specifically related to mental switching, interference effects, and other executive measures (Abulafia et al., 2019). Another publication of our group reported that the same O-LOAD group exhibited an association between poor performance on inhibitory processes and lower connectivity in an extensive network involving subcortical/allocortical limbic structures and prefrontal regions. Additionally, the same paper observed reduced global functional connectivity of the entorhinal cortex (an EF hub) as well as lower connectivity with the orbitofrontal cortex and precuneus (Sanchez et al., 2017). Taken together, these results raised the question of whether there is a relationship between structural neuroimaging variables and executive function performance in this sample from Argentina, an underrepresented group in the LOAD literature.

In the present study, we tested the hypothesis that EF in O-LOAD was associated with gray matter thickness and amyloid deposits in absence of LOAD-related clinical symptoms, when compared to individuals with no family history of LOAD (CS). We predicted that O-LOAD would evidence reduced executive functioning, lower gray matter thickness, and increased in-vivo amyloid deposition in brain regions linked to executive functioning (Chang et al., 2010; Dickerson et al., 2011; Kang et al., 2019b; Loewenstein et al., 2016, 2015; Reinvang et al., 2012; Resnick et al., 2010), when compared to CS.

2. Materials and methods

2.1. Design and sample

From the initially recruited O-LOAD ($n = 32$) and CS with no family history of AD ($n = 28$) (Abulafia et al., 2019), subjects with available MRI (30 O-LOAD and 25 CS) and PET-PiB imaging (24 O-LOAD and 22 CS) were included in the present exploratory cross-sectional study to compare cognitive and brain imaging measures. For each participant, all measures were acquired within three months of recruitment. The Bioethics Committee of the Fleni Foundation, Argentina, approved the study protocol, which was performed in accordance with the Declaration of Helsinki. All participants provided written, informed consent for the study.

The inclusion and exclusion criteria have been previously described in detail elsewhere (Duarte-Abritta et al., 2018). In brief, the primary inclusion criteria for O-LOAD were: (1) having at least one parent diagnosed with probable LOAD using DSM-5 diagnostic criteria; (2) 40–65 years old at the time of recruitment; (3) formal education >7 years; and (4) no evidence of clinical depression as assessed by a consulting psychiatrist (MNC, SMG). Although we do not have post-mortem data for the participant́s parents affected by LOAD, all participants were asked for clinical information of affected family members. For individuals who had received no treatment at the FLENI Foundation ($n = 5$) the parents' diagnosis of LOAD was confirmed by a clinician. In addition to clinical confirmation of LOAD in the parents, structural MRIs were available to confirm atrophic changes suggestive of LOAD and absence of significant vascular disease in the parents of 15 participants.

Of these, three had a positive PET-PiB test. None of the evaluated participants had both parents diagnosed with LOAD. CS had the same inclusion criteria except that they reported no evidence of AD or other neurodegenerative disorders up to two degrees of kinship. The exclusion criteria for all participants were as follows: (1) Mini Mental State Examination (MMSE) score <25; (2) compromised intellectual ability measured by a complete neuropsychological battery that evaluated all cognitive domains; (3) evidence of current progressive neurological disease evaluated by a psychiatrist; (4) history of substance abuse (alcohol, benzodiazepines, and/or other drugs); and (5) Hachinski score>7, to screen out individuals with potential cerebrovascular compromise.

2.2. Cognitive assessment

Initially, potential participants were screened for inclusion in the study with the Mini Mental State Examination (MMSE) (Folstein et al., 1975), a screening measure for global cognitive performance (see above). All individuals that met inclusion criteria underwent a complete neuropsychological performance battery to ensure they were cognitively asymptomatic and had an intellectual ability within normal ranges. A series of standard neuropsychological tests which have been thoroughly validated and are extensively used in clinical practice (and thus require no detailed explanation) were administered as described in a previous publication (Abulafia et al., 2019). The neuropsychological battery included the following tests. Attention: Digits subtest from the WAIS III intelligence battery (Wechsler, 1997) to measure attention span; Trial Making Test part A (TMT-A) (Reitan and Wolfson, 1985) to assess sustained attention. Memory: Rey's Auditory Verbal Learning Test (RAVLT) (Rey, 1964; Schmidt, 1996) for verbal episodic memory. Language: verbal fluency (semantic and phonemic variants) (Spreen and Benton, 1977) and Vocabulary subtest from the WAIS III intelligence battery (Wechsler, 1997) to assess semantic memory and word knowledge. Executive functions: The Trail Making Test part B (TMT-B) was used to probe cognitive flexibility and set-shifting (Reitan and Wolfson, 1985); Design Fluency (DF) from the D-KEFS assessment battery was implemented to assess nonverbal productivity, inhibition and set-shifting (Delis et al., 2001); the Tower of London DX (TOL) was administered to measure planning and problem-solving abilities (Culbertson and Zillmer, 2001); and the Stroop Color and Word Test (Stroop) was used as a measure of inhibitory processes (Golden, 1978). Higher scores reflect better performance on all tests except for TMT-A, TMT-B and TOL, where higher scores reflect poorer performance.

Presence and severity of depressive symptoms were quantified using Beck's Depression Inventory-II (BDI-II, cutoff score = 14, (Beck, 1996 #1206)). Caregiver burden was screened with the 22-point Zarit Burden Interview (Zarit et al., 1985). Only two O-LOAD subjects reported being active caregivers during recruitment. The remaining O-LOAD parents were either living in a nursing home or had passed away. Of the two caregivers, only one obtained scores suggesting caregiver burden (cutoff score = 48 (Yu, 2019 #3160)). No CS reported being caregivers.

A trained neuropsychologist (CA) who was blind to participant's status (O-LOAD versus CS) administered all neuropsychological tests. All participants performed within normal limits on all administered neuropsychological tests according to local norms. None of the participants exhibited subjective cognitive complaints nor met diagnostic criteria for dementia or mild cognitive impairment.

2.3. MRI T1 image acquisition

MRI images were acquired on a 3T GE Signa HDxt MRI machine with an eight-channel head coil. High resolution T1 3D fast SPGR-IR images were acquired. One hundred-sixty-six sagital contiguous slices were obtained in an acquisition matrix of 256 × 256, TR=7.256 ms, TE = 2.988 ms, flip angle 8°, FOV = 26 cm, and slice thickness of 1.2 mm (Duarte-Abritta et al., 2018).

2.4. Positron emission tomography data acquisition

Positron Emission Tomography (PET) acquisition was performed on a PET/CT General Electric 690. [^{11}C] PIB synthesis was carried out using a GE TRACERlab FXC PRO module, which produces ^{11}C-labeled radiochemicals from $^{11}CO_2$. The module includes HPLC, which allows isolation of the labeled product from radioactive by-products and organic impurities in a fast and efficient way. The HPLC was performed with 0.009 M sodium citrate ethanol/water (60/40) as a mobile phase with a flow rate of 3 mL/min and a reverse phase high performance liquid chromatographic column. Chromatograms were registered using a UV-detector and a radioactivity detector in series. The [^{11}C]-PIB peak was cut from the chromatographic system through a switching from waste to product line. The [^{11}C] PIB fraction (retention time, 11–12 min) was transferred to a flask and diluted with 30 mL of saline solution to reduce the ethanol percentage, resulting in a final total volume of 36 mL. Then, the PIB solution was fractionated and filtered under sterile conditions. The 10 mCi (adjusted for weight) were administered and the image acquisition was performed 50 min after the administration of [^{11}C] PIB. Finally, dynamic tomographic images in 3D mode were acquired after 20 min.

2.5. MRI T1 and pet image preprocessing

Cortical reconstruction was performed with the FreeSurfer image analysis program version 6 (http://surfer.nmr.mgh.harvard.edu/). In brief, the FreeSurfer pipeline consists of removal of non-cerebral tissue (Segonne et al., 2004) and performs Talairach transformation and segmentation of subcortical structures (Fischl et al., 2002, 2004), intensity normalization (Sled et al., 1998), topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the GM/WM and GM/cerebrospinal fluid borders at locations where the greatest shift in intensity defines the tissue class transition (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000).

Preprocessing was performed independently for each hemisphere. The surfaces obtained were carefully reviewed and manually edited as necessary to conform to the anatomically-determined limits. Finally, surface maps were smoothed.

Whole-brain cortical thickness was measured. Cortical thickness was calculated as the shortest distance between the GM/WM boundary and pial surface at each vertex across the cortex. Maps were created not only with absolute signal intensity but with spatial intensity gradients across tissue classes.

To map participant's brains to a common space and perform analysis within groups, the software registered all cortical thickness maps to a spherical atlas (Fischl et al., 1999) and created a variety of surface-based data (eg: thickness, curvature or area surfaces).

PET images were processed along with MRI volumetric T1 images. MRI T1 images were obtained and analyzed in FreeSurfer as described above. Analysis was performed using PETSurfer scripts, which briefly consisted of: (1) creation of a high-resolution segmentation used to run Partial Volume Correction (PVC) (Greve et al., 2016), (2) co-registration of PET and structural T1 images, and (3) application of the PVC method (Ewers et al., 2014; Kantarci et al., 2001; Knopman et al., 2014; Landau et al., 2011).

2.6. Data management and statistical analysis

All processed brain imaging data (cortical thickness and PIB-PET intensities) were downloaded from Freesurfer onto Excel spreadsheets, merged with clinical and neuropsychological performance information, and imported onto R software version 3.3.1. First, the Kolmogorov–Smirnov normality test was performed on all variables. For cognitive and clinical variables, descriptive analyses was performed for both O-LOAD participants and CS groups. *T*-tests were used for mean

comparisons of continuous, normally distributed data (age, education, BDI-II, MMSE and neuropsychological test scores). Means and standard deviations (SD) were computed. Chi-square analyses were conducted for categorical variables (sex). Results were considered significant at two-tailed $p<0.05$.

We next evaluated unadjusted and age-adjusted Pearson correlation coefficients among neuropsychological tasks and brain imaging measures for each group (O-LOAD and CS) separately. A surface-based analysis was carried out using the command-line group analysis stream in Freesurfer, which implements the General Linear Model (GLM). Multiple comparisons were corrected with a Monte Carlo Simulation using a cluster-wise $p<0.05$ and vertex-wise/cluster-forming threshold of $p<0.05$ for cortical thickness analysis and $p<0.001$ for PET-PiB analysis. *P*-values and Pearson's coefficient (r) maps were obtained.

Results were visualized by overlaying significant cortical areas onto semi-inflated cortical surfaces in which clusters in warm colors (red shades) represent positive correlations and clusters in cold colors (blue shades) represent inverse correlations. Color intensity parallels correlation strength. Along with these representations, augmented maps of Pearson's coefficients of these specific areas and their corresponding scatter plots were displayed and representative r values were highlighted in each figure.

3. Results

Demographic and neuropsychological characteristics of the sample are shown in Table 1. CS and O-LOAD were comparable in age, sex, years of education, estimated IQ, and depressive symptoms. As a group, CS performed better on the RAVLT delayed recall than O-LOAD.

Although both O-LOAD and CS were similar in age, since this variable is one of the main risk factors for LOAD (Hebert et al., 2013), we performed age-adjusted and unadjusted correlations, obtaining analogous results in both models (adjusted correlations not shown). Cortical thickness was associated with EF performance in O-LOAD participants but not in CS (Figs. 1-3). Better performance in Design Fluency trial 1 ($D = 0.110$, $p = 0.488$) and Stroop ($D = 0.077$, $p = 0.941$) were associated with greater cortical thickness on the left lateral orbitofrontal cortex ($D = 0.080$, $p = 0.903$) (Fig. 1), and on the right rostral mid-frontal cortex ($D = 0.130$, $p = 0.256$) (Fig. 2) respectively. Left medial orbitofrontal cortex thickness ($D = 0.120$, $p = 0.463$) was associated with a longer time to complete the TMT-B (worse performance) ($D = 0.132$, $p = 0.313$) (Fig. 3).

β-Amyloid deposits in the right precuneus ($D = 0.150$, $p = 0.193$) were associated with a longer TOL total time (worse performance) ($D = 0.132$, $p = 0.372$) (Fig. 4).

Table 1
Demographic and clinical data of Argentine offspring of late-onset Alzheimer's disease (O-LOAD) participants and control subjects (CS).

	CS Mean or frequency ($N = 25$)	SD or %	O-LOAD Mean or frequency ($N = 30$)	SD or%	*p*-value
Female	21	84%	20	66,67%	0.142
Age (years)	51	7.6	54.4	7	0.091
Education (years)	17.6	2.7	17.4	3	0.813
Estimated IQ	107.4	6.4	105.3	6.3	0.233
BDI-II	8.1	7.5	8.9	6.6	0.676
RAVLT L	47.6	8.6	43.6	7.2	0.069
RAVLT D	10.3	2	8.5	3.0	**0.011**
RAVLT R	13.96	1.17	13	1.94	0.031
TMT-B (seconds)	67.2	18.2	71.9	19.4	0.380
Design Fluency trial 1	11.5	3.1	11.4	3.7	0.891
Design Fluency trial 2	13	3.5	12.1	3.4	0.354
Design Fluency trial 3	7.9	2.2	7.5	2	0.459
TOL Initiation Time (seconds)	57.3	32.4	76.2	44	0.109
TOL Execution Time (seconds)	221.8	87.3	255	113.7	0.227
TOL Total Time (seconds)	279.1	104.2	325.3	135.4	0.205
Stroop Index	2.9	7.9	3.0	6.3	0.938

*BDI-II: Beck's Depression Inventory, second edition; RAVLT L: Rey Auditory Verbal Learning Test, total learning; RAVLT D: Rey Auditory Verbal Learning Test, delayed recall; RAVLT R: Rey Auditory Verbal Learning, recognition; Test TMT-B: Trail Making Test, part B; TOL: Tower of London. Comparisons surviving FDR correction are marked in **bold.**

4. Discussion

The present study showcases associations between structural brain imaging outcomes and neuropsychological performance for the first time in an Argentine sample of adults with and without a family history of LOAD. Our findings were significant only for O-LOAD and are in line with the literature. First, we observed a positive association between cortical thickness and Design Fluency trial 1 specifically in the orbitofrontal cortex, a brain region that is strongly associated with executive functioning. Second, we observed a positive correlation between cortical thickness and Stroop score, and an inverse correlation between cortical thickness and TMT-B. Third, amyloid deposits in the precuneus were

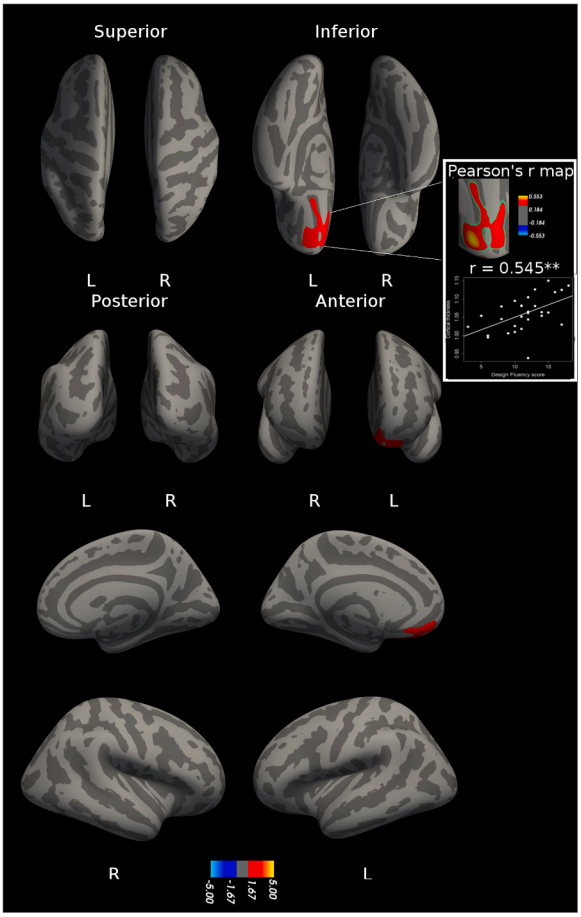

Fig. 1. Correlation between cortical thickness and Design Fluency trial 1 score in the O-LOAD group. Clusters in warm colors represent a positive correlation with the left lateral orbitofrontal cortex, the color bar at the bottom corresponds to -log(p) at $p<0.05$, followed by Monte Carlo correction. Augmented maps of Pearson's coefficients (r) of the specific area and its corresponding scatter plot are displayed, as well as a representative r value. Significance is exhibited as *$p<0.05$, **$p<0.01$, ***$p<0.005$).

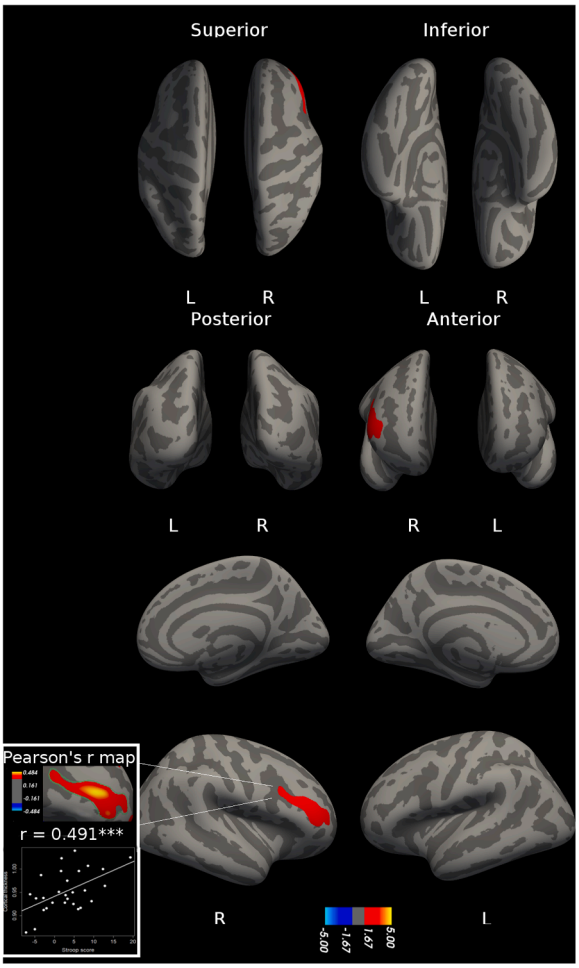

Fig. 2. Correlation between cortical thickness and Stroop score in the O-LOAD group. Clusters in warm colors represent a positive correlation with the right rostral mid-frontal cortex, the color bar at the bottom corresponds to -log (p) at $p<0.05$, followed by Monte Carlo correction. Augmented maps of Pearson's coefficients (r) of the specific area and its corresponding scatter plot are displayed, as well as a representative r value. Significance is exhibited as $*p<0.05$, $**p<0.01$, $***p<0.005$).

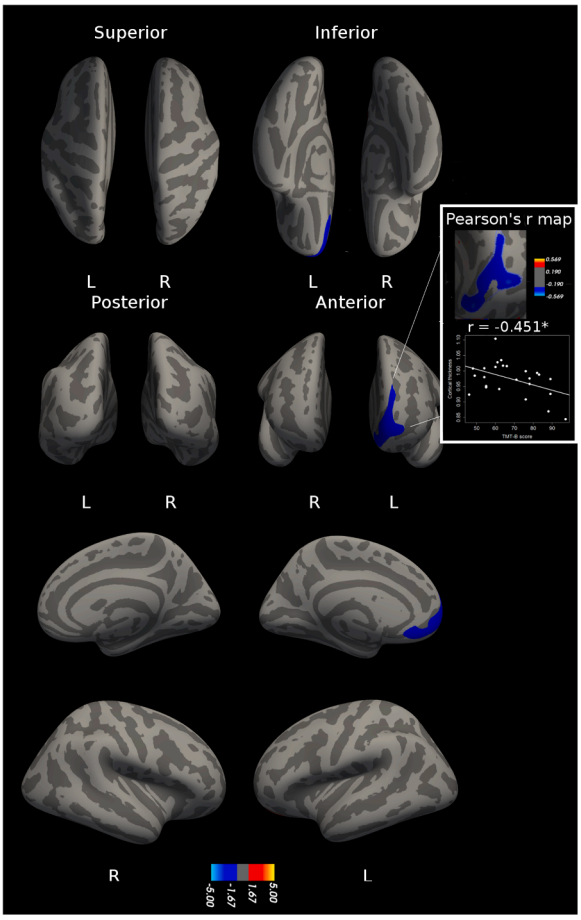

Fig. 3. Correlation between cortical thickness and TMT-B score in the O-LOAD group. Clusters in cold colors indicate an inverse correlation with the left medial orbitofrontal cortex, the color bar at the bottom corresponds to -log(p) with $p < 0.05$, followed by Monte Carlo correction. Augmented maps of Pearson's coefficients (r) of the specific area and its corresponding scatter plot are displayed, as well as a representative r value. Significance is exhibited as $*p<0.05$, $**p<0.01$, $***p<0.005$).

associated with worse EF. All these findings were observed only in the O-LOAD group, which further support for EF assessment as a sensitive tool in the early detection of LOAD-related changes in cognition.

Several studies show that executive control relies on three fronto-subcortical circuits: the dorsolateral prefrontal cortex, lateral orbital cortex and anterior cingulate cortex, which underlie working memory, inhibition, and response conflict processes (Cabeza and Nyberg, 2000; Cummings, 1993). The vast majority of studies focusing on brain correlates of fluency performance involve patients with focal lesions (Fama et al., 2000). Overall, these studies report a relationship between design fluency and orbitofrontal cortex (Baldo et al., 2001; Kolb and Whishaw, 2009). Fewer studies have investigated the brain-behavior correlates of design fluency performance in patients with widespread or multifocal brain dysfunction, such as Fama et al. (2000), who reported associations with frontal lobe gray matter volumes in LOAD. Another group focused on MCI patients found that bilateral superior frontal gyri and the right inferior frontal girus predicted design fluency performance (Peter et al., 2016). In line with these results, our findings show an association between cortical thickness and Design Fluency trial 1, specifically in the orbitofrontal cortex in O-LOAD. We also observed an inverse correlation between cortical thickness of the left medial orbitofrontal cortex and the TMT-B. Some authors suggest that lateral prefrontal cortex, particularly the left hemisphere, plays an important role in TMT-B in MCI and LOAD patients (Stuss et al., 2001; Yochim et al., 2007). A previous work on functional connectivity from our group supports the present findings. In Sanchez et al. (2017) we reported that the same O-LOAD group exhibited lower overall connectivity of the entorhinal cortex, specifically with the medial orbitofrontal cortex, when compared to CS. Together, structural and functional analysis evidence changes associated to this brain area, only in subjects with increased risk of developing LOAD. The fact that similar results were found in a young, healthy population at risk of LOAD represents an important contribution to the literature on the detection of early, subtle brain changes in potentially preclinical stages of the LOAD continuum.

The Stroop is a test of cognitive interference widely used in LOAD research (MacLeod, 1991; Stroop, 1935). Both structural and functional studies report associations between the Stroop and fronto-parietal areas such as anterior cingulate cortex, dorsolateral prefrontal cortex, inferior frontal gyrus, inferior and superior parietal cortex and insula (Laird et al., 2005; Roberts et al., 1998; Vasconcelos et al., 2014). Our results show that cortical thickness in right rostral mid-frontal cortex correlated positively with Stroop score only in O-LOAD, which reflects a greater susceptibility to interference in this group. In Sanchez et al. (2017) we studied the association between interference effect and functional connectivity and found that poorer performance on measures related to proactive interference in O-LOAD correlated with lower connectivity in a rather extensive network involving limbic structures, prefrontal

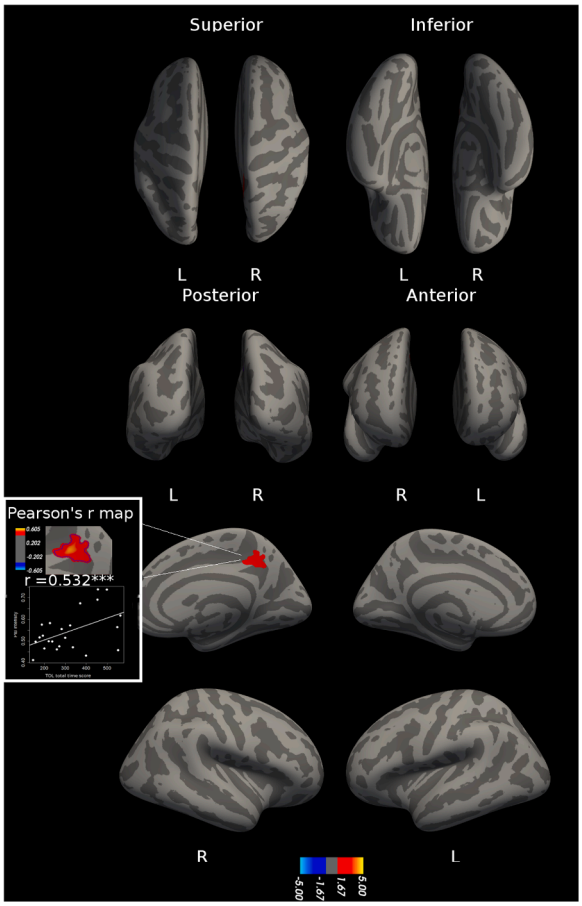

Fig. 4. Correlation between *β*-Amyloid deposits and TOL total time score in O-LOAD participants. Clusters in warm colors represent a positive correlation with the right precuneus. The color bar at the bottom corresponds to -log (p) at $p<0.01$, followed by Monte Carlo correction. Augmented maps of Pearson's coefficients (r) of the specific area and its corresponding scatter plot are displayed, as well as a representative r value. Significance is exhibited as $*p<0.05$, $**p<0.01$, $***p<0.005$).

neocortex and middle frontal gyrus. These functional results align with our current structural findings, supporting the sensitivity of interference measures for detection of frontal impairment within the LOAD continuum (Kang et al., 2019a).

The TOL has been widely used as a test of planning and problem-solving abilities in both clinical and healthy populations. Participants are asked to mentally plan a sequence of movements to match an initial set of discs to a target, and then manually execute the movements one by one (Culbertson and Zillmer, 2001). In our study, a positive correlation between amyloid deposition and TOL total time in an area associated with task performance like the precuneus was found. This association could be reflecting a worse performance (e.g., participants require longer time to complete the task) in O-LOAD. Similar results for initiation time and a difference in the execution time were also observed (data not shown). The precuneus has a leading role in the performance of high-order cognitive tasks. It influences an extensive network of cortical and subcortical structures involved in the generation of highly integrated and associative information, in addition to being strongly connected with the prefrontal cortex and multiple parietal areas related to the processing of visuospatial information and visual guidance of hand movement (Cavanna and Trimble, 2006).

Although, amyloid deposition in the precuneus occurs relatively early in LOAD (Aghakhanyan et al., 2018; Insel et al., 2020; Palmqvist et al., 2017), a prior study of our group on the same sample did not show significant differences between groups in amyloid deposition in the precuneus (Duarte-Abritta et al., 2018). These findings along with our present results suggest that there might be *some* change linked to amyloid deposition in O-LOAD underlying their association with executive functioning, yet this change might be still too subtle to manifest as significantly different from CS amyloid load.

In absence of clinically significant cortical atrophy (reported in (Duarte-Abritta, 2018), differences between groups related to cortical thickness are deemed as subtle, subclinical. One possible explanation for these reductions in gray matter thickness and their relationship to poorer cognitive performance could be underlying neuroinflammatory processes in subjects at risk of developing LOAD (Jefferson et al., 2007). According to the literature, cognitive deficits in LOAD can be directly related to changes in functional connectivity, which is mediated by microglia activation (Passamonti et al., 2019). Although neuroinflammation is mostly associated with elderly and/or clinical populations, it has been reported to drive gray matter loss and cognitive performance reduction even in healthy, middle-aged subjects (Marsland et al., 2015). Additionally, neuroinflammation has been associated with tau neurofibrillary tangles (tau) production (Metcalfe and Figueiredo-Pereira, 2010) – one of the earliest biomarkers of LOAD –, present several decades before disease onset (Braak and Braak, 1991), during which time it causes a number of alterations in the normal functioning of the neuron (Walsh et al., 2017). Tau production displays a progression curve very similar to that of cognitive decline in LOAD (Braak and Del Tredici, 2011; Walsh et al., 2017).

4.1. *Strengths and limitations*

The present study has both strengths and limitations. Among its strengths are the uses of cutting-edge brain imaging techniques and rigorous neuropsychological testing in a sample of Argentine adults who are underrepresented in the literature. Regarding limitations, the sample size used in this study is rather small and relatively homogeneous with regard to ethnicity, geographical area, culture, and years of education. Therefore, additional studies with larger, more diverse samples should be performed to confirm the present results. All participants have high educational level attainment, having completed at least 12 years of education, which is uncommon in Argentina (sample`s education level = 17.5 years, Argentina`s average education level = 11.2 years) (Tuñon, 2020). Higher levels of education may reflect higher levels of cognitive reserve, which could prevent the manifestation of subtle preclinical changes compared to those with lower cognitive reserve (Sperling et al., 2011). Due the absence of a postmortem diagnosis confirmation of the parents from the O-LOAD group it is possible that some participants whose parents had neurodegenerative dementias with LOAD-like symptoms but of different etiology were included. Moreover, it is also possible that some of the participants with no family history of LOAD have parents who might eventually develop LOAD. Inclusion of such participants may have reduced the sensitivity of our analyses. Furthermore, due to the cross-sectional nature of this study, we are unable to comment on causality. These findings need to be confirmed and expanded upon in future longitudinal studies of Argentine O-LOAD and CS. Nonetheless, the current results have significant implications for understanding the earliest pathogenesis of LOAD and is worthy of further research.

4.2. Conclusion

Our results have implications for understanding the earliest subtle changes in persons at risk for LOAD in Argentine adults. These data provide valuable support to current efforts directed toward the development of very early detection techniques for individuals at risk of developing LOAD and suggests that executive function alterations deserve further exploration in the LOAD literature.

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CRediT authorship contribution statement

Bárbara Duarte-Abritta: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Visualization. **Stella-Maris Sánchez:** Conceptualization, Software, Formal analysis, Visualization. **Carolina Abulafia:** Conceptualization, Formal analysis, Investigation. **Deborah R. Gustafson:** Conceptualization, Supervision. **Silvia Vázquez:** Investigation. **Gustavo Sevlever:** Resources. **Mariana N. Castro:** Investigation. **Leticia Fiorentini:** Supervision. **Mirta F. Villarreal:** Conceptualization, Methodology, Writing – original draft, Funding acquisition. **Salvador M. Guinjoan:** Conceptualization, Writing – original draft, Funding acquisition.

Declaration of Competing Interest

All authors declare they have no conflict of interest to disclose in relation to this publication.

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