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ORIGINAL COMMUNICATION

Mapping the neuroanatomy of functional decline in Alzheimer's disease from basic to advanced activities of daily living

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Abstract

Background Impairments in activities of daily living (ADL) are a criterion for Alzheimer's disease (AD) dementia. However, ADL gradually decline in AD, impacting on advanced (a-ADL, complex interpersonal or social functioning), instrumental (IADL, maintaining life in community), and finally basic functions (BADL, activities related to physiological and self-maintenance needs). Information and communication technologies (ICT) have become an increasingly important aspect of daily functioning. Yet, the links of ADL, ICT, and neuropathology of AD dementia are poorly understood. Such knowledge is critical as it can provide biomarker evidence of functional decline in AD.

Methods ADL were evaluated with the Technology–Activities of Daily Living Questionnaire (T-ADLQ) in 33 patients with AD and 30 controls. ADL were divided in BADL, IADL, and a-ADL. The three domain subscores were covaried against gray matter atrophy via voxel-based morphometry.

Results Our results showed that three domain subscores of ADL correlate with several brain structures, with a varying degree of overlap between them. BADL score correlated mostly with frontal atrophy, IADL with more widespread frontal, temporal and occipital atrophy and a-ADL with occipital and temporal atrophy. Finally, ICT subscale was associated with atrophy in the precuneus.

Conclusions The association between ADL domains and neurodegeneration in AD follows a traceable neuropathological pathway which involves different neural networks. This the first evidence of ADL phenotypes in AD characterised by specific patterns of functional decline and well-defined neuropathological changes. The identification of such phenotypes can yield functional biomarkers for dementias such as AD.

Keywords Alzheimer's disease · Functional impairment · Activities of daily living · Technology–activities of daily living questionnaire

Background

Alzheimer's disease (AD) is one of the most common form of age-related dementia, affecting more than 25 million people worldwide, with the number of new cases raising continuously, both in developed and developing countries [1, 2]. The diagnosis of dementia due to AD is based on the presence of a gradual onset of cognitive impairment, mainly an episodic memory impairment with evidence of cognitive dysfunction in at least one other cognitive domain, whose severity has led to a significant functional decline in activities of daily living (AD), interfere with the ability to function at work or at usual activities [3].

The confirmation of the presence and severity of impairment in ADL is critical for the diagnosis of dementia [3]. Commonly, ADL have been divided in basic ADL (BADL) and instrumental ADL (IADL). BADL are defined as activities related to basic physiological and self-maintenance needs, including tasks such as eating, toileting or getting dressed.

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IADL include activities, essential to maintain independent living and maintaining life in community, such as managing finances, shopping, handle medications or using the public transport [4, 5]. Recently, advanced ADL (a-ADL) has emerged as an additional important category in ADL [5, 6]. a-ADL are defined as more complex activities, not being essential to maintain an independent life, are considered voluntary [7] and include activities necessary for complex interpersonal or social functioning such as using household technology, going on holidays, practice hobbies, etc. [4, 6, 8]. a-ADL that require higher levels of cognitive, physical, and social functions, are very sensitive to subtle cognitive impairment and could contribute to early diagnosis of dementia [4]. Nonetheless, the definition of a-ADL and its division from IADL is complex and need to consider cultural variability, since ADL performance is influenced by cultural events [9–12]. Moreover, as culture evolves, any scale that is sensitive to early ADL deficits must also evolve to measure newly relevant activities.

In the last decades, information and communication technologies (ICT) have become an increasingly important aspect of daily functioning and the use of electronic devices are essential in different everyday life tasks, such as communication, work or recreational activities. The use of everyday technology may be of particular concern in people with dementia because most patients typically continue to live at home, in the same social context as before the disability and, as a result, they are expected to manage the everyday technology that is common in that context [13]. ICT could include either IADL or a-ADL depending on the complexity of the technology and sociocultural factors shaping technology use [6, 14].

Despite recent advances in the development of ADL scales, the relationship between those outcomes and structural brain changes in AD is poorly understood, especially considering the neural correlates of IADL or BADL. BADL dysfunction in AD was associated with atrophy in the temporal, cingulate, hippocampus, caudate, frontal, and parietal regions, whereas IADL dysfunction was linked to atrophy in the frontal, temporal, parietal, insula, and caudate regions [15]. Hippocampal and cortical gray matter volume loss was associated with rapid IADL decline in AD [16]. Parietal and temporal lobe atrophy at baseline predict further IADL impairment over time [17]. Complementary, PET studies have reported an association between greater rate of IADL impairment over time and middle frontal, orbitofrontal and posterior cingulate hypometabolism in AD [18].

However, to our knowledge, there is no study investigating the neural correlates of a-ADL. Nor is their evidence that such correlates differ from those reported for BADL and IADL. Moreover, no study has incorporated ICT as an important aspect of functional assessment. The aim of this study was to investigate the neural correlates of the global score and subscores of the Technology–Activities of Daily Living Questionnaire (T-ADLQ) in patients with AD in comparison to healthy controls (HC). Specifically, we examined which brain areas were associated with a-ADL impairment in AD in comparison with BADL and IADL scores. In a first step, total T-ADLQ scores, BADL, IADL and a-ADL subscores were regressed against gray matter atrophy via voxel-based morphometry (VBM). In a second step, we performed an inclusive masking analysis to verify which areas of brain atrophy would overlap between BADL and a-ADL, and between IADL and a-ADL. Finally, we performed an exclusive masking analysis to verify areas of brain atrophy displaying no overlap between BADL, a-ADL, and IADL. We hypothesized that these three ADL domains would exhibit shared and segregated neuroanatomical substrates and that a-ADL would be associated to regions involved in more complex cognitive tasks.

Methods

Participants

A cohort comprising 63 participants was recruited for the study. This cohort was divided into two groups matched according to sex, age, and years of education: 33 subjects with a clinical diagnosis of AD and 30 healthy controls (HC). Patients were recruited from the Memory and Neuropsychiatric Clinic at Hospital del Salvador, and the Neurology and Neurosurgery Department at Hospital Clínico Universidad de Chile (HCUCH), both located in Santiago, Chile. HC were recruited from a variety of sources, including spouses or relatives of patients with dementia. The inclusion criteria considered Spanish-speaking participants older than 60 years of age. All participants required a reliable proxy who had known them for at least 5 years. Specifically, a proxy was someone who was able to provide information about ADL performance, behavioral changes, and patients' general medical history. The exclusion criteria included illiteracy, underlying neurological or psychiatric illness that could affect cognition (except AD), physical disability, and sensory disturbance that could interfere with the neuropsychological assessment. All AD patients met the NINCDS-ADRDA criteria for probable AD [3]. Diagnosis was made by consensus between senior neurologists (AS and CD) based on extensive clinical protocol, interviews with a reliable proxy, laboratory tests and global cognitive functioning. Briefly, AD patients displayed a history of significant episodic memory loss, within the context of preserved behavioral and personality, and scored above 0.5 on the Clinical Dementia Rating scale (CDR) [3]. HC did not report memory complaints, had a score of 0 on the CDR [3], and their cognitive performance was considered normal

according to local normative data for the Addenbrooke's Cognitive Examination—Revised Chilean Version (ACE-R-Ch) (> 76) [19]. Scores of the T-ADQL were not considered to establish the diagnosis. Ethical approval for this study was obtained from the Ethical and Scientific Committees of the East Metropolitan Health Service and the HCUCH. All the participants, and their caregivers, provided informed consent in accordance with the Declaration of Helsinki.

Clinical and neuropsychological examination

All proxies and participants were interviewed separately to obtain the CDR scores. The T-ADLQ was completed by proxies as we have previously described [20]. Experienced clinical psychologists trained in the administration of our neuropsychological protocol and blinded to the diagnosis of each subject carried out the neuropsychological assessment. In addition to the MMSE [21], and the ACE-R-Ch [19] to assess global cognitive functioning, the neuropsychological protocol included The Boston Naming Test as an index of naming abilities. The Rey-Osterrieth Complex Figure Test was used to measured visuospatial constructional abilities [22]. Forward and backward digit-span tasks provided an index of working memory while the Word Free and Cued Selective Reminding Test (FCSRT) was used to assess episodic memory. The Frontal Assessment Battery (FAB), which is a screening test for executive dysfunction that assesses conceptualization, mental flexibility, motor programming, resistance to interference, inhibitory control, and environmental autonomy, was also applied [23]. Other tests of executive functions (EF) included the Modified Version of the Wisconsin Card Sorting Test (MCST) [24], which informs on cognitive flexibility, verbal fluency tests including both Phonemic Verbal Fluency test (i.e., words beginning with letters F, A, and S in 1 min) and Semantic Fluency test (i.e., animals in 1 min) and the Trail Making Test A and B [25, 26].

T-ADLQ

The T-ADLQ [20] consists of seven subscales: self-care, household care, employment and recreation, shopping and money, travel, communication and ICT. Each item is rated on a four-point scale. For each activity, a rating is provided for instances in which the patient may have never performed that activity in the past, stopped the activity prior to the onset of dementia, or for which the proxy did not have information [27].The overall functional impairment (FI) was calculated for each domain as well as for the global questionnaire as follows: (sum of all ratings not rated ND/DK)/ (3 × total number of items not rated ND/DK). The denominator represents the score that would have been obtained if the most severe level of impairment had been indicated for all items rated not ND/DK [27]. This equation ensures that the functional impairment score was based on the actual functioning of the patients relative to their own premorbid functioning. Higher percentage scores indicate greater deterioration.

An expert panel (two neurologists, three psychologists, one occupational therapist) gathered the activities of the T-ADLQ in three domains (BADL—IADL—a-ADL). To ensure consistency of the division, each expert classified each activity independently and then a consensus was reached to harmonize the different classifications. The outcomes from the consensus classification are presented in Table 1.

Statistical analyses for demographic and neuropsychological data

The Statistical Package for the Social Sciences (SPSS) version 20 for Windows (IBM Corp., Armonk, NY, USA) was used to analyze the demographic and neuropsychological data. We obtained descriptive statistics for such data, used Chi-squared for the categorical variables, and performed two-tailed independent-sample *t* tests for the comparisons between AD and HC. Differences with a $p < 0.05$

Table 1 Division of the three domains of the Technology—Activities of Daily Living Questionnaire (T-ADLQ)

Basic ADL	Instrumental ADL	Advanced ADL
Eating	Taking pills or medicine	Employment
Dressing	Handling cash	Recreation
Bathing	Managing finances	Organization
Elimination	Public transportation	Travel
Interest in personal appearance	Driving	Internet access
	Mobility around the neighborhood	Email access
	Traveling outside familiar environment	Computer use
	Preparing meals, cooking	
	Setting the table	
	Housekeeping	
	Home maintenance	
	Home repair	
	Laundry	
	Food shopping	
	Using the telephone	
	Talking	
	Understanding	
	Reading	
	Writing	
	Cell phone use	
	ATM use	

The T-ADLQ scale is presented in supplementary files

were considered significant. Additionally, the effect sizes (Cohen's-*d* statistic) were calculated to determine the magnitude of the group differences. According to Cohen, effect sizes between 0.2 and 0.49 are considered small; those between 0.5 and 0.79, moderate; and those 0.8, large [28].

MRI acquisition

MRI acquisition was performed in two 1.5 T MRI scanners, a Philips Intera Nova Dual gradient system (45mT/m), and a Siemens Symphony Maestro Class (Erlangen, Germany) with 20 mT/m gradient system. High resolution anatomical scans were obtained using a T1-weighted three dimensional gradient recalled echo acquisition: 3D T1 fast field echo sequence on Philips scanner, and 3D T1 fast low angle shot on Siemens scanner, both with the same acquisition parameters (TE = 4.6 ms, TR = 25 ms; flip angle = 30°, field of view on frequency = 250 mm, 256 × 256 matrix, isotropic voxel size 1 × 1 × 1 mm).

VBM analysis

MRI data were analyzed with FSL-VBM, a (Voxel-based Morphometry) VBM analysis [29, 30] that is part of the FSL software package (http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html) [31]. First, tissue segmentation was carried out using FMRIB's automatic segmentation tool (FAST) from brain-extracted images [32]. The resulting grey matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MNI152) using the nonlinear registration approach using FNIRT [33] which uses a b-spline representation of the registration warp field [34]. A study-specific template was created, combining AD and HC images, to which the native gray matter images were re-registered nonlinearly. The registered partial volume maps were then modulated (to correct for local expansion or contraction), by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm (FWHM: 8 mm).

The statistical analysis was performed via a voxel wise general linear model (GLM) to investigate gray matter intensity differences. Permutation-based nonparametric testing (with 5000 permutations per contrast) [35] was used to form clusters with the threshold-free cluster enhancement (TFCE) method [31]. The significance threshold was $p < 0.05$ and tests were corrected for multiple comparisons via Family-wise Error (FWE) correction across space, unless otherwise stated. For uncorrected results, a threshold of 100 contiguous voxels was used, at $p < 0.001$ to reduce the likelihood of significant clusters. Regions of significant atrophy were superimposed on the MNI standard brain, with maximum coordinates provided in MNI space. Areas of significant gray matter loss were localized with reference to the Harvard-Oxford probabilistic cortical and subcortical atlas.

In a first step, differences in gray matter intensities between AD patients and HC were assessed. To control for a possible scanner site effect, we introduced scanner site as a nuisance covariate for the group contrasts. Next, correlations between gray matter atrophy and T-ADLQ total score and the scores of the three domains of the T-ADLQ, i.e., BADL, IADL and a-ADL subscores, were entered as covariates in the design matrix of the VBM analysis for AD patients combined with HC. This procedure improves the statistical power to detect brain-behavior relationships [36]. In a third step, we explored the overlap of brain atrophy between the BADL, IADL and a-ADL subscores performing an inclusive masking analysis. For statistical power, a covariate-only statistical model with a t-contrast was used, providing an index of association between brain atrophy and scores on the functional scales. The statistical maps generated from the contrast using BADL, IADL and a-ADL subscores as covariate, were scaled using a threshold of $p < 0.001$, following which, the scaled contrasts were multiplied to create an inclusive, or overlap, mask across groups. In a fourth step, we performed a contrast analysis between the three subscores BADL, IADL and a-ADL subscores of the T-ADLQ to study the existence of significant anatomical differences between the different domains. For the exclusive masks, the same procedure described above was adopted. However, the scaled images were subsequently subtracted from each other, to create an exclusive mask for each condition.

Result

Demographic and neuropsychological data

Demographic and neuropsychological scores are shown in Table 2. AD and HC groups did not differ in terms of sex, age, or education (all $p > 0.05$). In brief, AD patients exhibited scores significantly higher on assessments of severity of the disease (CDR) and lower on measures of global cognitive efficiency (ACE-R-Ch and MMSE) and episodic memory (FCSRT) relative to HC. Compared to the HC group, the AD group was impaired on the global scores of T-ADLQ [F (1,67) = 70.981, $p < 0.001$]; the three ADL domains and the ICT subscores (see Table 2) The details of the neuropsychological battery in HC and AD subjects are shown in Supplementary Table 1.

VBM: groups comparison analysis

Results are shown in Table 3 and Fig. 1. The AD group was contrasted with HC group to reveal patterns of brain atrophy. The AD group showed significant grey matter atrophy

Table 2 Demographic, global cognitive, and functional characteristics of AD and HC

	AD	Control	*t* test/χ^2	Effect size (Cohen's *d*)	95% CI	
					Lower	Upper
N	33	29				
Sex (m:f)	13:20	9:20	0.492			
Age (years)	73.09 ± 6.96	72.03 ± 5.99	0.636	0.163	− 2.265	4.378
Education (years)	12.21 ± 4.45	12.59 ± 3.73	− 0.356	− 0.092	− 2.476	1.728
MMSE	20.79 ± 4.88 (30)	28.07 ± 1.67 (30)	− 7.648**	− 1.996	− 9.185	− 5.377
ACE-R	62.24 ± 15.64 (100)	92.55 ± 5.60 (100)	− 9.887**	− 2.580	− 36.441	− 24.177
CDR	1.66 ± 0.65 (3)	0 ± 00 (3)	13.648**	3.611	1.413	1.899
CDR-SB	5.84 ± 2.82 (18)	0 ± 00 (18)	11.157**	2.928	4.796	6.892
CDR-AlG	1.13 ± 0.83 (3)	0 ± 00 (3)	7.269**	1.925	0.815	1.435
T-ADLQ (%) Total	38.00 ± 16.96 (100)	8.41 ± 8.90 (100)	8.425**	2.184	22.562	36.611
BADL domain subscore of the T-ADLQ (%)	5.70 ± 11.56 (100)	0.93 ± 2.94 (100)	2.158*	0.565	0.347	9.184
IADL domain subscore of the T-ADLQ (%)	43.73 ± 19.39 (100)	7.79 ± 10.23 (100)	8.939**	2.318	27.893	43.975
a-ADL domain of the T-ADLQ (%)	52.33 ± 22.00 (100)	19.76 ± 19.85 (100)	6.087**	1.554	21.869	43.280

Data are presented in mean ± standard deviation (total score)

AD Alzheimer's diseases, *CDR* clinical dementia rating, *CDR-SB* clinical dementia rating—sum of box, *CDR-AlG* clinical dementia rating—algorithm, *MMSE* mini-mental state examination, *ACE-R* Addenbrooke's cognitive examination revised, *MoCA* Montreal cognitive assessment, *T-ADLQ* technology of daily living questionnaire, *BADL* basic activities of daily life, *IADL* instrumental ADL, *a-ADL* advanced activities of daily life

*$p < 0.05$, **$p < 0.001$

Table 3 VBM showing significant gray matter intensity decrease in AD in contrast HC uncorrected by scanner

Regions	Hemisphere	MNI coordinates			Number of voxel
		x	*y*	*z*	
Hippocampus	Left	− 24	− 34	− 10	1513
Hippocampus	Right	24	− 36	− 8	1155
Precentral gyrus	Left	− 38	0	28	122
Precuneus cortex	Right	16	− 64	32	119
Inferior frontal gyrus, par opercularis/precentral gyrus	Right	36	8	26	117
Inferior temporal gyrus/temporal fusiform cortex, posterior division	Right	44	− 14	− 30	111

All results corrected for multiple comparisons (family-wise error) at $p < 0.05$; only cluster with at least 100 contiguous voxels included

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in bilateral hippocampal brain regions, bilateral precentral gyrus, and a right lateralized atrophy in the precuneus cortex, inferior frontal gyrus (par opercularis), inferior temporal gyrus, and temporal fusiform cortex (posterior division) ($P_{\text{fwecorr}} < 0.05$). Similar results were obtained in the analysis covarying for scanner site (see Supplementary Table 2 and Supplementary Figure 1).

Correlations with T-ADLQ subscores

VBM correlations with T-ADLQ total score are presented in supplementary files (see Supplementary Table 3 and Supplementary Figure 2). In brief, T-ADLQ total score covaried with bilateral atrophy in the parahippocampal gyrus (anterior division) and the inferior temporal gyrus (posterior division and temporo-occipital region), and a right lateralized atrophy in the lateral occipital cortex (inferior and superior division) ($p_{\text{unorr}} < 0.001$).

BADL, IADL and a-ADL subscores of the T-ADLQ were entered as covariate in the design matrix of the VBM analysis. Results are shown in Table 4 and Fig. 2. For the AD group, the score on the BADL domain covaried with atrophy in the left supplementary motor cortex and right frontal regions (orbital cortex and superior/middle frontal gyrus) ($p_{\text{unorr}} < 0.001$). The IADL subscore covaried with atrophy in several areas widely distributed, highlighting the left

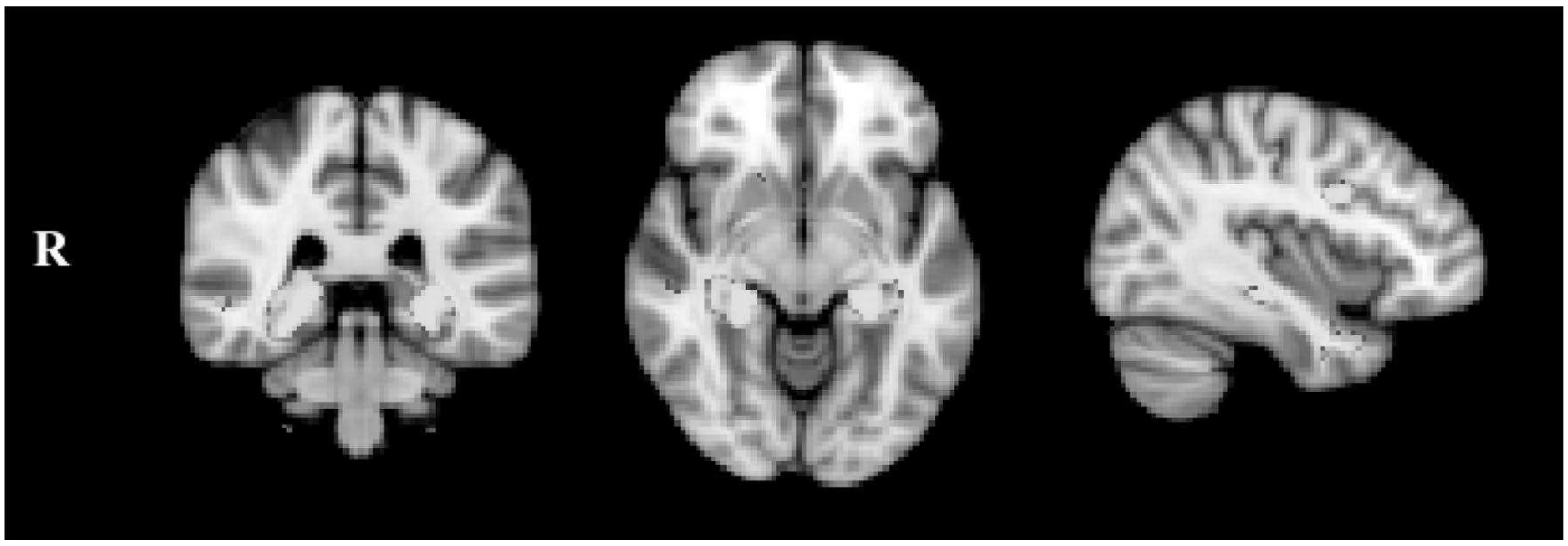

Fig. 1 VBM showing significant gray matter intensity decrease in AD in contrast HC uncorrected by scanner. VBM analysis showing brain areas of decreased gray matter intensity in AD patients in comparison with controls (MNI coordinates $X=-38$; $Y=-36$; $Z=-8$). Colored voxel show regions that were significant in the analysis with $p<0.05$ corrected for multiple comparisons (family-wise error), with a cluster threshold of 100 contiguous voxels. Clusters are overlaid on the MNI standard brain

Table 4 VBM correlation with T-ADLQ subscores in AD in comparison with HC uncorrected by scanner

Regions	Hemisphere	MNI coordinates			Numberof voxel
		x BADL	*y* IADL	*z* a-ADL	
BADL domain subscore					
Supplementary motor cortex	Left	−14	6	50	274
Frontal orbital cortex	Right	32	28	0	260
Superior frontal gyrus/middle frontal gyrus	Right	24	26	44	139
IADL domain subscore					
Para cingulate gyrus	Left	−4	34	26	3363
Temporal fusiform cortex, anterior division	Right	32	−2	−40	1936
Temporal fusiform cortex/parahippocampal gyrus, anterior division	Left	−28	−10	−38	1418
Intracalcarine cortex	Right	8	−66	12	836
Frontal operculum cortex/central opercular córtex	Right	42	10	10	512
Parahippocampal gyrus, posterior division/temporal fusiform cortex, posterior division	Left	−32	−34	−16	379
Intracalcarine cortex	Left	−12	−70	10	191
Precentral gyrus	Left	−38	0	22	185
Lateral occipital cortex, inferior division	Right	34	−78	10	146
Lingual gyrus/occipital fusiform gyrus	Right	20	−74	−6	107
Superior parietal lobule/angular gyrus	Right	32	−50	42	101
a-ADL domain subscore					
Lingual gyrus/intracalcarine cortex	Left	−14	−62	4	1379
Parahippocampal gyrus, anterior division	Left	−24	−10	−38	1169
Parahippocampal gyrus, anterior division	Right	30	−14	−28	732
Paracingulate gyrus	Left	−12	28	32	324
Superior frontal gyrus	Right	12	10	58	175
Superior frontal gyrus	Left	−18	8	46	131
Paracingulate gyrus/superior frontal gyrus	Right	12	30	40	107
Paracingulate gyrus	Right	4	26	40	106

BADL basic ADL, *IADL* instrumental ADL, *a-ADL* advanced ADL, *MNI* Montreal Neurological Institute

All results uncorrected at $p<0.001$. Only cluster with at least 100 contiguous voxels included

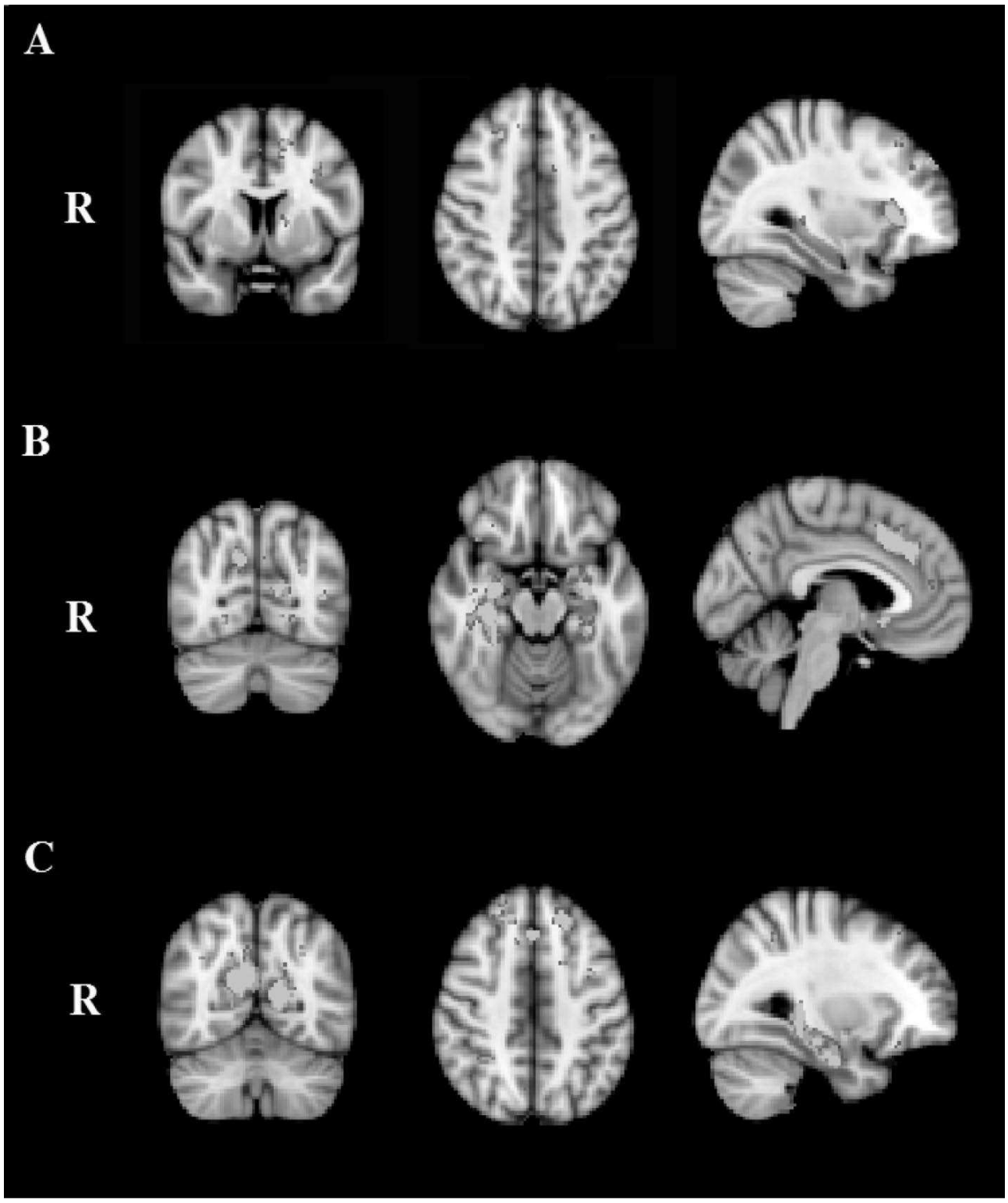

Fig. 2 VBM correlations with T-ADLQ subscores in AD in comparison with HC uncorrected by scanner. VBM analysis showing brain areas in which gray matter intensity correlates significantly with T-ADLQ subscores respectively: **a** BADL (MNI coordinates $X=32$; $Y=6$; $Z=44$), **b** IADL (MNI coordinates $X=-4$; $Y=-70$; $Z=-16$) and **c** a-ADL subscores (MNI coordinates $X=30$; $Y=-62$; $Z=46$) in AD in comparison with HC. Colored voxel show regions that were significant in the analysis with $p<0.001$ uncorrected. For all analysis, a cluster threshold of 100 contiguous voxels was used. Clusters are overlaid on the MNI standard brain

paracingulate gyrus, bilateral temporal fusiform cortex, left parahippocampal gyrus (anterior division), and right intracalcarine cortex ($p_{\text{unorr}}<0.001$). Finally, the a-ADL score covaried mainly with atrophy in the left lingual gyrus, intracalcarine cortex, and bilateral parahippocampal gyrus (anterior division) ($p_{\text{unorr}}<0.001$). We present the VBM results showing regions of significant gray matter intensity decrease that covary with the ICT subscale in supplementary material (see Supplementary Table 4 and Supplementary Figure 3).

Overlap analysis

We performed an inclusive masking analysis to verify which areas of brain atrophy overlap when accounting for functional impairment in AD as measured respectively by IADL domain and a-ADL domain, BADL domain, and a-ADL domain. Results show that the BADL domain overlap with neither the IADL nor the a-ADL domain subscores of the T-ADLQ. We found an overlap between the IADL and a-ADL domain subscores of the T-ADLQ (see Table 5 and Fig. 3).

Contrast analysis

In a final step, we performed a contrast analysis between the BADL, IADL and a-ADL domain subscores of the T-ADLQ to study the existence of significant anatomical differences between the different domains. Results shows that a-ADL were exclusively associated with one cluster in the left lingual gyrus and the anterior division of the parahippocampal gyrus. The score of the IADL covariated exclusively with atrophy in several areas, mainly the left paracingulate and cingulate gyrus (anterior division), the right and left temporal fusiform cortex (anterior division) and the right middle frontal gyrus (puncorr <0.001) (see Table 6 and Fig. 3).

Table 5 VBM overlap between IADL and a-ADL subscores in AD compared with HC uncorrected by scanner

Regions	Hemisphere	MNI coordinates			Number of voxel
		x	*y*	*z*	
Regions of overlap					
Parahippocampal gyrus, anterior division	Right	30	−14	−28	471
Precuneus cortex	Right	14	−56	12	463
Parahippocampal gyrus, anterior division	Left	−28	−12	−36	373
Parahippocampal gyrus, posterior division	Left	−28	−36	−14	232
Paracingulate gyrus	Left	−10	28	36	191
Intracalcarine cortex	Left	−12	−68	10	108

All results uncorrected at $p < 0.001$. Only cluster with at least 100 contiguous voxels included

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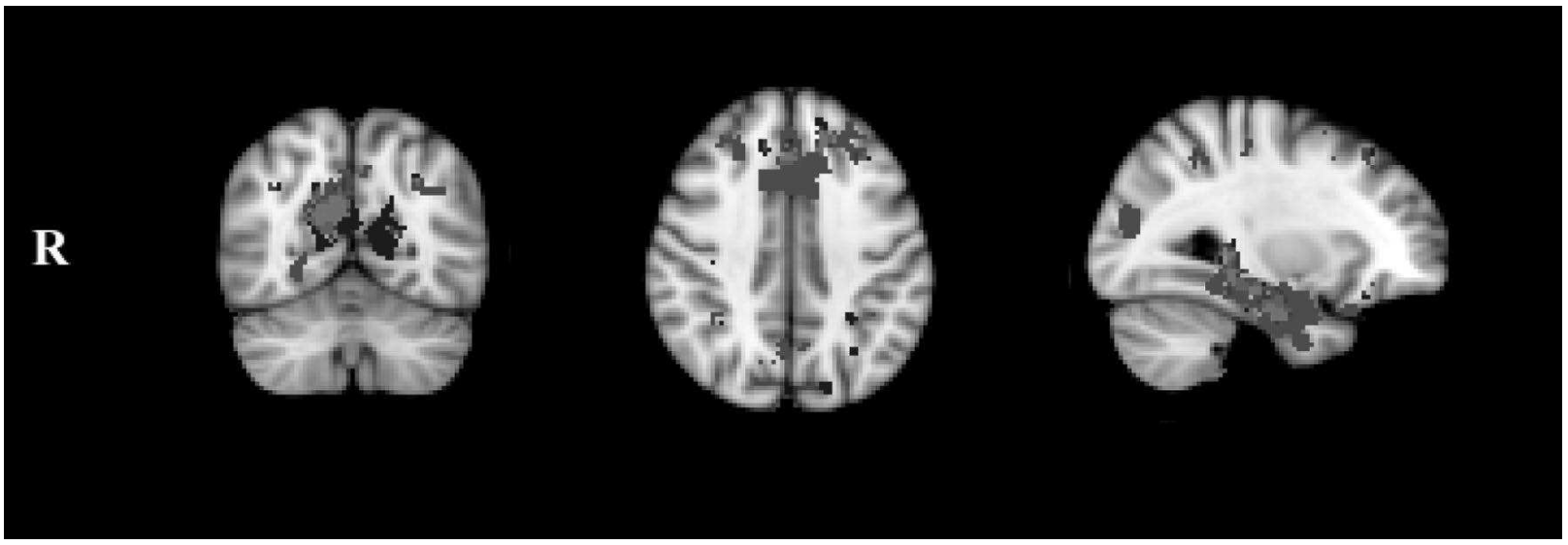

Fig. 3 VBM overlap and exclusive mask analysis for IADL and a-ADL in AD compared with HC. VBM analysis showing overlap brain regions between T-ADLQ IADL and a-ADL domain subscores (green), and regions that correlate exclusively with IADL (red) and a-ADL (blue) in AD in comparison with HC (MNI coordinates $X = 30$; $Y = -62$; $Z = 40$). Colored voxel show regions that were significant in the analysis with $p < 0.001$ uncorrected. For all analysis, a cluster threshold of 100 contiguous voxels was used. Clusters are overlaid on the MNI standard brain

Table 6 VBM exclusive regions that correlate with IADL and a-ADL subscores in AD compared with HC

Regions IADL domain subscores	Hemisphere	MNI coordinates			Number of voxel
		x	*y*	*z*	
Paracingulate gyrus/cingulate gyrus, anterior division	Left	−8	36	22	1930
Temporal fusiform cortex, anterior division	Right	30	−2	−42	1258
Temporal fusiform cortex, anterior division	Left	−30	0	−40	862
Middle frontal gyrus	Right	26	26	40	731
Central operculum cortex	Right	42	8	10	482
Precuneus cortex	Right	18	−58	20	242
Central operculum cortex	Left	−36	0	20	185
Lateral occipital cortex, inferior division	Right	36	−82	8	146
Occipital fusiform gyrus	Right	26	−66	−8	107
a-ADL domain subscores					
Lingual gyrus	Left	−16	−62	2	646
Parahippocampal gyrus, anterior division	Left	−20	−10	−40	340

All results uncorrected at $p < 0.001$. Only cluster with at least 100 contiguous voxels included

IADL instrumental ADL, *a-ADL* advanced ADL, *MNI* Montreal Neurological Institute

Discussion

To the best of our knowledge, this is the first study assessing the neural correlates of a-ADL and ICT in AD. Our results showed that T-ADLQ subscores correlate with several brain structures, with a varying degree of overlap when the three domains of activities of the questionnaire were considered. The BADL score correlated mostly with frontal atrophy, IADL with more widespread frontal, temporal and occipital atrophy and a-ADL with occipital and temporal atrophy. The inclusive masking analysis did not show areas that overlap between BADL, IADL and a-ADL. However, the bilateral parahippocampal region (PHR) and the precuneus cortex are implicated in both, the IADL and a-ADL. In the exclusive masking analysis, we found an association between IADL and the paracingulate gyrus and the temporal fusiform cortex, while a-ADL correlated more with lingual gyrus atrophy.

T-ADQL total score correlated with a large cluster centered in the temporal fusiform cortex (anterior division) and parahippocampal gyrus (anterior division). Concerning the association with the temporal cortex, our results are in line with studies in both AD and other neurological disorders. Medial temporal lobe atrophy has been associated with functional impairment in both subjects with stroke [37] and mild cognitive impairment (MCI) [38]. The association with the PHR is not surprising due to the involvement of the PHR in multiple cognitive process relevant to everyday functioning as visuospatial processing, episodic memory, and contextual associative processing [39]. Moreover, PHR atrophy has been reported as an early biomarker of AD [40], and hypometabolism in this region has been associated with greater decline in IADL performance [18]. Concerning BADL, AD patients assessed in our study were in mild to moderate stages of the disease and presented mild impairment in some BADL activities (average of 5% of impairment). BADL correlated with two small clusters in left supplementary motor cortex and right frontal regions (orbital cortex and superior/middle frontal gyrus). Although we acknowledge that these results should be interpreted with caution due to the characteristics of our samples, they are in agreement with several studies which have reported that motor abilities are crucial for BADL [41–43] and tend to decline as the disease progresses [44].

IADL correlated with the left paracingulate gyrus, bilateral temporal fusiform cortex, left parahippocampal gyrus (anterior division), and right intracalcarine cortex, among others. Our results are in agreement with previous studies on the neural correlates of IADL [15]. IADL impairment has been associated with inferior temporal and lateral parietal (supramarginal) atrophy [17], decreased gray matter volume in the medial frontal and temporo-parietal cortices in early stages of AD [45], and white matter lesion [46]. The multiple brain areas related with IADL have been attributed to the complex nature of these activities and their increased demand [15].

a-ADL correlated with the left lingual gyrus, intracalcarine cortex, and bilateral parahippocampal gyrus (anterior division), areas that has been associated with higher-order cognitive functions [39], such as explicit memory [47]. As Braak and Braak described, the brain atrophy of AD patients progresses following a hierarchical model, with early atrophy in the hippocampus and parahippocampus gyrus [48], linked to memory and visuospatial impairments in the early stages of the disease, progressing to a generalized pattern of brain atrophy linked to a wide deterioration of cognitive domains [49].

In the overlap analysis, we found that the bilateral atrophy of the parahippocampal gyrus, the paracingulate gyrus, and the intracalcarine cortex are associated to both IADL and a-ADL impairments. Atrophy of these areas has been associated with impairment in episodic memory, language, praxis and visual perception. These symptoms appear in the early stages of AD [47, 50], corresponding to the typical progression of the disease, starting with impairment in complex cognitive domains, including IADL, to difficulties in BADL in the most advanced stages [51].

In the exclusive analysis, we found that left parahippocampal gyrus correlated exclusively with a-ADL. This area has been extensively associated with topographical learning and spatial navigation [52–54], and is crucial for normal adaptive behaviors in work, traveling, or during other activities that comprise a-ADL.

Finally, we found that the ICT subscale is associated with atrophy in the precuneus, area that has been related with visuospatial functioning, attentional shift, and processing speed [55, 56]. It has also been considered a higher-order area that is generally involved in controlling spatial aspects of motor behavior, and episodic memory retrieval [57]. Evidence shows that attentional and visuospatial abilities are necessary for internet searching [58]. Attentional engagement has also been described in motor-cognitive skills when working with touch-screen terminal [59]. Recent evidence suggests that hypometabolism in the precuneus may be a biomarker of potential progression to AD [60]. From this perspective, functional changes associated to this region may reflect the earliest manifestations of the impact of AD on ADL, suggesting that these novel functional assessment tools could be considered sensitivity tools to aid in the early diagnosis of AD. Longitudinal studies in AD and other dementias are mandatory to support this hypothesis.

Our division of the T-ADLQ items in BADL, IADL and a-ADL should be interpreted with caution as it was performed based on an expert panel in clinical diagnosis of dementia and research in functional assessment. Although

experts hold experience in cognitive neurology (AS and CD), neuropsychology (CMN, FH and GF) and occupational therapy (EM), some of such decisions can be influenced by sociocultural factors. For example, classification of computer use as an a-ADL and use of mobile phones as an IADL may not be representative of every sociocultural or generational context. The study here presented was carried out in 2015 when only 10% of the targeted elderly population reported use of internet, 80% of them had access to the internet via landline connectivity and only 20% via mobile phones [61, 62]. Moreover, elderly people in Chile, as in other countries such as Portugal, report that they mainly use mobile phones for basic functions such as answering and calling [63]. Also, in a recent paper by our group [64], we provide additional evidence on the validity of our proposed division of the T-ADLQ in the BADL, IADL and a-ADL categories. Nevertheless, further studies need to address the subdomains characterization of evolving T-ADLQ, which would need to be updated considering intra-country specificity and sociocultural factors [5, 65].

Some methodological issues warrant consideration. First, our neuroimaging results regarding the correlation between VBM and subscore domain did not survive conservative corrections for multiple comparisons and were therefore reported uncorrected at $p < 0.001$. However, we reduced the likelihood of false positive results, by applying cluster extent thresholds of 100 contiguous voxels in the analysis. Importantly, Monte Carlo simulations and experimental data demonstrate that cluster thresholding is an effective tool to reduce the probability of false positive findings without compromising the statistical power of the study [66]. Given our sample size, the application of stringent cluster extended thresholds, and our a priori assumptions, we are confident that our results do not represent false positive findings. However, it will be important to replicate these findings in larger patient cohorts using corrected neuroimaging approaches. Second, the diagnosis of AD was established on clinical grounds without any neuropathological confirmation for the diagnoses. Nevertheless, AD patients presented bilateral atrophy in the hippocampal region, a structural biomarker of AD. Moreover, clinical pathological studies suggested that NINCDS-ADRDA criteria are reliable for the diagnosis of AD. Finally, patients included in the study also fulfilled criteria for Alzheimer's clinical syndrome according to the latest NIA-AA Research Framework [67].

In conclusion, our study suggests that combining a domain specific approach to ADL with neuropathological data drawn from MRI, specific functional phenotypes can be identified. We have demonstrated that in the sample of AD investigated here such a phenotype is characterized by widespread atrophy of the prefrontal, temporal and occipital brain regions significantly associated with functional impairments that follow a gradient of deterioration in the diseases continuum. Such functional phenotypes seemingly inform about such a continuum. Our data also suggest that ADL assessment via such an approach can be very sensitive to neurodegenerative processes, and that the association of types of functional decline and AD progression does follow a traceable neuropathological pathway that involves different neural network. Our results are consistent with the existence of a specific pattern of functional loss in the activities of daily living, namely functional phenotypes, beginning with impairment in the a-ADL, followed by losses in IADL and finally progressing to BADL [4].

Further studies need to address the contribution of white matter lesion to functional impairment [68]. Finally, generalization of our results to other neurodegenerative diseases should be made with cautious. Nevertheless, futures studies are needed to investigate if other neurodegenerative disease leads to functional phenotypes different to those seen in AD. Indeed, ADL dysfunction in FTD is associated with atrophy in network different to that reported in AD and the left superior frontal gyrus is the only region implicated in IADL dysfunction in both FTD and AD [15].

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All the procedures conducted with the participants of this study were carried out according to the Declaration of Helsinki. Ethical approvals were provided by the Ethical and Scientific Committees of the East Metropolitan Health Service and Hospital Clínico Universidad de Chile from Santiago, Chile.

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