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Impairment in complex activities of daily living is related to neurodegeneration in Alzheimer's disease–specific regions

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ABSTRACT

Impairment in instrumental activities of daily living (IADL) is an early clinical feature of Alzheimer's disease (AD). The neurobiology underlying IADL disruptions is still unclear. We aimed to investigate the relationship between IADL functioning and cortical atrophy across the AD spectrum. We selected 162 memory-clinic subjects with subjective cognitive decline (n = 49), mild cognitive impairment (n = 26) or AD dementia (n = 87), and an available structural MRI acquired at 3.0 Tesla and Amsterdam IADL Questionnaire (A-IADL-Q) assessment. We used linear regression correcting for age, sex, education, vascular injuries, and total intracranial volume to investigate the association between gray matter volume and A-IADL-Q score, and voxel-based morphometry to investigate whether any associations were specific for distinct regions. Less gray matter volume was associated with lower A-IADL-Q scores (β = 0.346, 95% CI = [0.185-0.507], $p < 0.001$), specifically in cortical regions covering the medial temporal lobes, cingulate cortex, and precuneus (all p(familywise error–corrected) < 0.05). Results were similar when repeating the analyses in amyloid-positive subjects (n = 78). Our findings illustrate that the A-IADL-Q detects functional impairment related to AD-specific neurodegeneration.

1. Introduction

The clinical course of dementia is characterized by progressive cognitive decline and increased interference in daily living (American Psychiatric Association, 2013). The first reported problems in everyday life typically involve the more cognitively complex activities such as cooking, managing finances, and operating devices (Lawton and Brody, 1969), usually referred to as "instrumental activities of daily living" (IADL). Alzheimer's disease (AD) is the most common cause of dementia worldwide (Scheltens et al., 2016). Several studies have shown that IADL impairment can already be detected in individuals with subjective cognitive decline (SCD) and mild cognitive impairment (MCI) (Jutten et al., 2017; Kaur et al., 2016; Reppermund et al., 2013) which are considered to be at risk and prodromal stages of AD (Albert et al., 2011; Jessen et al., 2014). IADL performance has been related to quality of life of both patients and their caregivers (Giebel et al., 2015), making it an important assessment in clinical practice. In the context of intervention studies and disease-modifying treatments, IADL assessment is often used to evaluate treatment effects on everyday cognition because improvement on a clinical meaningful measure is required for approval according to the Food and Drug Administration guidelines (Food and Drug Administration, 2018). In summary, IADL functioning is considered a highly relevant outcome in both AD research and clinical practice. Still, it remains unclear to what extent IADL functioning is related to neurodegenerative processes of AD.

Cortical atrophy is one of the hallmark neuronal injury characteristics of AD (Ewers et al., 2011; Jack et al., 1997). It is one of the strongest neural correlates of cognitive functioning across the AD clinical spectrum, with hippocampal atrophy showing the most robust correlations with decline on memory tests (Di Paola et al., 2007; Fox et al., 1999; Petersen et al., 2000; Smits et al., 2014).

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However, performance on cognitive tests only explains part of the variance in an individual's functional status (Royall et al., 2007), and so it remains unclear to what extent atrophy is related to complex everyday life functions. Previous studies addressing this topic found that worse performance of everyday activities was related to global brain atrophy and atrophy in a priori defined regions such as the hippocampi (Cahn-Weiner et al., 2007; Farias et al., 2013; Marshall et al., 2014; Okonkwo et al., 2010; Rueda et al., 2015). However, studies using unbiased volumetric imaging techniques have shown that IADL-related atrophy may not be confined to the hippocampal formation, but might involve much more widespread anatomical areas (Vasconcelos et al., 2011; Vidoni et al., 2010). However, those studies studied relatively small groups that did not include prodromal stages of AD (Vasconcelos et al., 2011), or used functional measures that focus less on modern everyday life activities (Vidoni et al., 2010) and therefore may be less relevant for the current elderly population (Jekel et al., 2015; Sikkes et al., 2009). Therefore, the relation between atrophy and more complex activities of daily living across the AD spectrum warrants further investigation.

We recently developed a modern scale to assess everyday functioning in an early-onset AD population: the Amsterdam IADL Questionnaire (A-IADL-Q). The A-IADL-Q is an informant-based measure and was developed with input from patients, caregivers, and health care professionals (Sikkes et al., 2012). It assesses the performance of a broad range of specific everyday activities, including modern ones such as the use of technological devices. The A-IADL-Q has good content validity, good reliability, adequate diagnostic accuracy, and was found to be sensitive to changes over time in incipient dementia (Koster et al., 2015; Sikkes et al., 2013b). It was validated against other clinical measures for global cognition and quality of life (Sikkes et al., 2013a), but so far it had not been compared with a biological marker of neurodegeneration.

The aim of this study was to investigate the relationship between IADL performance as measured with the A-IADL-Q and cortical atrophy in a memory-clinic population covering the clinical spectrum from SCD to AD dementia. Using exploratory voxel-based morphometry (VBM), we investigated whether worse IADL performance was related to less global gray matter volume, and whether such associations were specific for distinct brain regions.

2. Methods

2.1. Study population

We selected 162 participants from the memory-clinic–based Amsterdam Dementia Cohort (van der Flier, 2018) when they had (1) a diagnosis of SCD, MCI, or AD dementia; (2) availability of a structural brain MRI scan on a 3.0 Tesla scanner; and (3) a completed A-IADL-Q assessment. All participants had undergone a complete diagnostic workup in the VU University Medical Center (VUmc) Alzheimer Center between January 2010 and September 2015. This included a diagnostic interview, medical history, physical and neurological examination, neuropsychological assessment, laboratory tests, and structural brain imaging. During this visit, the subject's study partner (mostly a spouse, child or close relative) completed the A-IADL-Q independently on an iPad. Reliability of the study partner was based on the clinician's impression during the diagnostic interview. Diagnoses were made in a multidisciplinary consensus meeting according to the clinical criteria for MCI, possible or probable AD (Albert et al., 2011; McKhann et al., 2011), and research criteria for SCD (Jessen et al., 2014). Attendees of this meeting were unaware of the subject's A-IADL-Q score and the diagnosis was therefore made independently of the A-IADL-Q.

The medical-ethical committee of the VUmc approved the study. All participants and study partners gave written informed consent to use their clinical data for research.

2.2. Amsterdam IADL Questionnaire

IADL functioning was measured with the A-IADL-Q: an informant-based scale with 70 items covering a broad range of cognitive IADL (Sikkes et al., 2012, 2013a,b). Compared with existing IADL instruments, the A-IADL-Q includes more complex IADL activities that are prone to decline in early stages of dementia, as well as more modern activities that are nowadays relevant in everyday life (Sikkes et al., 2009). Overall, the content of the items can be described as household activities, administration, work, computer use, leisure time, appliances, transport, and other activities. Example items include "using a mobile phone", "using e-mail," and "using electronic banking". The A-IADL-Q is computerized and has an adaptive approach as the items are tailored to individual responses, resulting in a minimum of 47 and a maximum of 70 items for each respondent. Difficulty in performance is rated on a 5-point Likert scale, ranging from "no difficulty in performing this task" to "no longer able to perform this task". Scoring is based on item response theory (IRT): a paradigm linking responses to a test battery to an underlying construct (or latent trait) (Embretson and Reise, 2013). For the A-IADL-Q, the construct underlying the items reflects "IADL functioning" (Jutten et al., 2017; Sikkes et al., 2013a). An important advantage of the IRT scoring method is that one's latent trait score can be estimated from any set of items resulting from the A-IADL-Q. Therefore, IRT is able to handle missing data that may result from the adaptive approach. To ease interpretation of the scores, IRT scores are converted to normally distributed T-scores ($M = 50$, $SD = 10$), with lower scores reflecting poorer IADL functioning.

2.3. MRI acquisition and preprocessing

All participants had undergone a high resolution structural whole-brain MRI-scan on a 3.0 Tesla scanner (SignaHDxt; GE Healthcare, Milwaukee, WI, USA). T1-weighted 3D gradient echo sequences were obtained with the following acquisition parameters: repetition time 7.8 ms, echo time 3.0 ms, flip angle 12°; 176 sagittal slices, field of view 240 mm^2; slice thickness 1 mm; voxel size $0.94 \times 0.94 \times 1$ mm^3. A 3D fluid attenuation inversion recovery sequence was obtained for the visual rating of white matter hyperintensities (WMH) and lacunes. The quality of the scans was checked by an experienced neuroradiologist.

Preprocessing of the 3D T1 images was performed using the Statistical Parametric Mapping 12 (SPM12) software (Wellcome Trust Centre for Neuroimaging, University College London, UK) running in MATLAB 2011a (MathWorks Inc, Natick, MA, USA). Before preprocessing, the origin in each scan was manually set to the anterior commissure. Scans were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Next, to account for atrophy in the sample, we created a sample-specific Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (Dartel) template (Ashburner and Friston, 2000) of the Dartel imported gray matter segmentations. Finally, the gray matter segmentations were warped to this Dartel template and normalized to Montreal Neurological Institute space with a Gaussian filter of 8-mm full width at half maximum. RJJ visually checked the quality of all individual segmentations. Total GM (i.e., the sum of all GM voxels) and total intracranial volume (TIV; i.e., GM + WM + CSF volume) were derived from the segmented images in native space (units in liter). The smoothed, normalized, and modulated images were used for the VBM analyses.

2.4. Covariates

Educational level was scored according to the Dutch Verhage classification system, ranging from 1 (low education, i.e., not finished primary school) to 7 (high education, i.e., a master's or doctor's degree). To correct our analyses for markers of vascular injury, we also included information on WMH and total number of lacunes, which were scored by a trained neuroradiologist. Severity of WMH was rated using the visual Fazekas scale ranging from 0 (no WMH) to 3 (severe WMH).

2.5. Statistical analyses

Statistical analyses were performed using SPSS version 22.0 and SPM12. Significance level was set at $p < 0.05$, unless mentioned otherwise. Demographic differences between the diagnostic groups were investigated with one-way analyses of variance followed by Hochberg's post hoc tests for continuous data measured on interval level, and a Kruskal-Wallis test for ordinal variables or as nonparametric alternative. Sex differences between groups were investigated using χ^2 tests. We investigated the association between normalized gray matter volume (independent, defined as total GM divided by TIV) and A-IADL-Q score (dependent) in the total group using a linear regression analysis. We also investigated a second model including age, sex, education, and WMH as covariates by entering them to the regression model based on the strength of their correlation with A-IADL-Q score. We reported the standardized regression coefficients including standard error and 95% confidence intervals. To explore the relation between IADL functioning and cortical atrophy within each group, we repeated these analyses after stratifying for diagnostic group (i.e., SCD, MCI, or AD dementia). We also repeated the analyses in a subsample of individuals with abnormal amyloid to assess whether findings are specific for biomarker-confirmed AD. CSF data that had been obtained during the same day as the MRI scan was available for 78% of the subjects (n = 124). Amyloid positivity was determined based on amyloid beta 1-42 levels, with a cutoff of 813 pg/mL as defined for the Amsterdam Dementia Cohort (Tijms et al., 2018).

In case a significant association between normalized gray matter volume and A-IADL-Q score was found, we used voxel-based morphometry (VBM) (Ashburner and Friston, 2000) analyses to identify whether any such association was specific for distinct regions. The voxelwise association between gray matter volume and A-IADL-Q score was determined using multiple linear regression in SPM12, with A-IADL-Q score as primary predictor and age, sex, education, and TIV entered as covariates. To limit the analysis to areas of gray matter, an absolute threshold masking was set to only include voxels with gray matter probabilities exceeding 0.10. For each analysis, this resulted in an expected cluster size as indicated by SPM, which we used as minimum extent threshold to select significant clusters or peaks for that specific analysis. Analyses in the total group were corrected for multiple comparisons using the familywise error (FWE) method (significance level of $p < 0.05$). We repeated the analyses stratified for diagnostic group, and we also explored within group associations in the amyloid-positive group. These exploratory analyses were initially uncorrected for multiple comparisons, with a significance level set at $p < 0.001$. If significant clusters were identified, we additionally investigated whether these would survive the FWE-correction. We reported the location of peak voxels within significant clusters with reference to the Montreal Neurological Institute standard space and corresponding brain regions according to the anatomical automatic labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

3. Results

After preprocessing, we identified 2 outliers in the gray matter and A-IADL-Q distributions. The first was due to erroneous segmentation and the second appeared to have a cognitively impaired informant leading to an unreliable A-IADL-Q assessment. As these cases were considered measurement errors, we excluded them from our further analyses. These participants did not differ from the remaining group in terms of demographics and clinical characteristics.

Table 1 shows the demographic and clinical characteristics of the remaining total group (N = 160). The SCD group (n = 49, 62.3 years ±8.2) was significantly younger than the MCI group (n = 25, 69.8 years ±6.2, $p = 0.001$) and AD group (n = 86, 66 years ±7.5, $p = 0.021$). Total MMSE scores were significantly higher in SCD (27.3 ± 2.3) compared with AD (20.4 ± 4.5, $p < 0.001$) as well as for MCI (26.6 ± 2.9) compared with AD ($p < 0.001$). IADL scores were lower in the AD group (48.1 ± 8.6) compared with both the SCD group (58.6 ± 8.3, $p < 0.001$) and the MCI group (54.7 ± 6.9, $p = 0.002$). Participants with SCD had higher normalized gray matter volumes (0.442 ± 0.03) compared with MCI (0.402 ± 0.04, $p < 0.001$) and AD (0.388 ± 0.03, $p < 0.001$). Fazekas scores and amount of lacunes did not significantly differ between the groups. In fact, lacunes were absent in almost all participants and we therefore did not include this variable in our regression analyses.

3.1. Gray matter volume and IADL functioning

Across the clinical spectrum, lower normalized gray matter volume was associated with lower A-IADL-Q scores indicating

Table 1
Demographic and clinical characteristics

	Total group (N = 160)	SCD (n = 49)	MCI (n = 25)	AD dementia (n = 86)	*p*-value[b]	Significant pairwise differences[a]
Age	65.4 (7.9)	62.3 (8.2)	69.8 (6.2)	66.0 (7.5)	<0.001	SCD < MCI, SCD < AD
Female (%)	70 (43.8%)	16 (32.7%)	8 (32%)	46 (53.5%)	0.023	N/A
Education	5.0 (1.3)	4.9 (1.4)	5.2 (1.6)	5.0 (1.1)	0.626	N/A
MMSE score	23.6 (4.9)	27.3 (2.3)	26.6 (2.9)	20.6 (4.5)	<0.001	SCD > AD, MCI > AD
A-IADL-Q score	52.4 (9.5)	58.6 (8.3)	54.7 (6.9)	48.1 (8.6)	<0.001	SCD > AD, MCI > AD
Normalized gray matter volume	0.406 (0.04)	0.442 (0.03)	0.402 (0.04)	0.388 (0.03)	<0.001	SCD > MCI, SCD > AD
Fazekas score	1 (0–1)	1 (0–1)	1 (0–2)	1 (0–1)	0.124	N/A
Lacunes	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.073	N/A

Data for age, sex, education, MMSE, A-IADL-Q, and normalized gray matter volume (unit in liters) are presented as mean (standard deviation); data for Fazekas score and lacunes are presented as median (Q1-Q3).
Key: SCD, subjective cognitive decline; MCI, mild cognitive impairment; AD, probable Alzheimer's disease; A-IADL-Q, Amsterdam IADL Questionnaire; MMSE, Mini-Mental State Examination; N/A, not applicable as no group differences were detected.
[a] $p < 0.05$ according to Hochberg post hoc tests.
[b] Tested using one-way ANOVA, χ^2 or Kruskal-Wallis test if appropriate.

worse IADL functioning (β = 0.297, 95% CI = [0.147–0.447], p < 0.001; Fig. 1, Table 2). This association remained significant after correcting for age, sex, education, and WMH (corrected β = 0.346, 95% CI = [0.185–0.507], p < 0.001, Table 2). When we stratified analyses according to diagnostic group, we observed that lower normalized gray matter volume was associated with worse A-IADL-Q scores at a trend level in the AD group after correcting for age, sex, WMH, and education (p = 0.076, Table 2). We found no significant associations within the SCD and MCI groups.

Stratification on amyloid status resulted in 78 amyloid-positive and 46 amyloid-negative subjects (see Table 3). Age (M = 66.4, SD = 7.1), education level (M = 5.0, SD = 1.3), and sex (50% female) did not significantly differ between the amyloid-positive and the amyloid-negative group. Scores on the MMSE (M = 21.9, SD = 4.8), A-IADL-Q (M = 49.8, SD = 8.5) and GMV (M = 0.396, SD = 0.03) were all lower for the amyloid-positive group (all p-values <0.001, Table 3). Regression analyses in the amyloid-positive group yielded comparable results as in the total sample, in which lower normalized gray matter volume was associated with a lower A-IADL-Q score (β = 0.234, 95% CI = [0.011–0.456], p = 0.04). This association remained significant after correcting for age, sex, education, and WMH (corrected β = 0.249, 95% CI = [0.021–0.478], p = 0.03). We did not find any significant associations in the amyloid-negative group. Further repeating analyses for the amyloid-positive AD dementia group (n = 67) showed similar effects as in the total AD dementia group; however this effect did not reach statistical significance (corrected β = 0.181, p = 0.16).

3.2. Voxelwise association between gray matter and IADL functioning

The VBM analysis in the total group showed 10 clusters where less gray matter volume was related to a lower A-IADL-Q score (all p (FWE-corrected) < 0.05, Fig. 2, Table 4). The largest clusters were located bilaterally in the cingulum, medial temporal lobes, and hippocampi, and we also found associations in the left precuneus, inferior parietal cortex, and angular gyrus (Table 4).

Because regression analyses stratified for diagnostic group showed a trend toward a relation between A-IADL-Q score and gray matter volume in the AD group, we only repeated the VBM analyses in this subgroup. The VBM showed no significant associations on cluster level, but several peaks of gray matter were significantly associated with IADL functioning (all p(unc) < 0.001). These were located in the left and right medial temporal lobes, left and right thalamus, and around the left fusiform gyrus and parahippocampal gyrus (Fig. 3, Table 5).

VBM analyses in the amyloid-positive group showed 2 significant associations on cluster level in the left hippocampus and medial temporal lobe and several peaks bilaterally in the medial temporal lobes, precuneus, and cingulum where IADL functioning was related to gray matter volume (all p(unc) < 0.001). After correcting for multiple comparisons, only 1 cluster located in the left hippocampus survived the correction (p (FWE-corrected) < 0.05).

4. Discussion

We found that worse IADL functioning as measured with the A-IADL-Q was related to less gray matter volume across the clinical spectrum ranging from SCD to AD dementia. We demonstrated that this relationship was independent of age, sex, education, and markers for vascular injury. VBM indicated that associations between IADL and gray matter volume were mostly specific for typical AD brain regions, such as the medial temporal lobes including the hippocampi and the cingulate cortex and associated areas including the precuneus. After stratifying on clinical diagnosis, these associations were only apparent in the AD group and mostly localized in

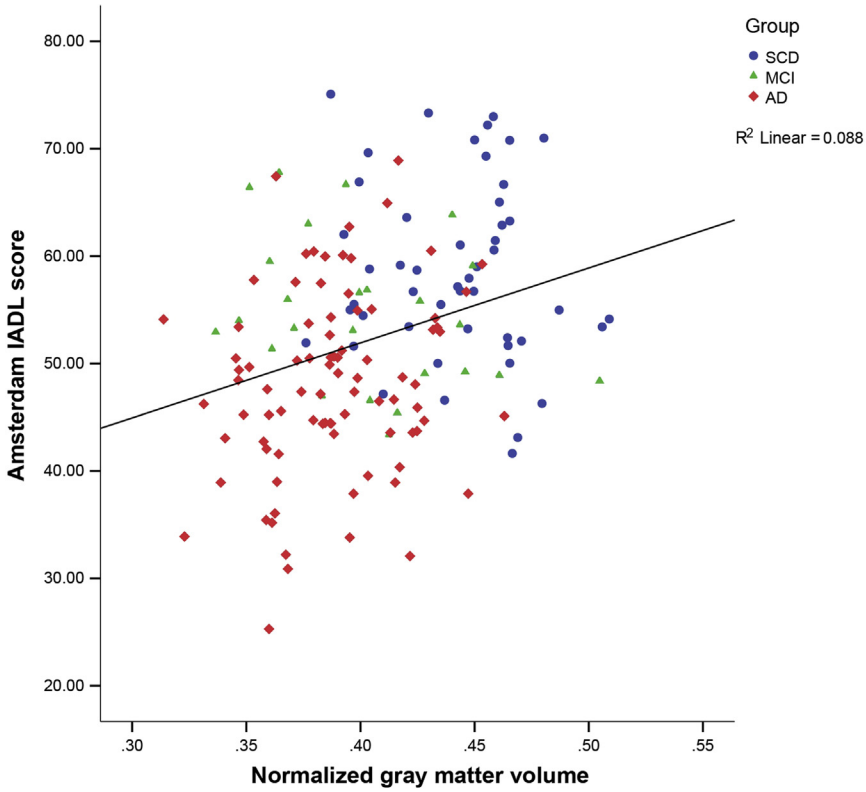

Fig. 1. Scatterplot displaying the relation between normalized gray matter volume (corrected for total intracranial volume) and A-IADL-Q score across the AD clinical spectrum. Abbreviations: A-IADL-Q, Amsterdam IADL Questionnaire; AD, Alzheimer's disease.

Table 2
Standardized regression coefficients for A-IADL-Q score, for the total group and after stratification based on diagnostic group

Model	Total group (N = 160)			SCD (n = 49)			MCI (n = 25)			AD (n = 86)		
	β (SE)	95% CI	*p*-value	β (SE)	95% CI	*p*-value	β (SE)	95% CI	*p*-value	β (SE)	95% CI	*p*-value
1 nGMV	0.297 (0.08)	0.147 to 0.447	<0.001	−0.088 (0.15)	−0.381 to 0.204	0.546	−0.329 (0.2)	−0.736 to 0.079	0.109	0.184 (0.11)	−0.03 to 0.397	0.091
2 nGMV	0.346 (0.08)	0.185 to 0.507	<0.001	−0.142 (0.18)	−0.501 to 0.217	0.43	−0.364 (0.25)	−0.892 to 0.164	0.166	0.202 (0.11)	−0.02 to 0.425	0.076
Age	0.042 (0.09)	−0.131 to 0.216	0.631	−0.189 (0.18)	−0.542 to 0.163	0.285	−0.25 (0.22)	−0.217 to 0.717	0.276	0.023 (0.13)	−0.226 to 0.273	0.852
Sex	−0.079 (0.08)	−0.231 to 0.072	0.303	0.231 (0.15)	−0.065 to 0.527	0.123	0.236 (0.19)	−0.169 to 0.641	0.238	−0.049 (0.12)	−0.282 to 0.184	0.678
WMH	0.127 (0.08)	−0.039 to 0.293	0.133	0.145 (0.16)	−0.171 to 0.462	0.36	0.152 (0.18)	−0.219 to 0.523	0.401	0.058 (0.13)	−0.207 to 0.322	0.666
Edu	0.122 (0.08)	−0.027 to 0.272	0.109	0.169 (0.15)	−0.129 to 0.466	0.26	0.375 (0.19)	−0.025 to 0.776	0.065	0.058 (0.11)	−0.166 to 0.282	0.608

Key: β, standardized regression coefficient; SE, standard error; SCD, subjective cognitive decline; MCI, mild cognitive impairment; AD, probable Alzheimer's disease; A-IADL-Q, Amsterdam IADL Questionnaire; nGMV, normalized gray matter volume; WMH, white matter hyperintensities (Fazekas score 0–3); Edu, education.

the medial temporal lobes. When restricting the sample to amyloid-positive subjects only, we again found that IADL functioning was related to gray matter volume across the AD spectrum profoundly in the left medial temporal lobes and precuneus. These findings further suggest that the associations we found are specific for the AD neurodegenerative process.

Our findings regarding overall gray matter volumes and IADL are largely in line with previous studies reporting that more overall cortical atrophy is associated with worse performance in activities of daily living across the AD clinical spectrum (Cahn-Weiner et al., 2007; Farias et al., 2013; Marshall et al., 2014; Okonkwo et al., 2010). The present study further contributed to these previous studies by also investigating this relationship specifically in individuals who were biomarker-positive for AD. It should be noted that the associations we found were only moderately strong, which is often seen in MRI studies associating global atrophy with clinical measures (Schmand et al., 2014). This suggests that, besides the degree of cortical atrophy, there are potentially other biological factors or interindividual differences that contribute to the severity of clinical symptoms such as IADL impairment.

VBM analyses in the total group demonstrated that associations between gray matter volume and IADL functioning were specific for anatomical regions that are known to be involved in the pathological process of AD. Atrophy in the medial temporal lobes and especially the hippocampus is a major hallmark of AD and has been associated with IADL interference before (Cahn-Weiner et al., 2007; Farias et al., 2013). We showed that regions outside the medial temporal lobes were also associated with IADL functioning, such as the cingulate cortex and the more posterior located precuneus and temporal-parietal located angular gyrus. These areas are all part of or closely connected with the posterior cingulate cortex (PCC), a region that was found to be affected early in neurodegenerative disorders and particularly in AD (Buckner et al., 2005; Leech and Sharp, 2014). The PCC is assumed to play a key role during attention regulation and internally directed cognitive functions, which are all involved in performing IADL. Recent studies using cerebral metabolism have additionally shown that worse everyday functioning is associated with brain dysfunction in posterior brain regions including the PCC (Melrose et al., 2011; Roy et al., 2014). Other functional neuroimaging studies also showed an association between IADL dysfunction and cerebral activity in parietal regions in patients with AD, which largely overlaps with the regions identified in our study (Nadkarni et al., 2012; Salmon et al., 2005).

It should be noted that we did not find any associations between IADL functioning and brain regions located more frontally in the brain. This was somewhat unexpected because frontal regions are known to be involved in executive functions (Schmand et al., 2014), which are assumed to play an important role in successfully performing IADL (Gold, 2012). However, our findings were in line with the study of Cahn-Weiner et al. showing that, while both the cognitive domains memory and executive functions were associated with decline in IADL, hippocampal volume was the only neuroimaging marker predicting these IADL changes (Cahn-Weiner et al., 2007). Together with the findings from the present study, this suggests that atrophy in memory-related brain structures plays an important role in predicting one's level of IADL performance.

The present study has some limitations to take into account. These include the relatively small sample sizes of the SCD and particularly the MCI group, which possibly led to a power problem for detecting significant associations within these groups. It should also be noted that there was little variance in the gray matter volumes and A-IADL-Q scores in the SCD group, which further reflects their normal cognition and these ceiling effects are probably the reason why no association between these measures was observed in this subgroup. In addition, although both SCD and MCI are considered to be at risk stages for developing AD dementia, we do not know which of them will actually convert to AD dementia. Longitudinal data on the A-IADL-Q is currently collected in a larger clinical sample, and suggestions for future research include the use of these data to investigate the association between gray matter volume and IADL functioning in SCD or MCI participants who eventually develop AD. This would also enable us to investigate which specific brain regions are related to IADL changes over time and may thereby be useful for predicting future decline in IADL functioning.

Strengths of our study include the use of the A-IADL-Q to measure everyday functioning. In constrast to other widely used IADL scales, the A-IADL-Q is a well-validated and comprehensive measure of everyday functioning, containing modern and relevant IADL activities in early AD (Sikkes et al., 2009). Furthermore, the use of VBM rather than regional analyses is a major strength of our

Table 3
Demographic and clinical characteristics after stratification based on amyloid status

	Amyloid positive (n = 78)	Amyloid negative (n = 46)	*p*-value[a]
Clinical diagnosis (SCD/MCI/AD)	5/9/63	33/12/1	N/A
Age	66.4 (7.1)	63.6 (9.5)	0.067
Female (%)	39 (50%)	15 (32.6%)	0.059
Education	5.0 (1.3)	5.1 (1.4)	0.875
MMSE score	21.9 (4.8)	26.9 (3.1)	<0.001
A-IADL-Q score	49.8 (8.5)	57.7 (8.2)	<0.001
Normalized gray matter volume	0.396 (0.03)	0.433 (0.04)	<0.001
Fazekas score	1 (0–1)	1 (0–1)	0.621
Lacunes	0 (0–0)	0 (0–0)	0.224

Data for age, sex, education, MMSE, A-IADL-Q, and GMV are presented as mean (standard deviation); data for Fazakas score and lacunes are presented as median (Q1-Q3).
Key: SCD, subjective cognitive decline; MCI, mild cognitive impairment; AD, probable Alzheimer's disease; MMSE, Mini-Mental State Examination; A-IADL-Q, Amsterdam IADL Questionnaire; N/A, not applicable.
[a] Tested using oneway ANOVA, Chi Square or Kruskal-Wallis test if appropriate.

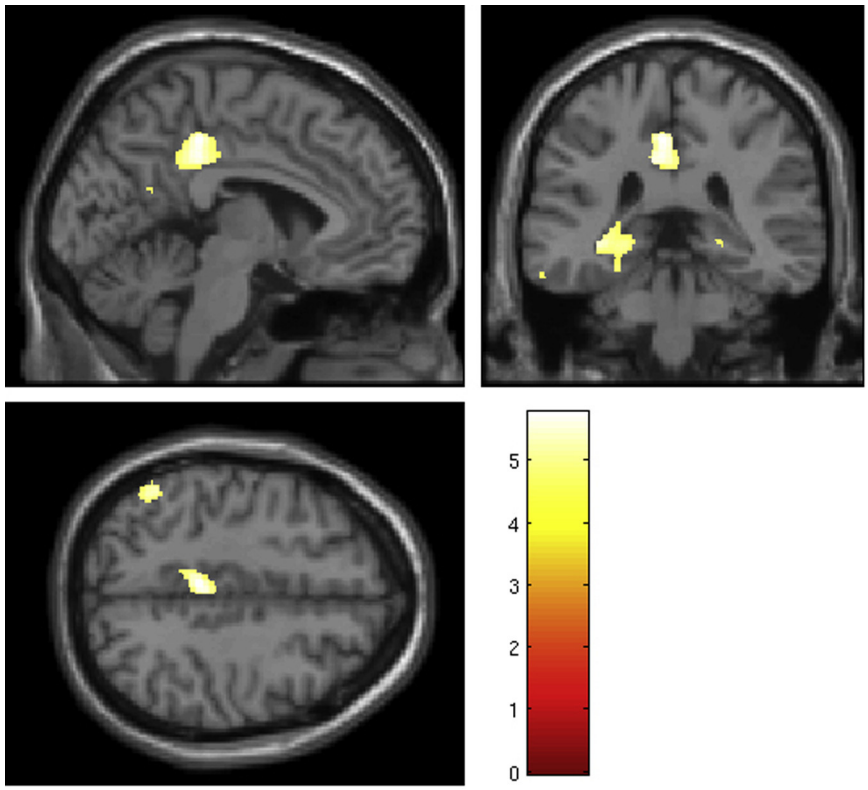

Fig. 2. Significant clusters of regression gray matter volume and A-IADL-Q score across the AD clinical spectrum (T-statistic indicating the strength of association with lighter colors representing stronger associations). Abbreviations: A-IADL-Q, Amsterdam IADL Questionnaire; AD, Alzheimer's disease. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

study because VBM has several advantages regarding efficiency, comprehensiveness, and freedom from observer bias (Ashburner and Friston, 2000). The use of this unbiased method in relating atrophy to IADL functioning was a novel aspect of this study because most previous studies on IADL and atrophy restricted their analyses to only a few a priori defined brain regions. Finally, the additional analyses in the amyloid-positive group are an important and novel aspect of this study, as it enabled us to further investigate whether the relation between IADL and cortical atrophy was specific to AD pathology.

Table 4
Regions of significant gray matter volume associated with A-IADL-Q score across the AD clinical spectrum (N=160)

Cluster level			Peak level			Coordinates in MNI space (x, y, z)	Brain region (AAL atlas)
p(FWE-corr)[a]	p(unc)[b]	Number of voxels (k)	p(FWE-corr)[a]	p(unc)[b]	T-statistic		
<0.001	0.000	904	<0.001	<0.001	5.76	−4, −34, 45	Cingulum medial left
			0.001	<0.001	5.55	−6, −34, 36	Cingulum medial left
			0.036	<0.001	4.66	2, −21, 34	Cingulum medial right
<0.001	0.005	438	0.001	<0.001	5.60	2, −46, 4	Temporal medial left
			0.006	<0.001	5.12	52, −45, 14	Temporal superior right
<0.001	0.000	1843	0.002	<0.001	5.45	−33, −36, −4	Hippocampus left
			0.003	<0.001	5.29	−27, −12, −18	Hippocampus left
			0.007	<0.001	5.09	−32, −24, −12	Hippocampus left
0.002	0.037	217	0.002	<0.001	5.39	−48, −56, 46	Parietal inferior left
			0.021	<0.001	4.81	−48, −68, 33	Angular gyrus left
<0.001	0.006	414	0.005	<0.001	5.19	−57, −15, −14	Temporal medial left
			0.008	<0.001	5.04	−50, −3, −32	Temporal inferior left
			0.018	<0.001	4.85	−54, −10, −22	Temporal medial left
0.002	0.045	197	0.006	<0.001	5.11	46, −18, −9	Temporal medial right
			0.023	<0.001	4.78	51, −20, −2	Temporal superior right
0.004	0.084	141	0.008	<0.001	5.07	−52, −60, 21	Temporal medial left
0.008	0.162	89	0.014	<0.001	4.92	−8, −58, 21	Precuneus left
0.001	0.021	275	0.014	<0.001	4.92	30, −20, −16	Hippocampus right
			0.026	<0.001	4.75	24, −32, −6	Parahippocampal gyrus right
0.015	0.299	48	0.020	<0.001	4.83	−60, −38, −21	Temporal inferior left

Significant clusters detected a p(FWE) < 0.05, cluster size k > 48.
Key: A-IADL-Q, Amsterdam IADL Questionnaire; MNI, Montreal neurological institute; AAL, anatomical automatic labeling.
[a] p(FWE-corr) = Familywise error corrected p-value.
[b] p(unc) = uncorrected p-value.

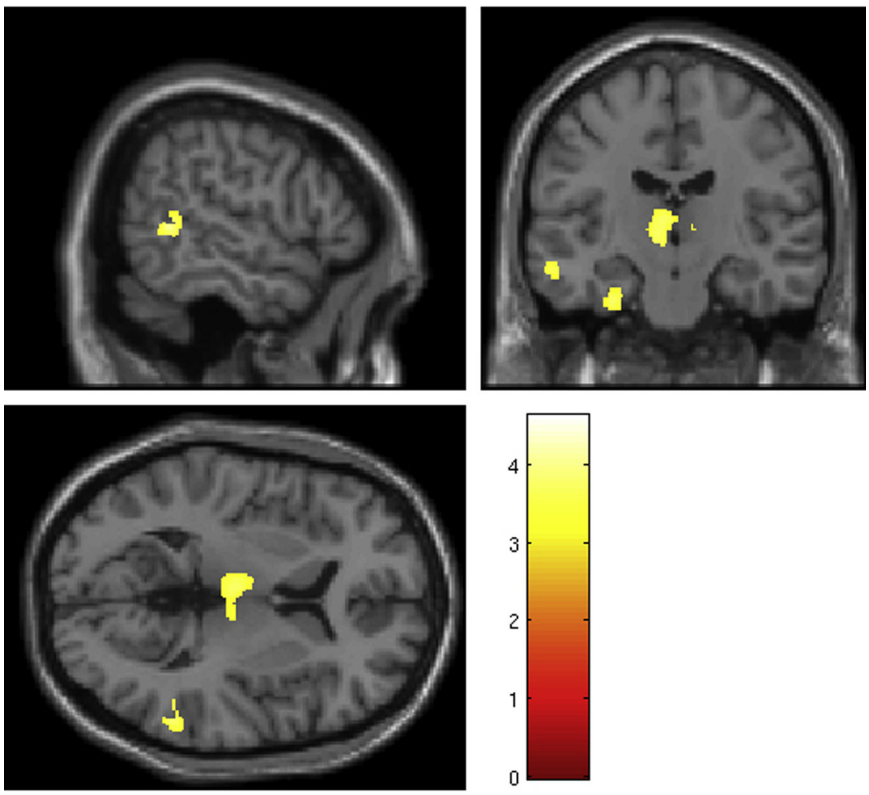

Fig. 3. Significant peaks of regression between gray matter volume and A-IADL-Q score in the AD dementia group (T-statistic indicating the strength of association with lighter colors representing stronger associations). Abbreviations: A-IADL-Q, Amsterdam IADL Questionnaire; AD, Alzheimer's disease. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

In conclusion, we demonstrated that the A-IADL-Q is able to detect problems in complex activities of daily living that are associated with AD-specific neurodegeneration. Because IADL functioning is the core clinical feature of dementia, and therefore considered an important and clinically relevant construct in both research and clinical practice, it should be carefully assessed using a clinically meaningful metric reflecting the underlying pathology. The present study provides further evidence that the A-IADL-Q is a useful and valid instrument for these purposes.

Table 5
Regions of significant gray matter volume associated with A-IADL-Q score in the AD dementia group (n=86)

Cluster level		Peak level		Coordinates in MNI space (x, y, z)	Brain region (AAL atlas)
Number of voxels (k)	p(unc)[a]	T-statistic	p(unc)[a]		
370	0.083	4.63	<0.001	51, −48, 3	Temporal medial right
		3.92	<0.001	60, −46, 3	Temporal medial right
147	0.260	3.80	<0.001	−54, −12, −22	Temporal medial left
		3.59	<0.001	−57, −16, −16	Temporal medial left
548	0.039	3.73	<0.001	−6, −18, 3	Thalamus left
		3.30	<0.001	9, −20, 3	Thalamus right
265	0.136	3.69	<0.001	−28, −18, −30	Fusiform gyrus left
		3.50	<0.001	−21, −22, −24	Parahippocampal left

Significant peaks detected a p(unc) < 0.001, cluster size k > 124.
Key: A-IADL-Q, Amsterdam IADL Questionnaire; AD, Alzheimer's disease; MNI, Montreal neurological institute; AAL, anatomical automatic labeling.
[a] p(unc) = uncorrected p-value.

Disclosure

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