A cognitive perspective on clinical manifestations of Alzheimer s disease

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Regional atrophy is associated with impairment in distinct cognitive domains in Alzheimer's disease

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Abstract

Objective: In Alzheimer's disease (AD) some patients present with cognitive impairment other than episodic memory disturbances. We evaluated whether occurrence of posterior atrophy (PA) and medial temporal lobe atrophy (MTA) could account for differences in cognitive domains affected.

Methods: In 329 AD-patients we assessed five cognitive domains**:** memory, language, visuo-spatial functioning, executive functioning and attention. Magnetic resonance imaging (MRI) was visually rated for presence of MTA and PA. Two-way analyses of variance were performed with MTA and PA as independent variables and cognitive domain as dependent variables. Sex, age and education were covariates. As PA is often encountered in younger patients, analyses were repeated after stratification for age-of-onset (early onset: ≤65years).

Results: Mean age of patients was 67±8years, 175(53%) were female and MMSE was 20±5. Based on dichotomized MRI ratings, 84(26%) patients had MTA and PA, 98(30%) had MTA, 57(17%) had PA and 90(27%) had neither. MTA was associated with worse performance on memory, language and attention (all $p<0.05$), and PA with visuo-spatial and executive functioning (both $p<0.05$). Stratification for age showed in late onset AD (N=173) associations between MTA and impairment on memory, language, visuo-spatial functioning and attention (all $p<0.05$), in early onset AD (N=156) patients with PA tended to perform worse on visuo-spatial functioning.

Conclusion: Regional atrophy is related to impairment in specific cognitive domains in AD. The prevalence of PA in a large set of AD patients and it's association with cognitive functioning provides support for the usefulness of this visual rating scale in the diagnostic evaluation of AD.

Introduction

Alzheimer's disease (AD) is increasingly considered a heterogeneous disease, which may initially present with cognitive decline other than pronounced memory impairment [1-3]. Besides memory impairment, AD may also feature nonamnestic presentations with prominent dysfunction in language, visuo-spatial functions or executive functions. These atypical presentations are also recognized in the new clinical criteria for AD [4].

On magnetic resonance imaging (MRI), atrophy of the medial temporal lobe, especially the hippocampus, is considered a diagnostic hallmark of AD and relations with episodic memory impairment have frequently been shown [5-7]. Medial temporal lobe atrophy (MTA) can be scored using a visual rating scale [8]. This scale shows a good association with episodic memory and is widely used in clinical practice [7-9].

Nevertheless, not every patient with AD presents with MTA. Imaging studies have revealed prominent (fronto-)parietal atrophy in AD, especially in patients with an earlier age of onset [10-12]. Patients with posterior cortical atrophy (PCA) form a distinct subgroup, presenting with prominent visual problems, but posterior atrophy (PA) seems to be far more frequent in AD [13]. Recently, we developed a new visual rating scale for PA, which allows easy use in clinical practice [14,15]. It has been shown that PA discriminates early onset AD patients from younger controls independently of MTA [15]. It is attractive to assume that this scale is associated with cognitive impairment in AD, especially non-amnestic signs and symptoms, but this has not yet been proven.

In the current study, we therefore assessed associations between visual ratings of MTA and PA and cognitive impairment in a large set of patients with AD. Additionally, we stratified the analyses at age of onset, since PA is observed relatively often in early onset AD.

Methods

Subjects

Consecutive patients (n=344) with probable AD were included from the outpatient memory clinic of the Alzheimer Center of the VU University Medical Center (VUmc) between August 2008 and January 2012. For the diagnostic procedure, all patients underwent a standardized one-day assessment including medical history and family history for dementia, informant-based history, physical and neurological exam, neuropsychological assessment, laboratory tests, electroencephalogram (EEG) and MRI of the brain. Diagnoses were made in a multidisciplinary consensus meeting. All patients fulfilled the core clinical criteria for probable AD of the National Institute on Aging-Alzheimer's Association (NIA-AA) [4].

Inclusion criteria for this study were: a diagnosis of probable AD and available Mini-Mental State Examination (MMSE), Cambridge Cognitive Examination (CAMCOG) and neuropsychological assessment. Exclusion criteria were: frank vascular abnormalities (N=10) and missing MRI sequences (N=5). This resulted in a total study sample of 329 patients. Level of education was classified according to the system of Verhage ranging from 1 to 7 (low to highly educated) [16]. The study was conducted in accordance with regional research regulations and conformed to the Declaration of Helsinki. The local Medical Ethics Committee approved the study and all patients gave written informed consent for their clinical data to be used for research purposes.

Neuropsychological assessment

Cognitive functions were assessed with a standardized test battery, covering several cognitive domains. We used the MMSE and the CAMCOG for global cognitive decline [17,18]. For memory, we used the Visual Association Test (VAT) and total immediate recall and delayed recall of the Dutch version of the Rey auditory verbal learning task (RAVLT) [19-21]. To examine language, we used VAT naming, category fluency (animals) and the Dutch version of Controlled Oral Word Association Test (COWAT) (letter fluency) [19,22,23]. We used three subtests of the Visual Object and Space Perception Battery (VOSP) to assess visuo-spatial functioning, namely (i) incomplete letters, (ii) dot counting and (iii) number location [24]. For the attention domain we used Trail Making Test (TMT) A and the forward condition of Digit Span (extended version) [25,26]. We used TMT B and the backwards condition of Digit Span (extended version) to examine executive functioning [25,26].

MRI and image analysis

MRI was performed on a 3.0 T MR system (Signa HDxt, General Electric, Milwaukee). All subjects were examined according to a standard dementia MRI protocol including sagittal T1-weighted 3D fast spoiled gradient echo (FSPGR) sequences (field of view [FOV] = 25; matrix = 256 x 256; 1mm slices; echo time = 3ms; repetition time = 7.8ms; inversion time = 450ms; one signal acquired), 3D fluid-attenuated inversion recovery (FLAIR) (FOV = 25; matrix = 224 x 224; 1.2mm slices; echo time = 140ms; repetition time = 8000ms; inversion time = 2349ms; echo train length 230, one signal acquired) and axial fast spin-echo T2/PD sequences (FOV = 25; matrix = 384 x 384; 3mm slices; echo time = 23/114ms; repetition time = 9100ms; echo train length 24, two signals acquired). Multiplanar (MPR) reconstructions of 3D T1-weighted sequences were performed in sagittal (5mm) and oblique-coronal orientations (3mm slices perpendicular to the long axis of the hippocampus). MPR reconstructions of 3D FLAIR images were performed in transverse orientation using a 3mm section thickness.

The image analysis included a visual rating of MTA and PA [8,14]. T1-weighted images were viewed in the coronal plane and MTA-scores for the left and right hemispheres were given. The scale rates atrophy on a 5-point scale (0= absent, 1= minimal, 2= mild, 3=moderate, and 4= severe) based on the height of the hippocampal formation and the width of the choroid fissure and the temporal horn [8]. PA scoring was based

n the axial multiplanar reconstruction of the FLAIR sequences, and the coronal and sagittal reconstructions of the 3D T1-weighted sequence. The PA scale rates atrophy on a 4-point scale (0= absent, 1= mild sulcal widening and mild atrophy, 2= substantial widening and substantial atrophy, 3= end stage atrophy) based on the posterior cingulated- and parieto-occipital sulcus and sulci of the parietal lobes and precuneus [14]. MTA- and PA-score were dichotomized into relevant atrophy present or absent based on a mean score for left and right ≥1.5.

Statistical analysis

Since complete case analysis (exclusion of all patients with one or more missing neuropsychological tests) leads to loss of statistical power and biased results we imputed the data [27,28]. There was variance in the number of completed neuropsychological tests. On average, every test was completed by 260 patients, ranging from 306 (Digit Span forward) to 148 (TMT B). Tests were not finished because of cognitive impairment or lack of time. We used the software package Multivariate Imputation by Chained Equations (MICE, version 2.14.1 [29]) in the statistical program R (www.r-project.org) to perform multiple imputation of the data**.** Briefly, this method uses fully conditional specification, that constructs multivariate imputation models with a set of conditional densities for each variable. Age, gender and education level were included as predictor variables in addition to the neuropsychological test scores for imputation of the missing values.

We report pooled statistics over 5 imputed data sets. PASW Statistics 18.0 for Mac was used. TMT A and B scores were log-transformed because they were not normally distributed. All neuropsychological data were standardized into z-scores, to allow comparison of different neuropsychological tests within patients. TMT A and B scores were inverted by computing -1*z-score, because higher scores imply a worse performance. For each of the five cognitive domains the mean z-scores over the corresponding tests were calculated. Independent samples T-test and χ^2-tests were conducted where appropriate. To assess the relationships between MTA and PA and cognitive functions, we used two-way analyses of variance (ANOVA) with MTA and PA as independent variables and composite domain scores as dependent variables. Sex, age and education were entered as covariates. When there were no significant interactions, pooled p-values were derived from the model without interaction term. We repeated the two-way ANOVA after stratification based on age at diagnosis: early onset AD (≤65 years) and late onset AD (>65 years). For all analyses, the significance level was set at $p<0.05$.

Results

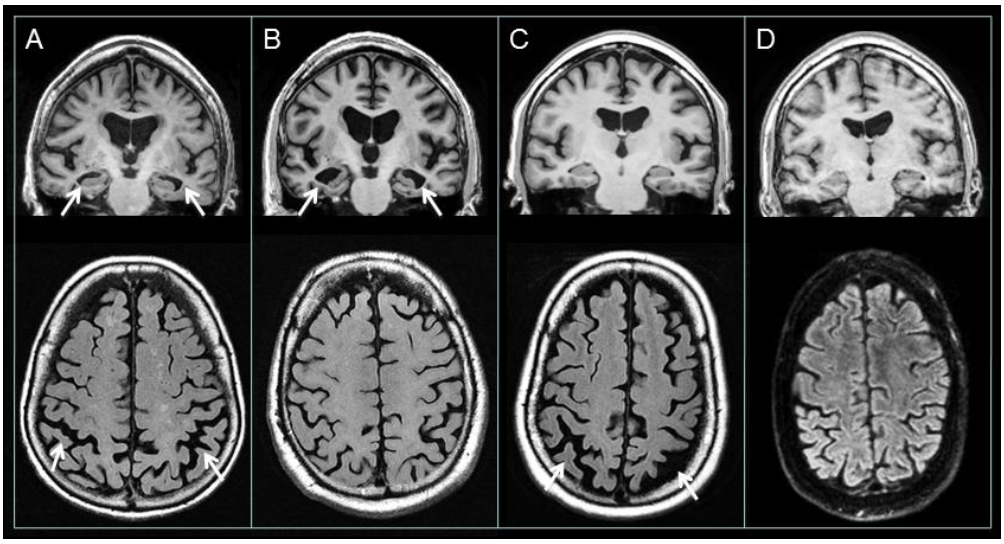
In the total sample age (mean±SD) was 67±8 years and 175 (53%) patients were female, see table 1 for demographics. MMSE was 20±5 and CAMCOG was 66±17. Based on dichotomized MRI ratings, 84 (26%) had both MTA and PA, 98 (30%) patients had only MTA, 57 (17%) had only PA and 90 (27%) had no atrophy. Figure 1 shows examples of patients with these specific atrophy patterns, all with comparably mild dementia (MMSE= 23).

In total 85 subjects completed all neuropsychological tests, and 244 patients missed at least 1 test. There was no difference in gender distribution between these two groups (complete 49%F vs missing 55%F; $p = 0.49$), nor was there a difference in age (complete = 68±7; missing = 67±8; $p = 0.35$). The complete group had a slightly higher education than the incomplete group (complete = 5.2±1.2 vs missing 4.7±1.3; $p = 0.001$). The complete group had less severe cognitive impairment as evidenced by higher MMSE scores than the missing group (complete = 23±3; missing = 19±5).

Regarding MRI, both groups had comparable ratings of MTA (complete 55% vs missing 55%; $p = 1.0$), and people with missing values were more likely to have PA (complete 32% vs missing 46%; $p = 0.04$). Table 1 also shows the raw neuropsychological test results according to presence of MTA and PA. Patients with MTA performed worse on total immediate recall of the Dutch RAVLT ($p<0.05$), incomplete letters ($p<0.05$) and Digit Span forward ($p<0.01$) than patients without MTA. Patients with PA performed worse on Digit Span backward than patients without PA ($p<0.01$). Regarding other cognitive tests we found no differences between patients with or without MTA, or patients with or without PA.

Subsequently, we used two-way ANOVA to assess the combined effects of MTA and PA on functioning in cognitive domains, with sex, age and education as covariates. There were no significant interactions between MTA and PA. Therefore pooled p-values were derived from models without interaction term. We found that patients with MTA performed worse on memory ($p<0.01$), language ($p<0.05$) and attention ($p<0.05$) compared to patients without MTA. There was no relation between MTA and visuo-spatial functioning ($p=0.12$) or executive functioning ($p=0.24$). Patients with PA performed worse on visuo-spatial functioning ($p<0.05$) and executive functioning ($p<0.05$) compared to patients without PA.

Figure 1. Illustrative MRI's (coronal T1 and axial FLAIR) of 4 patients with AD and comparably mild dementia (MMSE for all patients was 23).



A. Patient with both medial temporal lobe atrophy and posterior atrophy. This 77 years old female visited our memory clinic for a second opinion. Neuropsychological assessment revealed impairment of memory and visuo-spatial functioning, some executive impairment, including impaired flexibility. On MRI, a medial temporal lobe atrophy grade 2 (both hemispheres) and posterior atrophy grade 2 (both hemispheres) were seen. Also, a Fazekas-score of 2 was seen.

B. Patient with medial temporal lobe atrophy in absence of posterior atrophy. This 78 years old male visited our memory clinic and reported memory complaints and difficulties in word finding existing since 3 years. Neuropsychological assessment showed clear impairments in memory and word finding and some limitations in the other cognitive domains. MRI, showed MTA of 4 (both hemispheres), no posterior atrophy and some punctuate white matter abnormalities.

C. Patient with posterior atrophy in absence of medial temporal lobe atrophy. This 57 years old female visited our memory clinic for a third opinion. Earlier investigations did not yield a diagnostic conclusion. She was not able to work anymore because of her memory complaints. Her husband reported additional troubles with word finding and in attention; nevertheless she could function on her own. Neuropsychological assessment showed impairment in memory and visuo-spatial functioning. On MRI, major parietal atrophy and atrophy of the precuneus and posterior cingulate was seen. The medial temporal lobes showed also mild atrophy (both hemispheres grade 1).

D. Patient with no atrophy. This 62 years old man visited our memory clinic for further research regarding his cognitive complaints. He complains about forgetfulness and difficulties reading digital clocks. Neuropsychological assessment we found impairments in memory, language and executive functioning. MRI showed no abnormalities besides minimal posterior atrophy. Additionally, PIB PET-scan showed amyloid depositions and decreased amyloid-β and slightly increased tau in cerebrospinal fluid.

Table 1. Demographics and pooled neuropsychological test performance of patients with or without MTA or PA.

	All	MTA		PA	
	patients	**No atrophy**	**Atrophy**	**No atrophy**	**Atrophy**
N	329	147	182	188	141
Number of women, N (%)	175 (53)	84 (57)	92 (50)	103 (54)	73 (52)
Age in years	67 ± 8	65 ± 7	69 ± 8*	67 ± 7	66 ± 9
Level of education #	5 ± 1	5 ± 1	5 ± 1	5 ± 1	5 ± 1*
MMSE	20 ± 5	20 ± 5	19 ± 6	20 ± 5	20 ± 5
CAMCOG	66 ± 17	68 ± 15	64 ± 18*	67 ± 17	65 ± 17
Memory					
- VAT	5 ± 4	6 ± 4	5 ± 4	5 ± 4	5 ± 4
- RAVLT¶, total immediate recall	20 ± 7	21 ± 9	19 ± 8*	20 ± 8	20 ± 9
- RAVLT¶, delayed recall	2 ± 2	2 ± 2	1 ± 2	1 ± 2	2 ± 2
Language					
- VAT naming	11 ± 1	11 ± 2	11 ± 2	11 ± 2	11 ± 2
- Category Fluency	12 ± 5	12 ± 5	11 ± 6	12 ± 6	11 ± 6
- Letter Fluency	24 ± 11	24 ± 11	24 ± 12	24 ± 12	24 ± 12
Visuo-spatial Functioning					
- Incomplete Letters	14 ± 5	14 ± 6	14 ± 7*	14 ± 6	13 ± 6
- Dot Counting	9 ± 1	9 ± 2	9 ± 1	9 ± 1	9 ± 2
- Number Location	8 ± 2	8 ± 2	8 ± 2	8 ± 2	7 ± 2
Executive Functioning					
- TMT B §	270± 208	274 ± 135	268 ± 128	264 ± 138	280 ± 122
- Digit Span backward	6 ± 3	6 ± 3	6 ± 3	6 ± 3	6 ± 2*
Attention					
- TMT A §	106 ± 62	107 ± 77	106 ± 73	101 ± 74	113 ± 76
- Digit Span forward	10 ± 3	11 ± 3	10 ± 3*	10 ± 3	11 ± 3

Demographics and neuropsychological testing presented as mean ± standard deviation. Two-way analyses of variance were performed with age at onset as between-subject factor. Sex, age and education were entered as covariates.

According to the Verhage-system, ¶ Dutch version of the Rey auditory verbal learning task (RAVLT), § Higher scores imply worse performance.

* $p<0.05$.

There was no relation between PA and memory ($p=0.67$) or language ($p=0.19$). Figure 2 illustrates that according to presence of MTA and/or PA, groups show different cognitive profiles; patients with no atrophy showed relatively less impaired performance in comparison to the other groups. Patients with MTA were most impaired on memory. Patients with PA showed relatively good memory and performed worse on visuo-spatial functioning and executive functioning. Patients with MTA and PA in general performed worse on neuropsychological testing compared to other groups, with most prominent impaired performance on language, visuo-spatial functioning, and attention.

Next, we stratified the analysis for age, creating two groups; early onset (N=156) and late onset AD (N=173). Table 2 shows the demographics of both groups. Patients with early onset performed worse on MMSE and CAMCOG than late onset patients. Late onset patients had more severe MTA than early onset patients. The degree of PA in early onset patients however was just as severe as in late onset patients. In early onset AD, there was no relation between MTA and any cognitive domain. The performance of early onset patients with PA on visuo-spatial functioning tended to be worse than younger patients without PA ($p=0.055$). We did not find any other relation with PA in early onset patients, nor were there any interactions between MTA and PA. In late onset AD, patients with MTA performed worse on memory ($p<0.01$), language ($p<0.05$), visuo-spatial functioning ($p<0.05$) and attention ($p<0.01$) than patients without MTA. There was no relation between MTA and executive functioning, nor between PA and executive functioning. There were no interactions between MTA and PA in late onset patients.

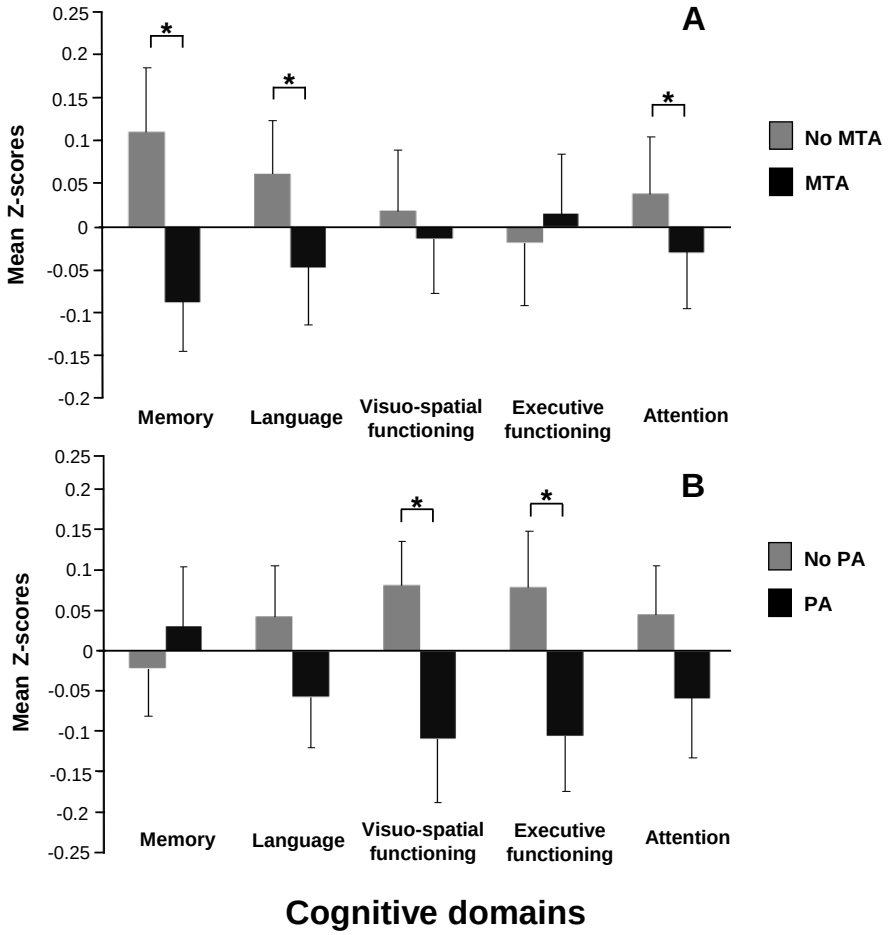
Table 2. Demographics of patients with early and late onset AD.

	Early onset	**Late onset**
N	156	173
Number of women, N (%)	90 (58)	85 (49)
Age in years	60 ± 4	73 ± 5*
Level of education #	5 ± 1	5 ± 1
Mean MTA	1.2 ± 0.8	1.6 ± 0.8*
Mean PA	1.3 ± 0.8	1.3 ± 0.7
MMSE	19 ± 5	21 ± 5*
CAMCOG	63 ± 17	69 ± 16*

Demographics, MMSE and CAMCOG presented as mean ± standard deviation. Independent samples T-test and χ^2-test were performed with onset as between-subject factor. # According to the Verhage-system

* $p<0.05$.

Figure 2. Mean neuropsychological Z-scores according to MTA and PA.



The x-axis shows the five cognitive domains: memory, language, visuo-spatial functioning, executive functioning and attention. A) Mean z-scores for patients with no MTA (N=147) compared with MTA (N=182; upper panel). B) Mean z-scores for patients with no PA (N=188) and with PA (N=141; lower panel). We performed two-way ANOVA to assess the combined effects of MTA and PA on functioning in cognitive domains, with sex, age and education as covariates.

* $p<0.05$.

Discussion

Using simple visual rating scales, we showed that MTA was associated with impaired memory, language and attention, while PA was associated with impaired visuo-spatial functioning and executive functioning. These findings provide evidence that despite comparable disease severity, clinical heterogeneity can be related to variability in regional atrophy in AD.

The visual rating scale for MTA has been used for over two decades now in both research and clinical settings [9,30]. It is increasingly acknowledged that evaluation of MRI in the context of AD should not be restricted to the medial temporal lobe. To facilitate use in clinical practice, we recently developed a visual rating scale for PA, but its clinical use has not been established yet. We used both scales in a large cohort of AD-patients, and found that MTA and PA are both frequently observed, together as well as in isolation. In our cohort, 17% of patients had PA in absence of MTA, less than in two former studies in which the numbers were 28% and 30%, respectively [14,15]. This difference can probably be explained by the fact that on average, patients in the current study were older than in one former study [15], while PA in isolation is more often observed in younger patients [10-12,31].

The association we found between PA and executive functioning at first seems rather counter-intuitive, but could be partly explained by worse performance on the TMT B, which – in addition to measuring executive functioning – also relies heavily on intact visuo-spatial abilities. Furthermore, atrophy of fronto-parietal regions influencing executive functioning has been demonstrated before [3]. Until now, only a few studies have been conducted using the PA scale, showing that the scale seems to discriminate AD from other dementias [14].

Furthermore, PA ratings could distinguish between younger controls and early onset AD, but not between older controls and late onset AD [15]. It has been suggested that in MCI patients, the MTA and PA scale may offer independent and complementary predictive information regarding to conversion to AD [32]. In the current study, we found that PA occurs in both early onset and late onset AD. Associations in the stratified analysis were no longer significant, probably due to lack of power. Our results are in line with these former findings, showing that ratings on both scales are related to cognitive impairment, albeit in different domains, underlining their complementary value.

The visual ratings of MTA and PA are easy to assess and the results are in line with more sophisticated methods, like volumetric MRI or voxel-based morphometry (VBM). A study in prodromal AD, showed that patients had mainly MTA, which was associated with severe memory impairment [5]. Another study where patients with AD were divided into typical and atypical subgroups, based on their neuropsychological performance, found that non-memory problems in AD were associated with thinning of the right superior parietal lobe, while memory impairment was related to thinning of the left entorhinal cortex [33]. In addition, in a former study of our own group, in a completely independent sample, atrophy of the precuneus was specifically related to impaired visuo-spatial functioning [11]. A volumetric study found in AD associations between MTA and memory impairment, and PA and praxis in AD [6].

A possible limitation of this study may be that we did not have post-mortem data available, so the possibility of misdiagnosis cannot be ruled out. Nevertheless, we have an extensive standardized work-up and all patients fulfilled core clinical criteria of probable AD. Furthermore, no specific tests for praxis and gnosis were included in our neuropsychological assessment, cognitive domains that also seems specifically related to PA. One of the strengths of this study is that we imputed the missing neuropsychological data. In this way we avoided a selection bias, which would be created by using only complete neuropsychological assessments. Further strengths are the

large cohort of patients with AD with available MRI, and the standardized neuropsychological test battery, including tests assessing visuo-spatial functioning

Benson was one of the first to describe PCA as a very exceptional syndrome [13]. Lately, it has been suggested that PCA can be considered as an independent nosology, with AD as the most common underlying cause [34]. Our results show that the observation of PA on MRI is not restricted to the rare and highly specific cases of patients with PCA. Rather, in the spectrum of AD, PA is a frequently observed MRI characteristic in both early and late onset. Furthermore, our results seemingly suggest that PA predisposes for specific non-memory symptoms. These symptoms are relatively often encountered in patients with early onset AD, providing additional relevance for using the visual rating scale in this group. Our results suggest that the visual rating scale for PA is a promising diagnostic tool in addition to the MTA scale, especially when taking into account the new clinical criteria for AD that include non-amnestic presentations as well [4].

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