GREY MATTER AND WHITE MATTER MRI MARKERS OF COGNITIVE PROGRESSION IN EARLY AND LATE ONSET VARIANTS OF ALZHEIMER'S DISEASE

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INTRODUCTION

- Alzheimer disease (AD) is not an unitary syndrome showing different clinical phenotypes. The most common one is late-onset AD (LOAD) with amnestic onset.
- Early-onset AD (EOAD) is characterized by an age at onset < 65 years, early multidomain cognitive impairment or focal presentations involving non-amnestic functions (language, visuospatial abilities, executive functions) (1-3), faster cognitive decline, and shorter survival than LOAD (2).
- In AD, age of onset influences clinical presentation, rate of progression (4, 5) and brain damage (6, 7).
- Longitudinal study investigating the differential impact of grey matter (GM) and white matter (WM) damage on disease progression in EOAD and LOAD are still missing.
- Understanding the relationship between MRI measures and clinical features and progression of these two variants might help to understand the underlying AD pathophysiological mechanisms.

OBJECTIVE

- To assess GM and WM MRI measures as predictors of cognitive progression in a sample of LOAD and EOAD patients with a mean follow-up of 13 months.

MATERIALS & METHODS (Subjects)

SUBJECTS	HCEOAD	EOAD	p*	HCLOAD	LOAD	p*	p#
N	24	28	-	20	48	-	-
Age at MRI [ys]	59.8 ± 1.9	60.3 ± 4.5	0.47	73.2 ± 4.5	73.9 ± 4.2	0.66	< 0.001
Gender [females]	14 (58%)	14 (50%)	0.55	12 (60%)	33 (69%)	0.49	0.10
Education [ys]	15.3 ± 5.0	9.2 ± 4.5	< 0.001	10.7 ± 3.6	9.3 ± 4.8	0.21	0.93
Age at onset [ys]	-	56.6 ± 4.7	-	-	70.6 ± 4.5	-	< 0.001
Disease duration [ys from onset to MRI]	-	3.7 ± 2.0	-	-	3.3 ± 2.1	-	0.33
CDR	-	1.3 ± 0.6	-	-	1.3 ± 0.6	-	0.97
CSF Aβ [ng/L] (n.v. >500)	-	315 ± 121	-	-	372 ± 120	-	0.55
CSF t-tau [ng/L] (n.v. 0-500)	-	619 ± 515	-	-	582 ± 311	-	0.57
CSF p-tau [ng/L] (n.v. 0-61)	-	99 ± 64	-	-	94 ± 36	-	0.53

*p values refer to the Mann-Whitney U or the Fischer's exact test (for gender only) between each patient group *vs* age-matched healthy controls; #p values refer to the Mann-Whitney U or the Fischer's exact test (for gender only) between patient groups. **Abbreviations.** CDR: clinical dementia rating scale; CSF: cerebrospinal fluid; HC: healthy controls; MRI: magnetic resonance imaging; n.v.: normal values; ys: years.

COGNITIVE TESTS (baseline)	EOAD	LOAD	p
MMSE (c.o.=24)	19.2 ± 4.3 (88.8%)	20.2 ± 4.2 (72.9%)	0.31
Verbal memory domain z score	-2.26 ± 0.55	-1.58 ± 0.67	<0.001
Visuospatial memory domain z score	-2.33 ± 0.60	-1.71 ± 0.94	0.01
Visuospatial domain z score	-5.37 ± 2.54	-2.43 ± 2.09	<0.001
Fluency domain z score	-1.81 ± 0.78	-1.16 ± 0.86	0.003
Executive domain z score	-2.25 ± 0.97	-1.09 ± 0.91	0.004
Language domain z score	-3.87 ± 2.08	-2.10 ± 2.06	0.02

MMSE and Z-scores means ± standard deviations. P values refer to the Mann-Whitney U test. **Abbreviations.** c.o.: cut-off; MMSE: Mini Mental State Examination;

MATERIALS & METHODS (MRI and statistics)

3T MRI scanner: T2-weighted spin echo (SE); fluid-attenuated inversion recovery (FLAIR); 3D T1-weighted fast field echo; and pulsed-gradient SE echo planar with sensitivity encoding and diffusion gradients applied in 35 non-collinear directions.

- GM atrophy: VBM and DARTEL in SPM8 (analysis adjusted for TIV and age, FWE <0.05). Specific masks were created for each of the 114 areas of AAL atlas and for each subject the mean volumes of those areas were measured.
- WM damage [fractional anisotropy, and mean, axial, and radial diffusivities]: Voxel wise analysis with Tract-Based Spatial Statistics (TBSS) version 1.2 in FSL (analysis adjusted for age, FWE <0.05). For each subject, mean fractional anisotropy (FA) and mean diffusivity (MD) values were derived for each WM tract of interest using JHU-White matter-atlas.

STATISTICAL METHODS

- Longitudinal linear models were used in order to: 1. Analyse serial neuropsychological data of LOAD and EOAD; modifications over time were summarized by the estimated slopes for each group and compared using specific contrasts 2. Test MRI measures as potential predictors of cognitive changes over time.

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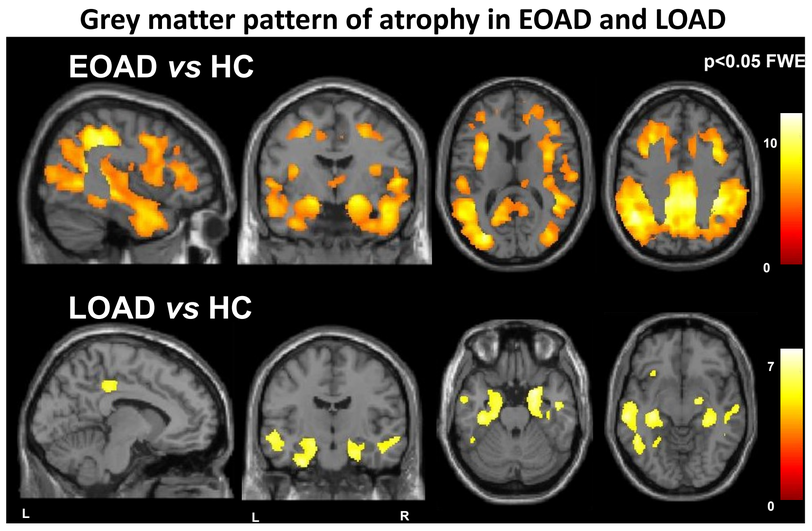
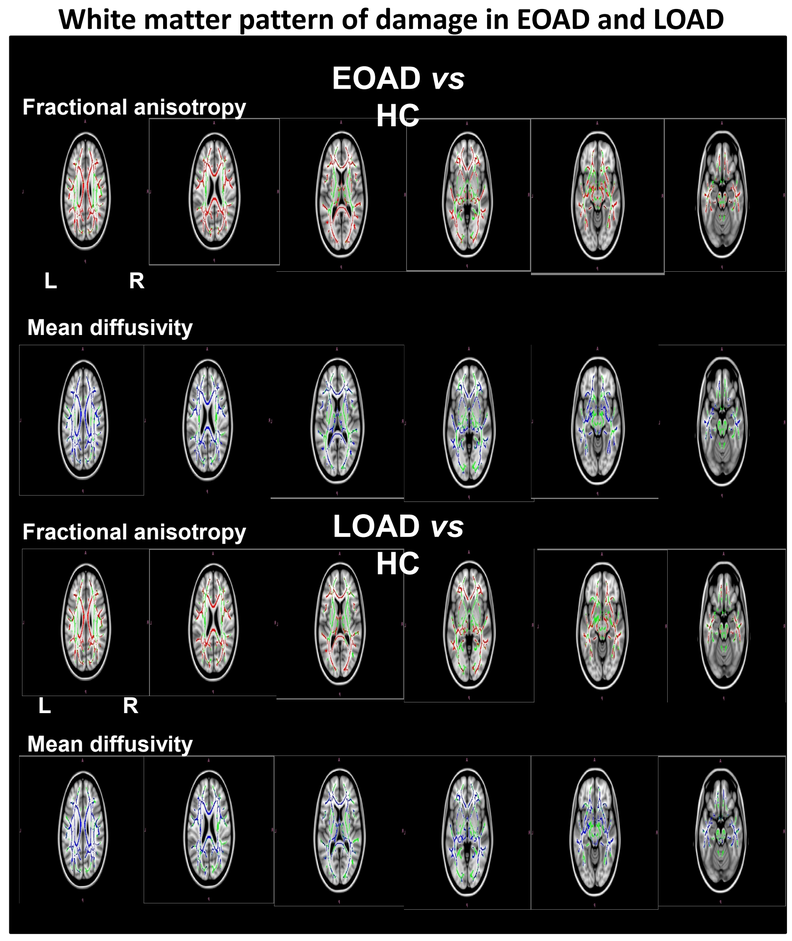
RESULTS

BASELINE MRI

Grey matter pattern of atrophy in EOAD and LOAD



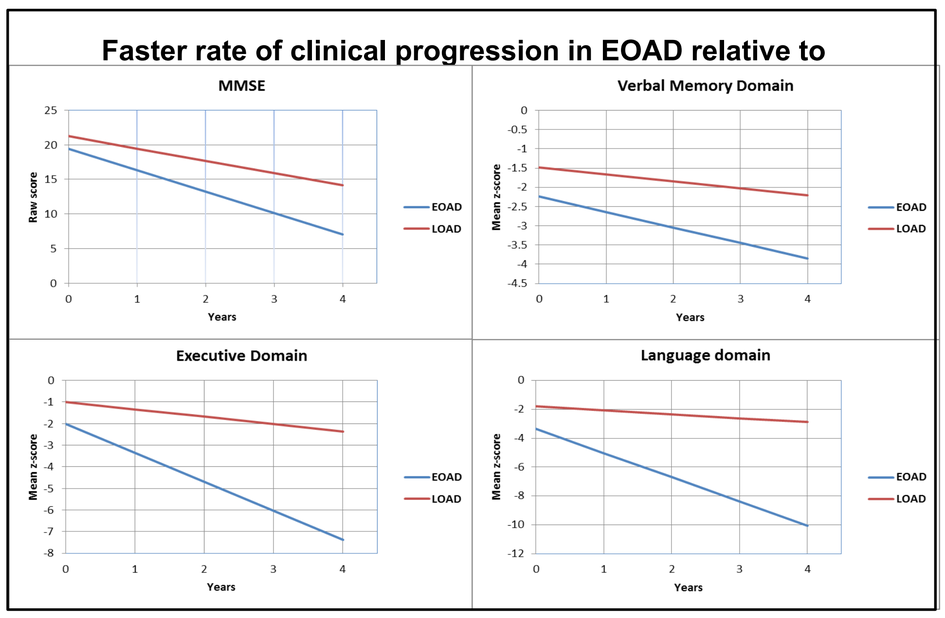
White matter pattern of damage in EOAD and LOAD



COGNITIVE CHANGES

Test		Estimate progression	p*	p#
MMSE	EOAD	-3.1	< 0.001	0.01
	LOAD	-1.78	< 0.001	
Digit span forward	EOAD	-0.43	0.007	ns
	LOAD	-0.09	ns	
Memory prose	EOAD	-0.20	0.003	ns
	LOAD	-0.12	0.01	
Verbal memory domain	EOAD	-0.40	0.002	ns
	LOAD	-0.18	0.02	
Visuospatial memory domain	EOAD	-0.37	0.03	ns
	LOAD	-0.09	Ns	
Clock drawing test	EOAD	-0.41	ns	ns
	LOAD	-1.01	0.008	
Visuospatial domain	EOAD	-0.09	ns	ns
	LOAD	-0.61	0.002	
Phonemic fluency	EOAD	-0.47	< 0.001	ns
	LOAD	-0.28	< 0.001	
Semantic fluency	EOAD	-0.53	< 0.001	ns
	LOAD	-0.37	< 0.001	
Fluency domain	EOAD	-0.50	< 0.001	ns
	LOAD	-0.33	< 0.001	
Raven Coloured Progressive Matrices	EOAD	-0.99	< 0.001	0.01
	LOAD	-0.41	< 0.001	
Attentive matrices	EOAD	-3.87	< 0.001	< 0.001
	LOAD	-0.15	ns	
Executive domain	EOAD	-1.33	< 0.001	< 0.001
	LOAD	-0.34	0.03	
Language domain	EOAD	-1.68	< 0.001	0.002
	LOAD	-0.27	ns	

*p values refer to longitudinal changes within each group. #p values refer to the comparison between longitudinal changes in EOAD *vs* LOAD.



BASELINE MRI *vs* COGNITIVE CHANGES

GM volumes at baseline *vs* cognitive changes

EOAD	
FLUENCY DOMAIN	
Temporal lobe	L MTG, L ITG, L MTP
Parietal lobe	L angular gyrus
Subcortical structures	R thalamus
EXECUTIVE DOMAIN	
Frontal lobe	Bi orbitofrontal cortex, R gyrus rectus, Bi SFG, L MFG, L IFG, Bi precentral gyrus, Bi ACC, R MCC, L rolandic operculum.
Insula	Bi insula
Temporal lobe	L parahippocampal cortex, R fusiform gyrus, L Heschl gyrus, Bi STG, Bi MTG, L ITG, L STP, L MTP, L fusiform gyrus
Parietal lobe	L SPL, L IPL, Bi paracentral lobule, L supramarginal gyrus, L angular gyrus, L PCC
Occipital lobe	L calcarine cortex, R cuneus, Bi lingual gyrus, L SOG, Bi MOG, Bi IOG

LOAD	
MMSE	
Frontal lobe	L ACC, Bi MCC
Insula	Bi insula
Temporal lobe	L MTG, L Heschl gyrus
Parietal lobe	L IPG, L PCC, L precuneus, L angular gyrus
FLUENCY DOMAIN	
Insula	L insula
EXECUTIVE DOMAIN	
Frontal lobe	L ACC, L IFG
Parietal lobe	L IPL
Insula	L insula
VISUOSPATIAL MEMORY DOMAIN	
Subcortical structures	R thalamus, Bi caudate
VERBAL MEMORY DOMAIN	
Subcortical structures	L thalamus
VISUOSPATIAL DOMAIN	
Subcortical structures	R caudate

Abbreviations. ACC: anterior cingulate cortex; Bi: bilateral; IFG: inferior frontal gyrus; IOG: inferior occipital gyrus; IPL: inferior parietal lobule; ITG: inferior temporal gyrus; L: left; MCC: middle cingulate cortex; MFG: middle frontal gyrus; MOG: middle occipital gyrus; MTG: middle temporal gyrus; MTP: middle temporal pole; PCC: posterior cingulate cortex; SFG: superior frontal gyrus; SOG: superior occipital gyrus; STG: superior temporal gyrus; STP: superior temporal pole.

WM metrics at baseline *vs* cognitive changes

EOAD		
FRACTIONAL ANISOTROPY		
VISUOSPATIAL DOMAIN	CC (genu - body - splenium)	
	Bi cingulate tract	
	Bi posterior IFOF/ILF	
	L SLF	
	R external capsule	
MEAN DIFFUSIVITY		
VISUOSPATIAL DOMAIN	CC (genu - body)	
	Bi cingulate tract	
	Bi fornix (cres)	
	Bi anterior IFOF/uncinate	
	Bi posterior IFOF/ILF	
	Bi rostral SLF	
	L SLF	
	Bi external capsule	
	R medial parietal WM	

LOAD	
FRACTIONAL ANISOTROPY	
MMSE	Fornix (body - left cres)
VERBAL MEMORY DOMAIN	L parahippocampal tract
	L medial parietal WM
	R SLF
	R cingulate tract
	Bi anterior IFOF/uncinate
	R external capsule
VISUOSPATIAL MEMORY	R parahippocampal tract
	R SLF
MEAN DIFFUSIVITY	
MMSE	Fornix (body - Bi cres)
EXECUTIVE DOMAIN	R SFOF
	R anterior IFOF/uncinate
	CC (genu)
VISUOSPATIAL DOMAIN	CC (body)
VERBAL MEMORY DOMAIN	CC (genu - body)
	R SLF
	R external capsule
	R parahippocampal tract
	Bi medial frontal WM
	R fornix (cres)

Abbreviations. Bi: bilateral; CC: corpus callosum; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; L: left; R: right; SLF: superior longitudinal fasciculus.

CONCLUSIONS

- Despite having similar disease duration at study entry, EOAD showed more severe cognitive deficits, faster progression and greater GM atrophy compared to LOAD. However, WM damage was severe and distributed in both groups.
- The cognitive progression of EOAD patients is driven mainly by their prominent baseline GM damage not only in temporoparietal but also in the frontal and occipital regions, and by WM damage to the CC and main fibers within the limbic (cingulum) and frontoparietal (SLF) and fronto-occipital (IFOF) networks.
- LOAD patients with baseline atrophy beyond the MTL were more likely to experience a worsening of cognitive abilities. In addition, most of the cognitive progression of LOAD patients was predicted by the diffuse WM tract damage.

References: 1. Migliaccio et al., Neurobiol Aging 2009; 2. Koedam et al., J Alzheimers Dis 2010; 3. Crutch et al., Alzheimers Dement 2012; 4. Jacobs et al., Neurology 1994; 5. Koss et al., Neurology 1996; 6. Frisoni et al., Brain 2007; 7. Canu et al., Neurobiol Aging 2013.