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Medial temporal lobe atrophy and posterior atrophy scales normative values

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ABSTRACT

Objectives: The medial temporal lobe atrophy (MTA) and the posterior atrophy (PA) scales allow to assess the degree hippocampal and parietal atrophy from magnetic resonance imaging (MRI) scans. Despite reliable, easy and widespread employment, appropriate normative values are still missing. We aim to provide norms for the Italian population.

Methods: Two independent raters assigned the highest MTA and PA score between hemispheres, based on 3D T1-weighted MRI of 936 Italian Brain Normative Archive subjects (age: mean ± SD: 50.2 ± 14.7, range: 20–84; MMSE > 26 or CDR = 0). The inter-rater agreement was assessed with the absolute intraclass correlation coefficient (aICC). We assessed the association between MTA and PA scores and sociodemographic features and APOE status, and normative data were established by age decade based on percentile distributions.

Results: Raters agreed in 90% of cases for MTA (aICC = 0.86; 95% CI = 0.69–0.98) and in 86% for PA (aICC = 0.82; 95% CI = 0.58–0.98). For both rating scales, score distribution was skewed, with MTA = 0 in 38% of the population and PA = 0 in 52%, while a score ≥ 2 was only observed in 12% for MTA and in 10% for PA. Median denoted overall hippocampal (MTA: median = 1, IQR = 0–1) and parietal (PA: median = 0, IQR = 0–1) integrity. The 90th percentile of the age-specific distributions increased from 1 (at age 20–59) for both scales, to 2 for PA over age 60, and up to 4 for MTA over age 80. Gender, education and APOE status did not significantly affect the percentile distributions in the whole sample, nor in the subset over age 60.

Conclusions: Our normative data for the MTA and PA scales are consistent with previous studies and overcome their main limitations (in particular uneven representation of ages and missing percentile distributions), defining the age-specific norms to be considered for proper brain atrophy assessment.

1. Introduction

In Alzheimer's disease (AD), neurodegeneration progresses from the hippocampus, towards the temporal lobes and the fronto-parietal associative areas, along with the underlying tauopathy, as demonstrated by neuropathological and neuroimaging studies (Braak and Braak, 1991; Marquié et al., 2017). Atrophy of the medial temporal and parietal lobe is thus common, although not specific, of AD. Volumetric

Abbreviations: MTA, medial temporal atrophy; PA, posterior atrophy; MRI, magnetic resonance imaging; MMSE, mini-mental state examination; CDR, clinical dementia rating; AD, Alzheimer's disease; MCI, mild cognitive impairment; APOE, apolipoprotein E

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studies of these areas show a 10% volume decrease in patients with mild cognitive impairment (MCI) due to AD (Chan et al., 2003; Frisoni et al., 2009) and a correlation of these volumes with the severity of cognitive impairment (Burke et al., 2018). Consistently, hippocampal atrophy and parietal atrophy are significant predictors of progression from MCI to dementia, most frequently due to AD (DeCarli et al., 2007; Jack et al., 1999; Da et al., 2013; Pyun et al., 2017; Yao et al., 2012). Thus, the usual employment of MRI with exclusionary role at the beginning of the diagnostic procedure can also have an inclusionary role to diagnose AD and related disorders.

The most informative volumetric measurements to this avail, requiring manual or semi-automated segmentation of the regions of interest, are time-consuming and require specific technical expertise. Visual rating scales allow a reliable but more feasible assessment of brain atrophy on MRI, mainly for clinical, but also research purposes (Scheltens et al., 1992; Koedam et al., 2011). The medial temporal atrophy (MTA) scale assesses the width of the choroid fissure and of the temporal horn, as well as the height of the hippocampus; the posterior atrophy (PA) scale assesses the width of the posterior cingulate- and parieto-occipital sulci, and the atrophy of the parietal lobe and precuneus. These scales demonstrated a similar accuracy in distinguishing healthy controls from subjects affected by dementia, especially due to AD, as automated measurement methods (Scheltens et al., 1992; Harper et al., 2016).

Different age-corrected cutoffs distinguishing AD dementia from normal aging were proposed, both for MTA (Scheltens et al., 1992; Pereira et al., 2014; Ferreira et al., 2015; Rhodius-Meester et al., 2017) and PA (Koedam et al., 2011; Ferreira et al., 2015; Rhodius-Meester et al., 2017). Cut-off values increase with age, denoting that a certain degree of hippocampal and parietal atrophy may occur also in normal aging. The distribution of MTA and PA scores in normal subjects can be inferred from the control groups in clinical studies. In Scheltens' and Koedam's original papers, most control subjects (67% and 88%, respectively) had an atrophy score of 0 or 1. Similar distributions were reported in further studies (Pereira et al., 2014; Ferreira et al., 2015; Rhodius-Meester et al., 2017), concluding that an MTA or PA score of 1 can be considered as normal. Population-based studies are unfortunately scarce. In 555 non-demented elderly individuals from the longitudinal study of aging "Swedish National study of Ageing and Care in Kungsholmen", aged between 60 and 97, Cavallin et al. (2012) confirmed that an MTA score of 0–1 is present in 95% of subjects aged 60- and 66-years old, a score of 0–2 in 98% of 72 and 78–years old, and a score of 0–3 in 99% of subjects over age 80. Consistently, a recent study in a homogeneous 75-year-old population-based cohort of 390 individuals from the "Prospective Investigation of the Vasculature in Uppsala Seniors", found that a MTA score ≤ 2 can be considered normal at the age of 75 (Velickaite et al., 2018). However, these values are obtained from small size samples with arbitrarily homogeneous age ranges (i.e., only 60, 66, 72, 75, 78, 81, 84, and over-87 years olds) (Cavallin et al., 2012; Velickaite et al., 2018), and do not provide information on the percentile distribution of MTA scores. On the other hand, studies of PA normative distribution in population-based samples are still missing.

The normal shrinkage in hippocampus and parietal lobe is larger than any other brain structure in normal aging (Jernigan et al., 2001; Lemaitre et al., 2012; Thambisetty et al., 2010), and may be modulated by specific confounders. To date, the reported relation between APOE genotype and the rate of volume loss is inconsistent in both brain regions (Soldan et al., 2015; Burggren et al., 2008; Chiang et al., 2011; Luo et al., 2017). However, gender and education were associated to the degree of hippocampal atrophy, with higher MTA scores being observed in men and in subjects with higher education (Velickaite et al., 2018).

The aim of this study was to establish normative data for the MTA and PA scales for the Italian population, considering the potential confounding role of gender, education and APOE genotype.

2. Materials and methods

2.1. Study population and design

We collected data from the "Italian Brain Normative Archive", a study on normal brain aging performed between 2001 and 2008 at the IRCCS Istituto Centro San Giovanni di Dio-Fatebenefratelli, in Brescia (Riello et al., 2005; Galluzzi et al., 2009). Participants were 802 cognitively unimpaired subjects selected from those undergoing brain MRI scan for reasons unrelated to cognition ("convenience" sample). Reasons to perform MRI were visual disturbances, paresthesias, migraine or headache, balance or auditory disturbances (hypoacusia, dizziness, tinnitus), and a variety of other less frequent complaints (olfactory symptoms; suspected ischemic lesions, syncope, trigeminal neuralgia, tremor, lower limb pain, orbital region study, lipothymia and breathing difficulty). A sample of 134 subjects participated as healthy volunteers undergoing MRI scan uniquely for research purposes.

Inclusion criteria included: (i) age > 18 years, (ii) mini mental state examination (MMSE) score > 26 (in person (Folstein et al., 1975) or telephone version (Metitieri et al., 2001)) or a score equal to 0 at the Clinical Dementia Rating Scale (CDR), (iii) availability of 3D T1-weighted MR images with no artifacts affecting atrophy assessment with MTA and PA scales. As exclusion criteria, we considered: developmental cognitive disorders, learning disabilities, diagnosis of a psychiatric disease and evidence of any major neurological disease (brain mass, white matter hyperintensities in patients undergoing MRI for suspected multiple sclerosis or suspected ischemic lesions, aneurysm larger than 10 mm, arteriovenous malformation besides developmental venous anomalies, congenital malformations of the central nervous system) after radiological assessment. If neurological symptoms were reported, subjects were enrolled only in the absence of objective neurological deficits on neurological examination.

All included subjects underwent multidimensional assessment, including clinical, neurological and neuropsychological evaluations. An extensive neuropsychological battery investigated global, verbal and non-verbal memory, verbal fluency, psychomotor speed and visuospatial abilities (Table S1). Subjects were enrolled in the study if neuropsychological assessment attested a normal cognitive performance (more detailed information is reported elsewhere (Galluzzi et al., 2009; Riello et al., 2005)).

For each atrophy scale, we compared the score distributions of the convenience sample ($N = 802$) and of the healthy volunteers ($N = 134$) to ascertain the representativity of the convenience sample. We defined the normative values using the whole sample of 936 subjects, after dividing it into seven age decades. The effect of gender, education and APOE was assessed on the whole sample and on the subsample of subjects over age 60.

The study was approved by the ethics committee of IRCCS Istituto Centro San Giovanni di Dio-Fatebenefratelli of Brescia, and carried out in accordance with the Declaration of Helsinki. Participants or their legal representatives provided written informed consent of participation in the study. No participant received financial compensation.

2.2. Magnetic resonance imaging

MRI scans were acquired in the Neuroradiology Units of "Città di Brescia" Hospital and of "Fondazione Poliambulanza", in Brescia (Italy), from March 2001 to December 2008, using two different scanners following the same standardized protocol. For this study we analysed 722 3D T1-weighted sequences acquired with (a) Gyroscan Intera 1 T (Philips Medical Systems, Best, Netherlands), and 214 with (b) Signa Excite 1.5 T (GE Healthcare, Waukesha, WI, USA). MTA and PA were rated on images acquired with the following parameters: (a) TR = 20 ms; TE = 2 ms; flip angle = 30°; FOV = 220 mm; acquisition matrix, 256 × 256; slice thickness = 1.3 mm; (b) TR = 21 ms, TE = 20 ms, flip angle = 10°, FOV = 256 mm, acquisition matrix

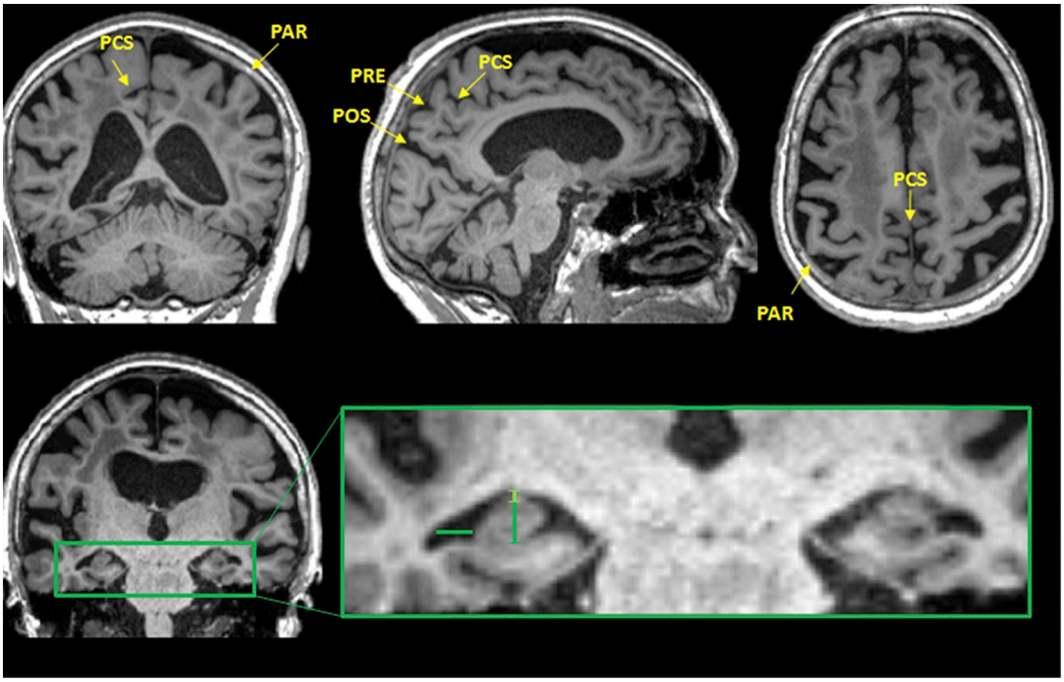

Fig. 1. Visual rating of MTA and PA scales.
PA visual rating is assessed on three orthogonal slice (coronal, sagittal, axial), with particular attention to precuneus (PRE), posterior cingulate sulcus (PCS), parieto-occipital sulcus (POS) and parietal lobe (PAR) (top panel). On the contrary, MTA visual rating is performed on a single coronal slice including hippocampus, with particular attention to the width of the choroid fissure and of the temporal horn, and to the hippocampus height (bottom panel).

256 × 256, slice thickness = 2 mm.

2.3. Visual rating

Based on Scheltens' original description (Scheltens et al., 1992), MTA scale was rated on 3D T1-weighted MR images, on the coronal slice parallel to the brainstem axis and passing through the aqueduct of Silvius. On this slice, we assessed both hemispheres providing a 0–4 score according to the following criteria: 0 no atrophy, 1 widening of the choroid fissure, 2 additional widening of the temporal horn of the lateral ventricle and slightly decreased hippocampal height, 3 moderate loss of hippocampal volume, and 4 end-stage increase of all these findings. Rating of PA was performed after evaluation on three orthogonal slices (paramedian sagittal, axial and coronal) passing through the parietal lobe. For both hemispheres we provided a 0–3 score denoting: 0 no atrophy, 1 mild widening of the sulci without evident volume loss of the parietal gyri, 2 substantial widening of the sulci and volume loss of the gyri, and 3 knife-blade atrophy (Koedam et al., 2011) (Fig. 1).

Visual ratings were performed by two independent raters (MCR and RB) after appropriate training by an experienced reader (CF for MTA, and SI for PA, both with > 3 years of experience in the visual rating and over 2500 neuroimages assessed from LANE and EPAD datasets). For each scale, in case of between-rater discordance in the highest score between the two hemispheres, the images were collegially re-discussed by raters in order to reach a final consensus. As most of the discordant scores differed by only one point, mainly due to evaluations performed on adjacent slices by the raters, in many cases the final consensus was easily obtained choosing the slice in which atrophy was more evident and better assessable; in the other cases, the experienced reader was consulted. Percentile data were computed per decade on the consensual scores.

2.4. Genetic analysis

Blood samples were available for 530 subjects. Genomic DNA was extracted from whole-blood samples according to standard procedures. APOE genotyping was carried out by PCR amplification and *Hha*I restriction enzyme digestion. Genotypes were resolved on 4% Metaphor Gel (BioSpa, Italy) and visualized by ethidium bromide staining (Hixson and Vernier, 1990).

2.5. Statistical analyses

The inter-rater reliability was estimated with a two-way random effects model of the intraclass correlation coefficient with absolute agreement (aICC), that accounts not only for correlations but also for the concordance of the absolute value of the measurement, based on the highest scores between hemispheres. Agreement was considered poor for aICC < 0.50, moderate for aICC 0.50–0.75, good with aICC 0.75–0.90, and excellent for aICC > 0.90 (Koo and Li, 2016).

Normative data were calculated on the consensual highest scores and the 50th and 90th percentiles were computed for each age decade. In order to assess the influence of gender, education and APOE status on the 50th and 90th percentiles, we used Chi square test for categorical variables, or Kruskal Wallis test and post-hoc Nemenyi test for non-normally distributed continuous variables. Moreover, we compared the scores distributions of the convenience sample and of the healthy volunteers with the Chi square to assess the goodness of fit (Table S2). All statistical analyses were conducted using R (version 3.3.3).

3. Results

3.1. Demographic and clinical features

Sociodemographic features, APOE, and cognitive status in the total sample and by age decades are summarized in Table 1. Individuals were continuously distributed in all age decades, prevailing between the fifth and the eight decade (72% between 40 and 79 years). The male-to-female ratio was equally distributed and consistent across all decades ($p = .144$), while education was significantly lower with increasing age ($p < .001$).

Table 1
Sociodemographic features, APOE, cognitive status in the total sample and among age groups.

	Total sample (*N* = 936)	20–29 (*N* = 84)	30–39 (*N* = 161)	40–49 (*N* = 209)	50–59 (*N* = 202)	60–69 (*N* = 189)	70–79 (*N* = 77)	≥80 (*N* = 14)
Sociodemographic features								
Age, years, mean ± SD	50 ± 15	25 ± 3	35 ± 3	45 ± 3	54 ± 3	64 ± 3	74 ± 3	82 ± 1
Gender, females, N (%)	572 (61%)	62 (74%)	103 (64%)	126 (60%)	123 (61%)	105 (56%)	46 (60%)	7 (50%)
Education, years, mean ± SD	11.2 ± 4.5	14.6 ± 3.2	12.5 ± 4.2	11.2 ± 3.8	11.1 ± 4.6	9.5 ± 4.4	9.1 ± 4.8	9.9 ± 5.1
APOE-ε4 status								
ε4 non-carriers, N (%)	430 (81%)	30 (83%)	61 (81%)	91 (76%)	98 (80%)	101 (82%)	44 (96%)	5 (62%)
ε4 heterozygous, N (%)	91 (17%)	6 (17%)	12 (16%)	25 (21%)	23 (19%)	20 (16%)	2 (4%)	3 (38%)
ε4 homozygous, N (%)	9 (2%)	0 (0%)	2 (3%)	3 (3%)	1 (1%)	3 (2%)	0 (0%)	0 (0%)
Cognition								
MMSE, mean ± SD	28.4 ± 1.4	28.7 ± 1.6	28.3 ± 1.5	28.4 ± 1.5	28.4 ± 1.4	28.1 ± 1.5	27.8 ± 1.5	26.8 ± 2.0

3.2. Inter-rater reliability

Raters reached a good agreement for both scales, agreeing in 90% of individually rated images for MTA (aICC = 0.86, 95% CI: 0.69–0.98) and in 86% for PA (aICC = 0.82, 95% CI: 0.58–0.98). Among the MRI scans with discordant rating, only 3 (0.3%) for MTA and only 1 (0.1%) for PA differed by 2 points.

3.3. Normative data

The distribution of the consensual scores was skewed for both rating scales, with 358 participants (38%) scoring MTA = 0, and 489 (52%) scoring PA = 0. Only 109 (12%) and 95 (10%) participants scored 2 or more, respectively for MTA and PA. No significant differences in the scores distribution were detected between the convenience sample and the healthy volunteers subgroup. Score distribution for each scale is reported in Fig. 2 (on the left). Median indicated a general integrity of the hippocampus (median = 1, IQR = 0–1) and of the parietal lobe (median = 0, IQR = 0–1) in the overall sample. The normative data per age decade are reported in Table 2. MTA and PA correlated positively with age (MTA: $p < .001$; PA: $p < .001$). The 90th percentile increased from 1 at age 20–59 to 2 at age 60–79, up to 4 over 80 years of age for MTA, while PA went from 1 at age 20–59 to 2 over 60 (Fig. 2, on the right). The prevalence of APOE-ε4 carriers did not differ significantly below and over the 90th percentile, both for MTA (19% vs 18%, $p = 1.00$) and PA (19% vs 13%, $p = 1.00$).

3.4. Effects of clinical features and APOE-ε4 on atrophy severity

Among the evaluated sociodemographic features (i.e. age, gender and education), older age was associated with significantly greater scores in both scales ($p < .001$). In particular, MTA increased progressively from the sixth decade of life up to the ninth, with a significant increase between the sixth and the seventh decade ($p = .006$), while PA increased from the third decade up to the ninth, with a significant increase between the fifth and sixth ($p = .005$) and between the sixth and the seventh ($p < .001$). No significant association of gender and education was found with MTA, while a trend to higher scores was observed in men than women in the last two decades (age 70–79: median (IQR): F = 1(0–1), M = 2(1–2), $p = .073$; age ≥ 80: F = 1(0–1), M = 3(1–3), $p = .056$). In the total sample, gender showed a significant effect on PA, with males scoring higher than females ($p = .010$). However, no significant difference was observed in the percentile distributions by age group. No significant association was found between PA and education. Likewise, APOE-ε4 status was not associated with neither MTA nor PA severity, in both the whole sample and in the subset of subjects over 60 years of age.

4. Discussion

With this study, we provide the normative data for the MTA and PA scales for the Italian population, based on a large sample of cognitively intact community-dwelling persons with age continuously distributed from 20 to 84. This normative distribution of MTA and PA values will help to assess data from individual patients. However, we recommend that these be considered within the whole clinical and biomarker assessment; we also remind that the definition of specific disease cutoffs require independent studies including appropriate target patient groups.

In previous studies, the hippocampal and parietal atrophy were investigated in cognitively normal subjects (from control groups) mainly with the aim to detect the MTA and PA cut-offs distinguishing AD from normal aging with best accuracy (Scheltens et al., 1992; Koedam et al., 2011; Pereira et al., 2014; Ferreira et al., 2015; Rhodius-Meester et al., 2017). However, these studies have relevant limitations: besides small samples size and uneven representation of ages, they do not report percentile distributions. Our study provided consistent, but more reliable norms, due to sounder methods for this specific aim. Recently, two other studies provided normative values for MTA in population-based samples. However, in both studies (Cavallin et al., 2012; Velickaite et al., 2018), the population investigated was grouped into arbitrary age-homogeneous categories (i.e., only 60, 66, 72, 75, 78, 81, 84, and over-87 years olds) rather than using a continuous and more representative age distribution. On the other hand, studies on normative PA distribution in population-based samples are still missing. To our knowledge, this is the first study obtaining normative values for both scales from a representative population-based sample of cognitively unimpaired subjects with a wide and continuous age range. Our normative values are consistent with the age-related cut-offs proposed previously, indicating as normal MTA ≤ 1 below age 60, MTA ≤ 2 at 60–80, and MTA up to 4 beyond age 80, and PA ≤ 1 below age 60, and PA ≤ 2 beyond 60 (Table 3). On the whole, this consistency in the data suggests that these normative values, although obtained exclusively from an Italian sample, can appropriately be used for other countries, especially the European ones.

As expected in a cognitively intact population, the scores distribution is markedly skewed. The high prevalence of subjects scoring MTA 1 suggests that a unilateral widening of the choroid fissure is a relatively common finding in the general population, possibly related to a physiological asymmetry in the rotation of the hippocampal head (Bronen and Cheung, 1991; Lucarelli et al., 2013). On the other hand, among the linear measures of cortical atrophy, the width of the temporal horn (MTA = 2) seems to be particularly sensitive to the early pathological change (Frisoni et al., 1996). Likewise, the fact that 38% of subjects score PA = 1 supports the idea that a slight enlargement of the cortical sulci may be a common finding, probably related to physiological aging, as also observed in voxel-based morphometry studies (Lemaitre

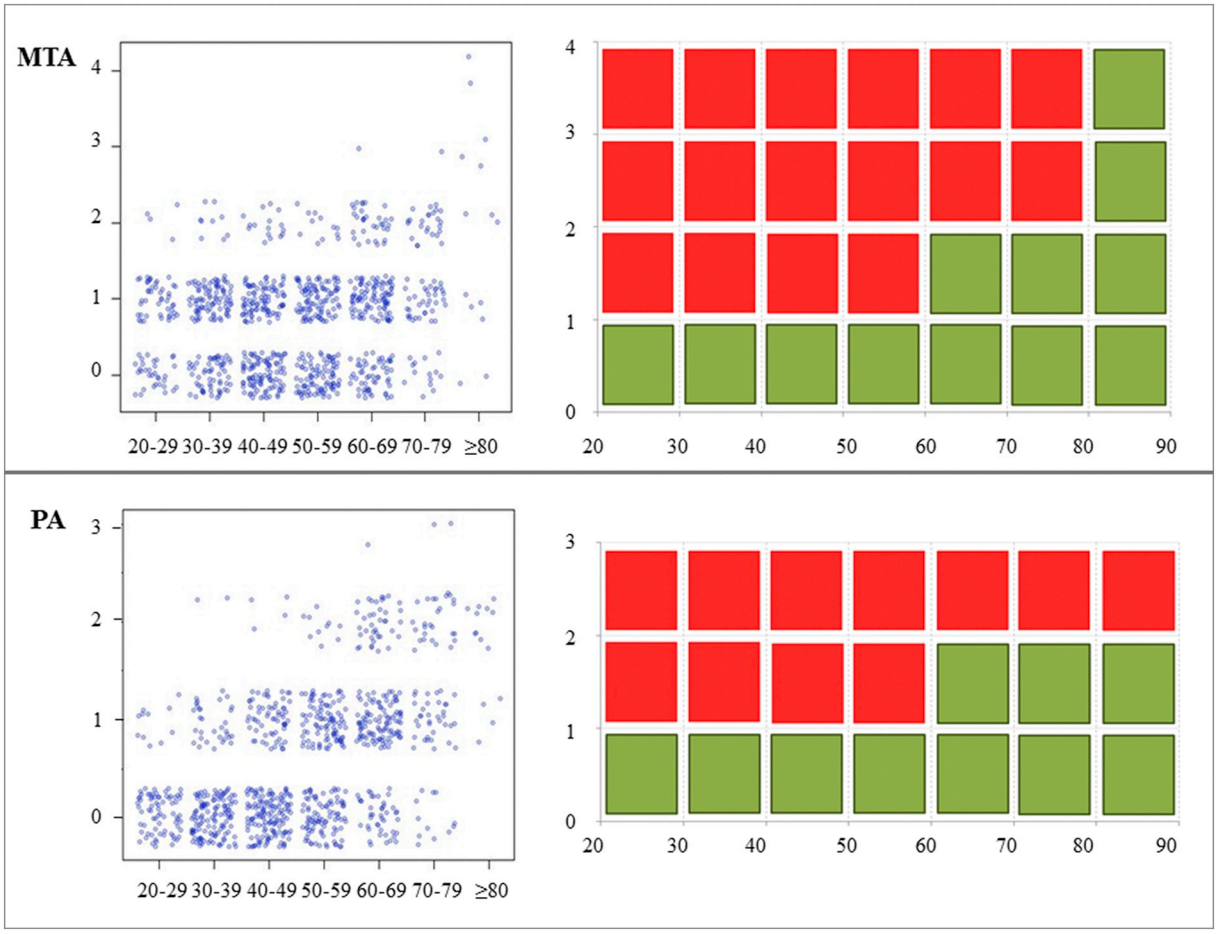

Fig. 2. MTA and PA scores distribution by age decades.
Left panels: Scatterplots of MTA (above) and PA (below) scores distributions. Right panels: heat plot of the 90th percentile distributions (green squares = scores under 90th percentile; red squares = scores over 90th percentile).

et al., 2012; Thambisetty et al., 2010). The presence of high scores (up to 4) in our healthy subjects over age 80 confirms that MTA is not useful in distinguishing between healthy and cognitively impaired individuals in this age range, consistently with previous evidence (Claus et al., 2017) and daily clinical practice. Also etiological biomarkers have a lower informative value with increasing age (Jansen et al., 2015). MTA retains diagnostic utility in younger age ranges, representing an important marker useful to support the presence of neurodegeneration plausibly related to Alzheimer's or related disorder.

In our sample, the association of MTA and PA with age, gender and education is also in line with previously reported data (Rhodius-Meester et al., 2017; Cavallin et al., 2012). Older age was associated to higher scores for both scales ($p < .001$), and thus higher 50th and 90th percentiles, reflecting age-related volumetric decline, known to affect mainly the hippocampal head (Jack Jr. et al., 1997), the parietal lobe and precuneus (Bourisly et al., 2015). In our study, gender did not affect MTA, although a trend for greater atrophy was observed in males in the last age decades taken into consideration. Velickaite et al. (2018) recently reported a similar gender-related trend for MTA, but they also identified an interaction between gender and education, with lower scores in females with low education. We did not observe any interaction among the three confounders. On the other hand, gender showed a significant effect on PA in the whole sample, consistent with cortical morphometry studies showing greater levels of atrophy in men

Table 2
MTA and PA scores by age decades in cognitively-unimpaired individuals.

Decade	MTA				PA			
	Range	IQR	Percentile distribution		Range	IQR	Percentile distribution	
			≤50th	≤90th			≤50th	≤90th
20–29	0–2	0–1	0–1	0–1	0–1	0–0	0	0–1
30–39	0–2	0–1	0–1	0–1	0–2	0–0	0	0–1
40–49	0–2	0–1	0–1	0–1	0–2	0–1	0	0–1
50–59	0–2	0–1	0–1	0–1	0–2	0–1	0–1	0–1
60–69	0–3	0–1	0–1	0–1–2	0–3	1–1	0–1	0–1–2
70–79	0–3	1–2	0–1	0–1–2	0–3	1–2	0–1	0–1–2
≥80	0–4	1–3	0–1–2	0–1–2–3–4	1–2	1–2	0–1–2	0–1–2

Table reports scores' range, interquartile range (IQR), 50th and 90th percentiles.

Table 3
MTA and PA scores of control subjects from different cohorts. The width of each cell denotes the stratification, or lack thereof, of age ranges analyzed to obtain the reported score.

	N		Age Range							
			20-29	30-39	40-49	50-59	60-69	70-74	75-79	≥80
MTA										
Scheltens et al. 1992	21		-	-	-	0-1		0-2		1-3
Cavallin et al. 2012	555		-	-	-	-	0-1	0-2		0-3
Pereira et al. 2014	345		-	-		0-1.5			0-2	
Ferreira et al. 2015	345		-	-		0-1.5			0-2	
Rhodius-Meester et al. 2017	906		-	-	-		0-1.5		0-2	
Velickate et al. 2018	390		-	-	-	-	-	0-2		-
Cotta Ramusino et al.	936	Range	0-2	0-2	0-2	0-2	0-3	0-3		0-4
(present study)	936	90th percentile	0-1	0-1	0-1	0-1	0-2	0-2		0-4
PA										
Koedam et al. 2011	38		-	-	-			0-2		-
Ferreira et al. 2015	345		-	-				0-1		
Rhodius-Meester et al. 2017	906		-	-	-		0-1		0-2	
Cotta Ramusino et al.	936	Range	0-1	0-2	0-2	0-2	0-3	0-3		1-2
(present study)	936	90th percentile	0-1	0-1	0-1	0-1	0-2	0-2		0-2

(Thambisetty et al., 2010). However, comparisons by age groups failed to identify gender-specific percentile distributions, in agreement with what already reported by Ferreira et al. (2015). Associations between temporal and parietal volume measurements and confounders, such as gender and education, are reported in middle-aged and elderly populations (Rhodius-Meester et al., 2017; Cavallin et al., 2012; Velickaite et al., 2018; Thambisetty et al., 2010; Jiang et al., 2014), but not in younger age ranges. This suggests that, in the last age decades, different rates of atrophy in specific subgroups should be kept in mind for a correct radiological assessment. The underlying presence of pathological aging, which remains clinically asymptomatic due to the compensatory effect of the individual brain reserve, as well as of anatomical variants or regional conformational anomalies, may contribute to these differences. Therefore, the normative values reported in this and in previous studies denote measures compatible with *cognitive* normality, but that do not necessarily correspond to the full brain health. On the other hand, using neurodegeneration biomarkers (CSF or PET) to exclude an underlying pathological aging (amyloidosis or tauopathy), and produce more robust norms, is questionable as to current clinical use and relative to current definitions of cognitive normality. Robust norms identify "disease-free" subjects not-representative of the general cognitively unimpaired population; on the other hand, such norms may be useful to identify pathological aging in the pre-clinical stage, and help define eligibility to possible disease-modifying treatments. Future research is warranted in this direction.

The prevalence of APOE-ε4 in our sample (19%) was similar to that reported in the Conselice Study of Brain Aging (15%), a previous Italian population-based survey conducted from 1999 to 2000 to measure dementia risk factors (Ravaglia et al., 2006). The lack of significant differences of APOE-ε4 prevalence in subjects with scores below- versus those with score beyond the 90th percentile cut-offs, and the lack of differences among the two distributions failed to demonstrate any impact of APOE on MTA and PA per each age decade in the normal Italian population. As widely reported in the literature, the ε4 allele of APOE gene causes a dose-dependent increase in risk of developing AD (Corder et al., 1993), and thus atrophy. However, the evidence concerning the effect of ε4 on hippocampal and parietal volume in healthy subjects, remains controversial, in particular in subjects over 40 (Espeseth et al., 2008). Recently, a voxel-based morphometry study on cognitively healthy middle-aged subjects failed to detect significant APOE-associated volume differences in the hippocampus and in the parietal lobe (Ten Kate et al., 2016), in accordance with our results.

The main limitation of this study consists in the use of a convenience sample, consisting of individuals who underwent MRI for neurological disturbances other than cognitive impairment. However, besides the demonstrated cognitive integrity, the convenience sample and the healthy volunteers subsample also included in our study were similar in all respects, assuring the representativity of the convenience sample. Further analyses with other populations are needed to confirm the supposed generalizability of these norms to other populations, in particular to the non-European ones, and to validate the 90th percentile distributions in clinical samples.

The generation of normative values in samples known for being free of incipient neurodegeneration based on biomarker assessment may provide robust norms possibly allowing to detect dementing neurodegenerative disorders at earlier stages than current clinical standards. However, also these norms may have limitations. In fact, also biomarker-based cohorts may not be exempt from selection bias (e.g. age and education related to voluntary participation), as observed for the US ADNI cohort (Petersen et al., 2010). In addition, the positivity to biomarker for neurodegenerative conditions is not necessarily associated to neither a present nor future development of cognitive disorders (Jansen et al., 2015), and norms based on "super-normals", also known as "robust norms", would lead to an excessive number of false positives based on the current concept of clinical health.

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Declarations of Competing Interest

None.

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Appendix A. Supplementary data

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References

Bourisly, A.K., El-Beltagi, A., Cherian, J., Gejo, G., Al-Jazzaf, A., Ismail, M., 2015. A voxel-based morphometric magnetic resonance imaging study of the brain detects age-

related gray matter volume changes in healthy subjects of 21-45 years old. Neuroradiol. J. 28, 450–459.
Braak, H., Braak, E., 1991. Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. Brain Pathol. 1, 213–216.
Bronen, R.A., Cheung, G., 1991. MRI of the temporal lobe: normal variations, with special reference toward epilepsy. Magn. Reson. Imaging 9, 501–507.
Burggren, A.C., Zeineh, M.M., Ekstrom, A.D., Braskie, M.N., Thompson, P.M., Small, G.W., Bookheimer, S.Y., 2008. Reduced cortical thickness in hippocampal subregions among cognitively normal apolipoprotein E e4 carriers. Neuroimage 41, 1177–1183.
Burke, S.L., Rodriguez, M.J., Barker, W., Greig-Custo, M.T., Rosselli, M., Loewenstein, D.A., Duara, R., 2018. Relationship between cognitive performance and measures of Neurodegeneration among Hispanic and white non-Hispanic individuals with normal cognition, mild cognitive impairment, and dementia. J. Int. Neuropsychol. Soc. 24, 176–187.
Cavallin, L., Bronge, L., Zhang, Y., Oksengård, A.R., Wahlund, L.O., Fratiglioni, L., Axelsson, R., 2012. Comparison between visual assessment of MTA and hippocampal volumes in an elderly, non-demented population. Acta Radiol. 53, 573–579.
Chan, D., Janssen, J.C., Whitwell, J.L., Watt, H.C., Jenkins, R., Frost, C., Rossor, M.N., Fox, N.C., 2003. Change in rates of cerebral atrophy over time in early-onset Alzheimer's disease: longitudinal MRI study. Lancet 362, 1121–1122.
Chiang, G.C., Insel, P.S., Tosun, D., Schuff, N., Truran-Sacrey, D., Raptentsetsang, S.T., Thompson, P.M., Reiman, E.M., Jack Jr., C.R., Fox, N.C., Jagust, W.J., Harvey, D.J., Beckett, L.A., Gamst, A., Aisen, P.S., Petersen, R.C., Weiner, M.W., 2011. Impact of apolipoprotein E4-cerebrospinal fluid beta-amyloid interaction on hippocampal volume loss over 1 year in mild cognitive impairment. Alzheimers Dement. 7, 514–520.
Claus, J.J., Staekenborg, S.S., Holl, D.C., Roorda, J.J., Schuur, J., Koster, P., Tielkes, C.E.M., Scheltens, P., 2017. Practical use of visual medial temporal lobe atrophy cut-off scores in Alzheimer's disease: validation in a large memory clinic population. Eur. Radiol. 27, 3147–3155.
Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923.
Da, X., Toledo, J.B., Zee, J., Wolk, D.A., Xie, S.X., Ou, Y., Shacklett, A., Parmpi, P., Shaw, L., Trojanowski, J.Q., Davatzikos, C., 2013. Alzheimer's neuroimaging initiative. Integration and relative value of biomarkers for prediction of MCI to AD progression: spatial patterns of brain atrophy, cognitive scores, APOE genotype and CSF biomarkers. Neuroimage Clin 4, 164–173.
DeCarli, C., Frisoni, G.B., Clark, C.M., Harvey, D., Grundman, M., Petersen, R.C., Thal, L.J., Jin, S., Jack Jr., C.R., Scheltens, P., 2007. Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. Arch. Neurol. 64, 108–115.
Espeseth, T., Westlye, L.T., Fjell, A.M., Walhovd, K.B., Rootwelt, H., Reinvang, I., 2008. Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E epsilon 4. Neurobiol. Aging 29, 329–340.
Ferreira, D., Cavallin, L., Larsson, E.M., Muehlboeck, J.S., Mecocci, P., Vellas, B., Tsolaki, M., Kłoszewska, I., Soininen, H., Lovestone, S., Simmons, A., Wahlund, L.O., Westman, E., AddNeuroMed consortium and the Alzheimer's Disease Neuroimaging Initiative, 2015. Practical cut-offs for visual rating scales of medial temporal, frontal and posterior atrophy in Alzheimer's disease and mild cognitive impairment. J. Intern. Med. 278, 277–290.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.
Frisoni, G.B., Beltramello, A., Weiss, C., Geroldi, C., Bianchetti, A., Trabucchi, M., 1996. Linear measures of atrophy in mild Alzheimer disease. AJNR Am. J. Neuroradiol. 17, 913–923.
Frisoni, G.B., Prestia, A., Rasser, P.E., Bonetti, M., Thompson, P.M., 2009. In vivo mapping of incremental cortical atrophy from incipient to overt Alzheimer's disease. J. Neurol. 256, 916–924.
Galluzzi, S., Testa, C., Boccardi, M., Bresciani, L., Benussi, L., Ghidoni, R., Beltramello, A., Bonetti, M., Bono, G., Falini, A., Magnani, G., Minonzio, G., Piovan, E., Binetti, G., Frisoni, G.B., 2009. The Italian brain normative archive of structural MR scans: norms for medial temporal atrophy and white matter lesions. Aging Clin. Exp. Res. 21, 266–276.
Harper, L., Fumagalli, G.G., Barkhof, F., Scheltens, P., O'Brien, J.T., Bouwman, F., Burton, E.J., Rohrer, J.D., Fox, N.C., Ridgway, G.R., Schott, J.M., 2016. MRI visual rating scales in the diagnosis of dementia: evaluation in 184 post-mortem confirmed cases. Brain 139, 1211–1225.
Hixson, J.E., Vernier, D.T., 1990. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J. Lipid Res. 31, 545–548.
Jack Jr., C.R., Petersen, R.C., Xu, Y.C., Waring, S.C., O'Brien, P.C., Tangalos, E.G., Smith, G.E., Ivnik, R.J., Kokmen, E., 1997. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. Neurology 49, 786–794.
Jack, C.R., Petersen, R.C., Xu, Y.C., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Waring, S.C., Tangalos, E.G., Kokmen, E., 1999. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 52, 1397–1403.
Jansen, W.J., Ossenkoppele, R., Knol, D.L., Tijms, B.M., Scheltens, P., Verhey, F.R., Visser, P.J., Amyloid Biomarker Study Group, Aalten, P., Aarsland, D., Alcolea, D., Alexander, M., Almdahl, I.S., Arnold, S.E., Baldeiras, I., Barthel, H., van Berckel, B.N., Bibeau, K., Blennow, K., Brooks, D.J., van Buchem, M.A., Camus, V., Cavedo, E., Chen, K., Chetelat, G., Cohen, A.D., Drzezga, A., Engelborghs, S., Fagan, A.M., Fladby, T., Fleisher, A.S., van der Flier, W.M., Ford, L., Förster, S., Fortea, J., Foskett, N., Frederiksen, K., Freund-Levi, Y., Frisoni, G.B., Froelich, L., Gabryelewicz, T., Gill, K.D., Gkatzima, O., Gómez-Tortosa, E., Gordon, M.F., Grimmer, T., Hampel, H., Hausner, L., Hellwig, S., Herukka, S.K., Hildebrandt, H., Ishihara, L., Ivanoiu, A., Jagust, W.J., Johannsen, P., Kandimalla, R., Kapaki, E., Klimkowicz-Mrowiec, A., Klunk, W.E., Köhler, S., Koglin, N., Kornhuber, J., Kramberger, M.G., Van Laere, K., Landau, S.M., Lee, D.Y., de Leon, M., Lisetti, V., Lleó, A., Madsen, K., Maier, W., Marcusson, J., Mattsson, N., de Mendonça, A., Meulenbroek, O., Meyer, P.T., Mintun, M.A., Mok, V., Molinuevo, J.L., Møllergård, H.M., Morris, J.C., Mroczko, B., Van der Mussele, S., Na, D.L., Newberg, A., Nordberg, A., Nordlund, A., Novak, G.P., Paraskevas, G.P., Parnetti, L., Perera, G., Peters, O., Popp, J., Prabhakar, S., Rabinovici, G.D., Ramakers, I.H., Rami, L., Resende de Oliveira, C., Rinne, J.O., Rodrigue, K.M., Rodríguez-Rodríguez, E., Roe, C.M., Rot, U., Rowe, C.C., Rüther, E., Sabri, O., Sanchez-Juan, P., Santana, I., Sarazin, M., Schröder, J., Schütte, C., Seo, S.W., Soetewey, F., Soininen, H., Spiru, L., Struyfs, H., Teunissen, C.E., Tsolaki, M., Vandenberghe, R., Verbeek, M.M., Villemagne, V.L., Vos, S.J., van Waalwijk van Doorn, L.J., Waldemar, G., Wallin, A., Wallin, Å.K., Wiltfang, J., Wolk, D.A., Zboch, M., Zetterberg, H., 2015. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 313, 1924–1938.
Jernigan, T.L., Archibald, S.L., Fennema-Notestine, C., Gamst, A.C., Stout, J.C., Bonner, J., Hesselink, J.R., 2001. Effects of age on tissues and regions of the cerebrum and cerebellum. Neurobiol. Aging 22, 581–594.
Jiang, J., Sachdev, P., Lipnicki, D.M., Zhang, H., Liu, T., Zhu, W., Suo, C., Zhuang, L., Crawford, J., Reppermund, S., Trollor, J., Brodaty, H., Wen, W., 2014. A longitudinal study of brain atrophy over two years in community-dwelling older individuals. Neuroimage 86, 203–211.
Koedam, E.L., Lehmann, M., van der Flier, W.M., Scheltens, P., Pijnenburg, Y.A., Fox, N., Barkhof, F., Wattjes, M.P., 2011. Visual assessment of posterior atrophy development of a MRI rating scale. Eur. Radiol. 21, 2618–2625.
Koo, T.K., Li, M.Y., 2016. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J. Chiropr. Med. 15, 155–163.
Lemaitre, H., Goldman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., Mattay, V.S., 2012. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiol. Aging 33 (617.e1-9).
Lucarelli, R.T., Peshock, R.M., McColl, R., Hulsey, K., Ayers, C., Whittemore, A.R., King, K.S., 2013. MR imaging of hippocampal asymmetry at 3T in a multiethnic, population-based sample: results from the Dallas heart study. AJNR Am. J. Neuroradiol. 34, 752–757.
Luo, X., Jiaerken, Y., Yu, X., Huang, P., Qiu, T., Jia, Y., Sun, J., Zhou, J., Zhang, M., Alzheimer's Disease Neuroimaging Initiative (ADNI), 2017. Affect of APOE on information processing speed in non-demented elderly population: a preliminary structural MRI study. Brain Imaging Behav 11, 977–985.
Marquié, M., Siao Tick Chong, M., Antón-Fernández, A., Verwer, E.E., Sáez-Calveras, N., Meltzer, A.C., Ramanan, P., Amaral, A.C., Gonzalez, J., Normandin, M.D., Frosch, M.P., Gomez-Isla, T., 2017. [F-18]-AV-1451 binding correlates with postmortem neurofibrillary tangle Braak staging. Acta Neuropathol. 134, 619–628.
Metitieri, T., Geroldi, C., Pezzini, A., Frisoni, G.B., Bianchetti, A., Trabucchi, M., 2001. The Itel-MMSE: an Italian telephone version of the mini-mental state examination. Int. J. Geriatr. Psychiatry 16, 166–167.
Pereira, J.B., Cavallin, L., Spulber, G., Aguilar, C., Mecocci, P., Vellas, B., Tsolaki, M., Kłoszewska, I., Soininen, H., Spenger, C., Aarsland, D., Lovestone, S., Simmons, A., Wahlund, L.O., Westman, E., AddNeuroMed consortium and for the Alzheimer's Disease Neuroimaging Initiative, 2014. Influence of age, disease onset and ApoE4 on visual medial temporal lobe atrophy cut-offs. J. Intern. Med. 275, 317–330.
Petersen, R.C., Aisen, P.S., Beckett, L.A., Donohue, M.C., Gamst, A.C., Harvey, D.J., Jack Jr., C.R., Jagust, W.J., Shaw, L.M., Toga, A.W., Trojanowski, J.Q., Weiner, M.W., 2010. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology 74, 201–209.
Pyun, J.M., Park, Y.H., Kim, H.R., Suh, J., Kang, M.J., Kim, B.J., Youn, Y.C., Jang, J.W., Kim, S., 2017. Alzheimer's disease neuroimaging initiative. Posterior atrophy predicts time to dementia in patients with amyloid-positive mild cognitive impairment. Alzheimers Res. Ther. 9, 99.
Ravaglia, G., Forti, P., Maioli, F., Chiappelli, M., Montesi, F., Bianchin, M., Licastro, F., Patterson, C., 2006. Apolipoprotein E e4 allele affects risk of hyperhomocysteinemia in the elderly. Am. J. Clin. Nutr. 84, 1473–1480.
Rhodius-Meester, H.F.M., Benedictus, M.R., Wattjes, M.P., Barkhof, F., Scheltens, P., Muller, M., van der Flier, W.M., 2017. MRI visual ratings of brain atrophy and white matter hyperintensities across the spectrum of cognitive decline are differently affected by age and diagnosis. Front. Aging Neurosci. 9, 117.
Riello, R., Sabattoli, F., Beltramello, A., Bonetti, M., Bono, G., Falini, A., Magnani, G., Minonzio, G., Piovan, E., Alaimo, G., Ettori, M., Galluzzi, S., Locatelli, E., Noiszewska, M., Testa, C., Frisoni, G.B., 2005. Brain volumes in healthy adults aged 40 years and over: a voxel-based morphometry study. Aging Clin. Exp. Res. 17, 329–336.
Scheltens, P., Leys, D., Barkhof, F., Huglo, D., Weinstein, H.C., Vermersch, P., Kuiper, M., Steinling, M., Wolters, E.C., Valk, J., 1992. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J. Neurol. Neurosurg. Psychiatry 55, 967–972.
Soldan, A., Pettigrew, C., Lu, Y., Wang, M.C., Selnes, O., Albert, M., Brown, T., Ratnanather, J.T., Younes, L., Miller, M.I., BIOCARD Research Team, 2015. Relationship of medial temporal lobe atrophy, APOE genotype, and cognitive reserve in preclinical Alzheimer's disease. Hum. Brain Mapp. 36, 2826–2841.
Ten Kate, M., Sanz-Arigita, E.J., Tijms, B.M., Wink, A.M., Clerigue, M., Garcia-Sebastian, M., Izagirre, A., Ecay-Torres, M., Estanga, A., Villanua, J., Vrenken, H., Visser, P.J., Martinez-Lage, P., Barkhof, F., 2016. Impact of APOE-ε4 and family history of dementia on gray matter atrophy in cognitively healthy middle-aged adults. Neurobiol. Aging 38, 14–20.
Thambisetty, M., Wan, J., Carass, A., An, Y., Prince, J.L., Resnick, S.M., 2010. Longitudinal changes in cortical thickness associated with normal aging. Neuroimage 52, 1215–1223.
Velickaite, V., Ferreira, D., Cavallin, L., Lind, L., Ahlström, H., Kilander, L., Westman, E., Larsson, E.M., 2018. Medial temporal lobe atrophy ratings in a large 75-year-old population-based cohort: gender-corrected and education-corrected normative data. Eur. Radiol. 28, 1739–1747.
Yao, Z., Hu, B., Liang, C., Zhao, L., Jackson, M., Alzheimer's Disease Neuroimaging Initiative, 2012. A longitudinal study of atrophy in amnestic mild cognitive impairment and normal aging revealed by cortical thickness. PLoS One 7, e48973.