ELSEVIER

Neurobiology of Aging 34 (2013) 73–82

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Visual ratings of atrophy in MCI: prediction of conversion and relationship with CSF biomarkers

Manja Lehmann[a,*], Esther L. Koedam[b], Josephine Barnes[a], Jonathan W. Bartlett[a,c], Frederik Barkhof[b,d], Mike P. Wattjes[b,d], Jonathan M. Schott[a], Philip Scheltens[a,b], Nick C. Fox[a,b], for the Alzheimer's Disease Neuroimaging Initiative

[a] *Dementia Research Centre, UCL Institute of Neurology, London, UK*
[b] *Alzheimer Centre and Department of Neurology, VU University Medical Centre, Amsterdam, the Netherlands*
[c] *Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK*
[d] *Department of Radiology, VU University Medical Centre, Amsterdam, the Netherlands*

Received 20 December 2011; received in revised form 14 March 2012; accepted 20 March 2012

Abstract

Medial temporal lobe atrophy (MTA) and cerebrospinal fluid (CSF) markers of Alzheimer's disease (AD) pathology may aid the early detection of AD in mild cognitive impairment (MCI). However, the relationship between structural and pathological markers is not well understood. Furthermore, while posterior atrophy (PA) is well recognized in AD, its value in predicting conversion from late-onset amnestic MCI to AD is unclear. In this study we used visual ratings of MTA and PA to assess their value in predicting conversion to AD in 394 MCI patients. The relationship of atrophy patterns with CSF Aβ1–42, tau, and p-tau(181) was further investigated in 114 controls, 192 MCI, and 99 AD patients. There was a strong association of MTA ratings with conversion to AD ($p < 0.001$), with a weaker association for PA ratings ($p = 0.047$). Specific associations between visual ratings and CSF biomarkers were found; MTA was associated with lower levels of Aβ1–42 in MCI, while PA was associated with elevated levels of tau in MCI and AD, which may reflect widespread neuronal loss including posterior regions. These findings suggest both that posterior atrophy may predict conversion to AD in late-onset MCI, and that there may be differential relationships between CSF biomarkers and regional atrophy patterns.

Keywords: Alzheimer's Disease Neuroimaging Initiative (ADNI); Visual rating scales; Posterior atrophy; Medial temporal lobe atrophy; Magnetic resonance imaging (MRI); cerebrospinal fluid (CSF); Biomarkers; Mild cognitive impairment (MCI); Alzheimer's disease (AD); Conversion

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia (Hebert et al., 2003). With aging populations, the number of patients with AD will rise dramatically, with it estimated to affect 81 million people worldwide by 2040 (Ferri et al., 2005). It is generally believed that patients with AD go through a "prodromal" phase before developing clinical AD. One prodromal stage which is increasingly well recognized is mild cognitive impairment (MCI) which is characterized by cognitive deficits (in particular memory) that are not severe enough to make a diagnosis of dementia (Morris et al., 2001; Petersen et al., 2001).

Histopathological studies have shown that the hallmarks of AD, namely amyloid plaques and neurofibrillary tangles, precede neuronal loss in presymptomatic AD patients (Price and Morris, 1999), and are also present in MCI subjects (Jicha et al., 2006; Markesbery et al., 2006; Price and Morris, 1999). Consistent with histopathological findings, cerebrospinal fluid (CSF) studies suggest that changes in Aβ1–42, tau, and phosphorylated tau (p-tau) levels precede clinical symptoms in AD (Fjell et al., 2008). More specifi-

* Corresponding author at: Dementia Research Centre, Box16 National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK. Tel.: +44 2034483962; fax: +44 2076762066.
E-mail address: m.lehmann@ucl.ac.uk (M. Lehmann).

0197-4580/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2012.03.010

cally, reduced levels of Aβ1–42 and elevated levels of tau and p-tau have been shown to reflect the presence of AD pathology (Blennow and Hampel, 2003) and predict progression from MCI to AD (Hansson et al., 2006). While concentrations of CSF Aβ1–42 have been shown to correlate well with density of plaques at postmortem (Strozyk et al., 2003), levels of tau and p-tau are not only correlated with density of neurofibrillary tangles (Tapiola et al., 1997), but are also indicative of neuronal injury. The accumulation of tau in neurons has been suggested to disrupt neuronal activity followed by the release of tau cytoskeletal elements into the extracellular space, which then appears in the CSF (Arai et al., 1995; Blennow et al., 1995).

A growing number of research studies have aimed to find imaging biomarkers that predict which patients with MCI will convert to AD. Hippocampal and medial temporal lobe atrophy on magnetic resonance imaging (MRI) is a characteristic and early feature of AD (Frisoni et al., 2010; van der Flier et al., 2011). The pattern of progression of atrophy through the brain appears to mirror that described for the appearance of tau pathology from autopsy studies (Braak and Braak, 1991; Likeman et al., 2005; Whitwell et al., 2008a). Both atrophy in the medial temporal lobe, in particular hippocampal atrophy, and CSF markers have been shown to be predictive of conversion from MCI to AD (Hampel et al., 2010a, 2010b; Hansson et al., 2006; Jack et al., 1999; Killiany et al., 2002; Whitwell et al., 2008b). As a result both MRI and CSF biomarkers have been included in proposed diagnostic criteria for AD (Albert et al., 2011; Dubois et al., 2007).

While a number of studies have examined associations between atrophy patterns and CSF biomarkers, these were often restricted to medial temporal lobe regions. For example, Aβ1–42 levels have been shown to be related to hippocampal volumes (Fjell et al., 2008) and hippocampal atrophy rates (Chiang et al., 2011; de Leon et al., 2006; Schuff et al., 2009) in MCI. Some studies have also reported associations of tau and p-tau levels with hippocampal volumes in MCI (Fjell et al., 2008) and AD (Hampel et al., 2005), however, others have not found such a relationship (Schuff et al., 2009). A study by Tosun et al. (2010) that used a region-unbiased approach to investigate relationships between atrophy and CSF markers across the brain found that tau and p-tau levels were associated with smaller caudate volumes, while baseline concentrations of CSF Aβ1–42 were associated with smaller gray matter volumes in lingual, pericalcarine, and postcentral cortices in AD.

In addition to the importance of medial temporal lobe atrophy in MCI and AD, posterior regions are increasingly recognized to be affected in AD (Jones et al., 2006; Karas et al., 2007). Posterior atrophy has been shown to be particularly prominent in early-onset AD cases (Frisoni et al., 2007; Ishii et al., 2005; Shiino et al., 2008), and aid distinction of AD from other dementias such as frontotemporal lobar degeneration (FTLD) (Du et al., 2007; Lehmann et al., 2012; Likeman et al., 2005), suggesting that it might be a useful additional biomarker for early-onset AD. However, the role of posterior atrophy in late-onset MCI is not well understood.

Visual rating scales are increasingly used to assess atrophy for routine clinical use (Scheltens et al., 1992, 1997). In the current study, visual rating scales are used to assess atrophy in the medial temporal lobe and in posterior cortical regions. The medial temporal lobe atrophy (MTA) scale (Scheltens et al., 1992) has been shown to discriminate well between AD and healthy controls (Scheltens et al., 1992, 1995), and to predict conversion from MCI to AD (Korf et al., 2004). We have recently developed a visual rating scale for posterior atrophy (PA), which includes the posterior cingulate gyrus, precuneus, and parietal lobe (Koedam et al., 2011; Lehmann et al., 2012). This scale has been shown to improve the distinction between patients with pathologically confirmed AD from those with pathologically confirmed FTLD, and may also be valuable in distinguishing early-onset AD from younger controls (Koedam et al., 2011; Lehmann et al., 2012).

The aims of this study were (1) to assess the value of MTA and PA visual ratings in predicting time to conversion from MCI to clinical AD, and (2) to investigate relationships between atrophy patterns and CSF levels of Aβ1–42, tau, and p-tau in controls, MCI and AD.

2. Methods

2.1. Subjects

All subjects were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, M.D., Veterans Affairs Medical Center and University of California—San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the USA and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for

Table 1
Subject demographics, CSF levels, and visual ratings in controls, MCI, and AD

	Control	MCI	AD	p^a
n	114	192	99	—
Age, y	75.6 (5.2)	74.7 (7.4)	74.9 (7.9)	0.79
Gender, % male	51%	67%	59%	0.02[b]
ApoE4 carrier, %	24%	54%	70%	<0.0001[b]
MMSE	29.1 (1.0)	26.9 (1.8)	23.6 (1.9)	<0.0001
ADAS-Cog	6.4 (2.9)	11.7 (4.5)	18.2 (6.2)	<.0001
TIV, mL	1508 (149)	1546 (148)	1523 (173)	0.12
Time between CSF and MRI, d	30.6 (25.0)	33.2 (25.4)	28.3 (16.5)	0.26
CSF biomarkers				
Aβ1–42, pg/mL	206 (55)	163 (54)	143 (41)	<0.0001
Tau, pg/mL	70 (30)	104 (61)	122 (58)	<0.0001
P-tau, pg/mL	25 (15)	36 (18)	42 (20)	<0.0001
Visual ratings				
MTA[c]	0.6 (0.6)	1.1 (0.9)	1.5 (1.0)	<0.0001
PA[c]	1.2 (0.8)	1.3 (0.8)	1.4 (0.7)	0.44

Shown are mean (SD) unless specified. Maximum score on MMSE = 30, and on ADAS-Cog, maximum errors = 70.
Key: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's disease Assessment Scale-cognitive subscale; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy; PA, posterior atrophy; p-tau, phosphorylated tau; TIV, total intracranial volume.
[a] Kruskal-Wallis test (except gender and ApoE ε4).
[b] Fisher's exact test.
[c] Mean left and right hemisphere.

3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information, see www.adni-info.org.

Data were downloaded from LONI (adni.loni.ucla.edu) in June 2011. MCI subjects were included in the time to AD conversion analysis (see below) if they had one 1.5 T MRI scan available. For the CSF analysis, control, MCI, and AD subjects were included if they had one 1.5 T MRI scan and CSF data available. Subjects were classified into diagnostic groups according to their baseline clinical diagnosis. Demographics of the 3 clinical groups used in the CSF analysis are shown in Table 1. The baseline scan and baseline CSF data were used for each subject. All subjects had a standardized cognitive assessment at baseline which included the Mini Mental State Examination (MMSE) and the 11-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog). CSF measures of Aβ1–42, tau, and p-tau(181) were performed centrally, as previously described (Shaw et al., 2009).

2.2. MR imaging

Details of the magnetic resonance (MR) methodology have previously been described (Jack et al., 2008). In brief, MR imaging was performed using standardized protocols on 1.5T MRI units. MR protocols included the acquisition of high-resolution volumetric T1-weighted, inversion recovery prepared, structural images. Postprocessing steps included corrections for distortion due to gradient nonlinearity, for image intensity non-uniformity, and scalings based on phantom measures. Total intracranial volumes (TIV) were calculated using Jacobian integration in statistical parametric mapping (SPM) Version 8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/).

2.3. Visual rating scales

All scans were assessed by 1 rater (M.D. with 4-year experience in imaging in dementia) blinded to diagnoses and clinical information.

2.3.1. MTA scale

MTA was assessed using a standardized scale (Scheltens et al., 1992, 1995). T1-weighted images were viewed in the coronal plane and scores for the left and right hemispheres were recorded. 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.

2.3.2. PA scale

PA was rated according to a previously described protocol which has been shown to have good intra- and interrater agreement (Koedam et al., 2011; Lehmann et al., 2012). In brief, PA was scored on T1-weighted images viewed in the sagittal, axial, and coronal planes (Fig. 1). Separate scores for the left and right hemispheres were obtained. The PA scale rates atrophy on a 4-point scale: grade 0 represents closed posterior cingulate and parieto-occipital sulci and closed sulci of the parietal lobes and precuneus; grade 1 includes a mild widening of the posterior cingulate and parieto-occipital sulci, with mild atrophy of the parietal lobes and precuneus; grade 2 shows substantial widening of the posterior cingulate and parieto-occipital sulci, with substantial atrophy of the parietal lobes and precuneus; and grade 3 represents end-stage atrophy with evident widening of the posterior cingulate and parieto-occipital sulci and knife-blade atrophy of the parietal lobes and

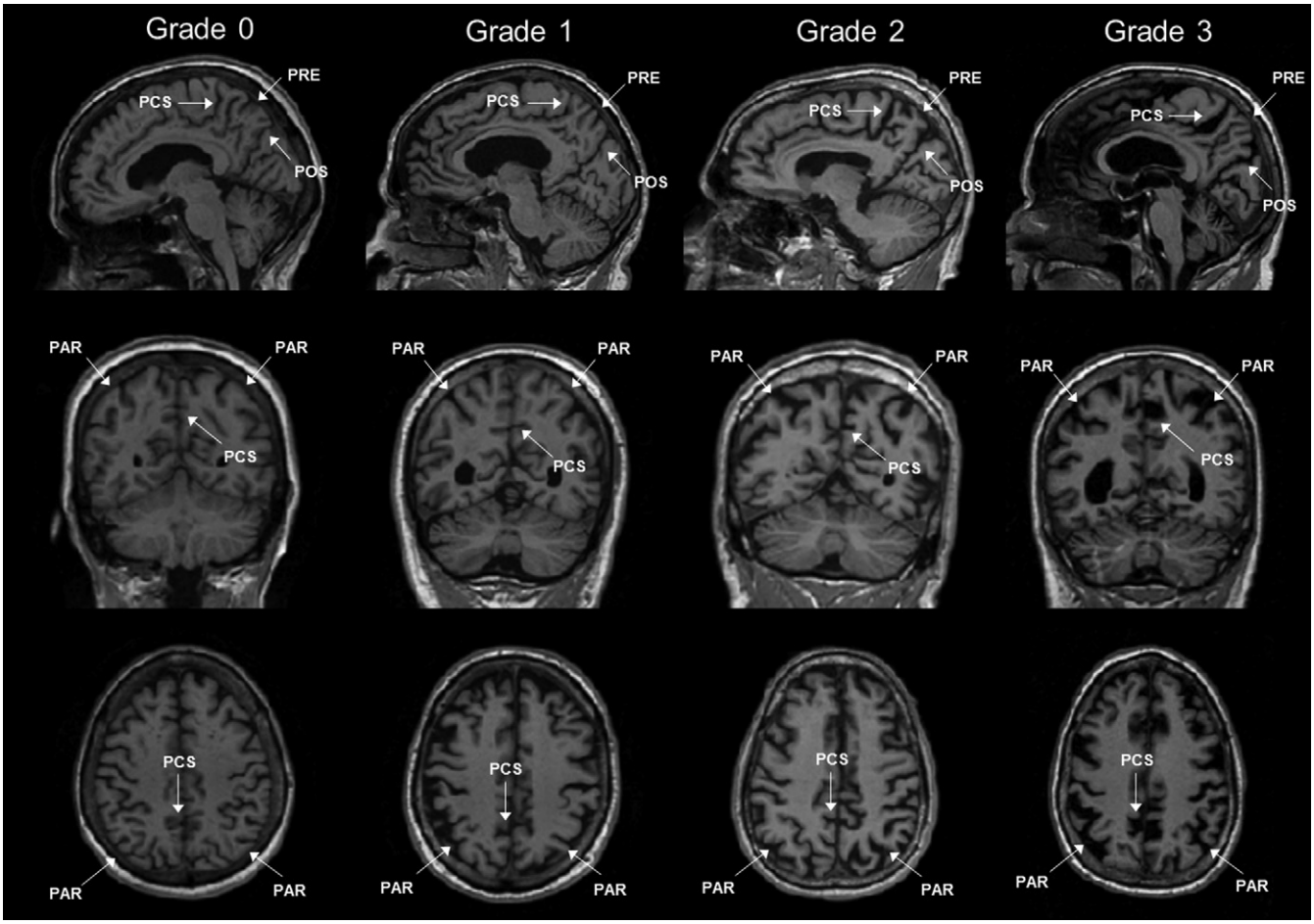

Fig. 1. T1-weighted sagittal (top), coronal (middle), and axial (bottom) images as examples for each grade of the posterior atrophy (PA) scale; grade 0 = no atrophy; grade 1 = minimal atrophy; grade 2 = moderate atrophy; and grade 3 = severe atrophy. Abbreviations: PAR, parietal lobe; PCS, posterior cingulate sulcus; POS, parieto-occipital sulcus; PRE, precuneus.

precuneus. When there was a difference between scores in the different planes (e.g., score 1 for the sagittal view and score 2 for the axial view), the highest score was given.

2.4. Statistical analysis

Statistical analyses were performed using Stata Version 11.2 (STATA Corp, College Station, TX, USA). Kruskal-Wallis tests were used to compare continuous or ordinal variables between the subject groups and Fisher's exact was used to compare binary variables.

2.4.1. Time to clinical AD conversion

The ability of visual rating scores to predict time to conversion from MCI to clinical AD was assessed using survival analysis methods. MCI subjects in ADNI were scheduled to be assessed at 6, 12, 18, 24, and 36 months post baseline. Due to the resulting discrete nature of the times to conversion, and because a small number of MCI subjects missed intermediate follow-up visits, we fitted parametric (Gompertz) models using the user-written Stata command, intcens, which accommodates interval censored data. Those subjects not seen to convert to AD were treated as right-censored at their last follow-up visit. For those subjects observed to convert to AD, the analysis assumes their time to conversion as having taken place at some point between their last visit at which they were still MCI and the first visit at which they were classified as AD. Models were fitted using (1) MTA rating, (2) PA rating, and (3) MTA and PA ratings as covariates, with the latter enabling an assessment of any predictive value of PA ratings independent of MTA ratings. In order to assess the predictive value of the visual ratings on their own, no other variables were adjusted for in this part of the analysis. Results are reported as hazard ratio (HR) for a 1 unit increase in the corresponding rating scale, with 95% confidence interval (CI). Estimates and 95% bias-corrected and accelerated bootstrap (2000 bootstrap samples) confidence intervals were found from the fitted models for the probability of conversion to AD by 1 and 3 years according to MTA/PA ratings. All MCI subjects that had one 1.5T MRI scan available were included in this part of the analysis.

2.4.2. Associations of visual rating scores with CSF biomarkers

In order to assess whether CSF biomarkers were associated with visual rating scores, a linear regression analysis was conducted with CSF biomarkers (Aβ1–42, tau, p-tau) as dependent variable and visual ratings (MTA and PA in separate models) as independent variable, adjusting for age, gender, and TIV. This analysis only included subjects that had both MRI and CSF data available (Table 1). Regressions were conducted separately in each clinical group. In order to assess the potential impact of ApoE ε4 status, the regression analysis was repeated including ApoE ε4 status as additional covariate. The analysis was further repeated adjusting for disease severity (in addition to age, gender, and TIV) using MMSE and ADAS-Cog scores as measures of general cognitive functioning and disease severity in 2 separate models.

3. Results

3.1. Subject demographics

In total 394 MCI subjects were included in the time to AD conversion analysis (age mean [SD] = 74.9 [7.4] years; 65% male), although 14 attended no follow-up visits and hence did not contribute any information. Of these 394 MCI subjects, 163 subjects (41%) had converted to a diagnosis of AD (time to conversion mean [SD] = 18.6 [9.3] months), whereas 231 subjects (59%) had not converted to AD at their last available assessment. The CSF analysis included 114 controls, 192 MCI, and 99 AD subjects (Table 1). Of the 192 MCI subjects, 87 subjects (45%) had converted to a diagnosis of AD (time to conversion mean [SD] = 18.8 [9.4] months), whereas 105 subjects (55%) had not converted to AD at their last available assessment. There was no significant difference in age or interval between MRI and CSF acquisition across all 3 clinical groups, however, there was a significant difference in gender distribution (p = 0.02), with significantly more male subjects in the MCI group than in the control and AD groups. As expected there was a significant difference in MMSE and ADAS-Cog scores ($p < 0.0001$), and ApoE ε4 status ($p < 0.0001$). For the CSF biomarkers there was the expected pattern of differences across the 3 groups in Aβ1–42 levels (with MCI and AD showing reduced levels, $p < 0.0001$), as well as tau and p-tau levels (with MCI and AD showing elevated levels, $p < 0.0001$). For the atrophy measures there were differences in MTA ratings ($p < 0.0001$) between the 3 groups. While PA ratings were also marginally higher in the MCI and AD groups compared with controls, this was not statistically significant (p = 0.44).

3.2. Time to conversion to clinical AD

There was strong evidence that MTA ratings were associated with hazard (instantaneous risk) of conversion to clinical AD, with a 1-point increase in mean rating estimated to increase hazard of conversion by 45% (95% CI, 23%–70%; $p < 0.001$). There was borderline statistically significant evidence (p = 0.047) that PA ratings were associated with hazard of conversion, with a 1-point increase associated with a 23% (95% CI, 0%–50%) increase in hazard. Including both MTA and PA ratings as covariates, MTA score remained independently predictive of hazard (HR, 1.45; 95% CI, 1.23–1.72), and PA also remained borderline statistically significant (HR, 1.22; 95% CI, 1.01–1.49), suggesting the 2 scales provide complementary predictive value. There was a 37% probability of converting to AD at 3 years for an MTA score of 0 (13% at 1 year, Table 2), while an MTA score of 3 produced an estimated probability of conversion of 76% at 3 years (34% at 1 year). The probability of converting to clinical AD for a PA score of 0 was 41% at 3 years (15% at 1 year), while a PA score of 3 showed an estimated probability of conversion of 62% at 3 years (26% at 1 year).

Table 2
Estimated probability (%) of conversion to AD by 1 and 3 years (95% CI) in patients with MCI according to mean MTA or PA grade at baseline

Mean grade	MTA		PA	
	1 y	3 y	1 y	3 y
0	13 (10–17)	37 (30–45)	15 (11–20)	41 (32–51)
1	18 (15–21)	49 (43–55)	18 (15–22)	48 (41–54)
2	25 (21–30)	62 (54–69)	22 (17–26)	55 (47–62)
3	34 (26–44)	76 (63–86)	26 (18–35)	62 (49–75)

Grades reflect mean of left and right hemisphere ratings.
Key: AD, Alzheimer's disease; CI, confidence interval; MCI, mild cognitive impairment; MTA, medial temporal lobe atrophy; PA, posterior atrophy.

3.3. Associations of visual ratings with CSF biomarkers

The results of the association analysis of visual ratings with CSF markers are presented in Table 3. For MTA the only significant association found was with Aβ1–42 in the MCI group (p = 0.02), with an increase in MTA score associated with a decrease in Aβ1–42. In contrast, higher PA ratings were significantly associated with higher levels of tau and p-tau in the MCI group (p = 0.02 for both markers), as well as higher levels of tau in the AD group (p = 0.005). There was no evidence of a significant association of PA ratings with Aβ1–42 in any of the 3 clinical groups, or with any of the 3 biomarkers in the control group. Similar results were found after adjusting for ApoE ε4 status (Supplementary Table 1).

Adjusting for disease severity (MMSE and ADAS-Cog, in separate models) revealed that the association of MTA ratings with Aβ1–42 levels in the MCI subjects became less significant (p = 0.04) when correcting for MMSE and nonsignificant (p = 0.08) for the ADAS-Cog. In contrast, the associations of PA ratings with tau and p-tau in MCI remained significant (MMSE: tau and p-tau p = 0.02; ADAS-Cog: tau p = 0.03; p-tau p = 0.04). The association

Table 3
Regression coefficients (95% CI) and significance level for associations of visual ratings with CSF markers

Scale	CSF marker	Controls	MCI	AD
MTA	Aβ1–42, pg/mL	3.3 (−14.4 to 20.9)	−10.8 (−20.0 to −1.6)*	3.0 (−5.8 to 11.9)
	Tau, pg/mL	−4.3 (−13.9 to 5.3)	0.1 (−10.4 to 10.5)	−5.7 (−18.6 to 7.2)
	P-Tau, pg/mL	−1.2 (−5.7 to 3.3)	−0.5 (−3.6 to 2.6)	−1.6 (−6.0 to 2.8)
PA	Aβ1–42, pg/mL	0.8 (−14.2 to 15.8)	1.7 (−8.5 to 11.8)	−0.5 (−12.0 to 10.9)
	Tau, pg/mL	0.7 (−7.5 to 8.9)	13.4 (2.2 to 24.5)*	23.4 (7.4 to 39.3)**
	P-Tau, pg/mL	3.7 (−0.1 to 7.5)	4.0 (0.7 to 7.3)*	4.7 (−0.9 to 10.3)

Estimated increase in CSF variables per 1 unit increase in medial temporal lobe atrophy (MTA); or posterior atrophy (PA) ratings. Ratings are mean score of left and right hemisphere. Regression model included age, gender, and total intracranial volumes (TIV) as covariates.
Key: AD, Alzheimer's disease; CI, confidence interval; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; p-tau, phosphorylated tau.
* $p \leq 0.05$.
** $p \leq 0.005$.

of PA ratings with tau levels in the AD group also remained highly significant ($p = 0.005$ for both MMSE and ADAS-Cog adjustments).

4. Discussion

This study assessed the predictive value of visual ratings of MTA and PA for the conversion to clinical AD in patients with late-onset amnestic MCI. It further assessed relationships of visual ratings with CSF biomarkers (Aβ1–42, tau, and p-tau) in controls, MCI, and AD. The probability of conversion from MCI to AD at either 1- or 3-year follow-up was approximately twice as high for those MCI subjects with the greatest medial temporal lobe atrophy scores when compared with those with no atrophy. The results further showed strong evidence that MTA ratings were predictive of hazard for conversion to AD, with a similar trend found for PA ratings, which was borderline significant. Larger MTA ratings were associated with lower levels of Aβ1–42 in the MCI subjects, although this became less statistically significant after adjustment for disease severity. Higher PA ratings were associated with higher levels of tau in both MCI and AD, which was independent of disease severity, and may reflect widespread neuronal loss including posterior regions in these groups. Finally, PA ratings were also associated with higher levels of p-tau in the MCI subjects, which may reflect that a significant proportion of these subjects have AD.

The finding of atrophy in the medial temporal lobes being predictive of the hazard of conversion from MCI to AD is in accordance with previous studies (Devanand et al., 2007; Fleisher et al., 2008; Jack et al., 1999; Vemuri et al., 2009). A study by Korf et al. (2004) showed that visual ratings of MTA were significantly associated with dementia at follow-up, with a hazard ratio of 1.5 for every point increase in atrophy score ($p < 0.001$). Higher PA ratings were also found to be predictive of hazard for progression to AD, which was borderline significant ($p = 0.047$). Combining MTA and PA ratings in the same model did not alter these, suggesting that both scales provide independent information regarding future risk of conversion. While only 13% of MCI subjects with a baseline grade 0 score on the MTA scale converted to AD at 1 year, over a third (34%) of those with the most severe MTA atrophy converted by 1 year. Interestingly, the rates of conversion at 1 and 3 years were very similar for those with a grade 0 on either the MTA or the PA scale and also similar for grade 1 or grade 2 on either scale, whereas the MTA grade 3 atrophy rating showed a higher probability of conversion than a grade 3 rating on the PA scale. The fact that the MTA scale showed a larger difference in probabilities of conversion between grade 0 and 3 (for both 1 and 3 years) than the PA scale further suggests a greater discriminatory ability of the MTA scale. The relatively low predictive value of PA ratings found in this study might be due to the relatively old age of the MCI subjects included (mean age 75 years). A recent imaging study showed that PA ratings improve the distinction of early-onset AD patients from younger controls, however, PA ratings were not found to aid the separation of late-onset AD patients from older controls (Lehmann et al., 2012). The relatively old age of the subjects included in this study may further explain why PA ratings were not significantly different between controls, MCI, and AD. Further investigation of the predictive value of the PA scale in younger MCI subjects is required to fully evaluate its potential for the early diagnosis of AD.

The CSF regression analyses revealed significant evidence that higher MTA ratings are associated with lower levels of Aβ1–42 in the MCI subjects. This finding is in accordance with previous cross-sectional and longitudinal studies (de Leon et al., 2006; Fjell et al., 2008; Schuff et al., 2009). In a cross-sectional study by Fjell et al. (2008) involving 19 MCI patients, levels of tau and Aβ1–42 were associated with lower volumes in the hippocampus, and entorhinal cortex. Decreased levels of Aβ1–42 at baseline have previously been shown to be associated with higher rates of hippocampal loss in MCI subjects (also ADNI; Chiang et al., 2011; Schuff et al., 2009). Because the hippocampus is relatively spared from early amyloid burden (Silbert et al., 2003), correlations between medial temporal lobe atrophy and decreased levels of CSF Aβ1–42 found in

research studies have been suggested to indicate that both measures provide complementary information about the presence of AD pathology (Schuff et al., 2009). In the current study, the association of MTA with Aβ1–42 became nonsignificant after correcting for disease severity as measured using the ADAS-Cog. This may suggest that this association is driven by the fact that the MCI group contains a bimodal population (i.e., it includes patients who have AD and poor neuropsychology scores, and patients who, most likely, do not have AD and have better cognitive scores).

In contrast, associations of PA ratings with tau in MCI and AD remained highly significant after adjusting for disease severity. Studies have suggested that increased levels of CSF tau are indicative of neuronal injury (Blennow et al., 1995; Tapiola et al., 2009). Because the PA scale encompasses a relatively large region, PA ratings represent widespread posterior atrophy. Both tau levels and PA ratings therefore reflect neuronal loss, which may explain the association seen between these 2 markers. Our finding of an association of posterior atrophy with tau levels is in accordance with a study by Fjell et al. (2008) that showed associations between tau levels and lower volumes in the inferior parietal lobe. A recent study using voxel-based morphometry to study associations between regional brain atrophy and CSF biomarkers in a combined cohort of 11 controls, 10 patients with subjective memory complaints, and 9 mild AD subjects revealed significant correlations between elevated levels of tau and gray matter atrophy in temporoparietal regions which was independent of disease severity as measured using the Clinical Dementia Rating Sum of Boxes (CDR-SB) scores (Sole-Padulles et al., 2011).

Additionally, PA ratings were also associated with p-tau levels in the MCI subjects. In contrast to total tau concentration, p-tau levels not only reflect neuronal injury, but may more directly reflect the phosphorylation state of tau in the brain, making them a more specific marker of AD pathology (Blennow and Hampel, 2003). The association of p-tau levels with PA ratings found in the MCI subjects therefore suggest that a proportion of these patients may indeed have AD pathology. In contrast, there was no evidence of an association between PA ratings and p-tau levels in the AD group, which may point to reduced variability in the p-tau levels in the AD group. It should also be noted that, while a lack of evidence for an association between visual ratings and CSF biomarkers may be driven by less variability in 1 of these markers in a specific group (e.g., Aβ1–42 levels may have plateaued in the AD group), it may also point to a lack of sensitivity to detect associations. For example, it is possible that, because the visual rating scales used in the current study include a relatively small number of categories, they may be less powerful measures of atrophy relative to other MRI atrophy measures (e.g., volumetrics).

The involvement of posterior regions in MCI has also been reported in studies using other imaging modalities such as fluorodeoxyglucose (FDG) PET which has been shown to be indicative of reduced synaptic functioning (Chételat et al., 2003; Herholz, 2003; Mosconi et al., 2004; Nestor et al., 2003). FDG-PET studies have also suggested that hypometabolism occurs first in posterior regions such as precuneus and posterior cingulate gyrus, and then lateral temporal and frontal regions (for review see Jack et al., 2010). MRI studies have also shown that posterior cingulate/precuneus atrophy may occur very early in the pathogenesis of familial AD (Scahill et al., 2002). The data presented in the current study suggest that posterior atrophy also plays a role in late-onset amnestic MCI, and that widespread neuronal loss in posterior regions is associated with other markers of neuronal injury such as CSF levels of tau.

With the strength of large subject numbers, the current study contributes to the growing interest of determining the relationship between atrophy patterns and CSF markers in MCI and AD. However, because the posterior visual rating scale represents an average of atrophy seen in several posterior regions, and therefore reflects global posterior atrophy, further studies are required to examine the relationship of atrophy in specific posterior regions (such as precuneus and posterior cingulate gyrus) with CSF biomarkers. Longitudinal studies are further needed to assess relationships between changes in atrophy (e.g., changes in volumes or cortical thickness) and changes in CSF levels of Aβ1–42, tau, and p-tau. Because we aimed to evaluate the predictive value of visual ratings in clinic practice, the ratings of 1 rater were used in this study. Previous studies have shown good inter- and intrarater reliabilities for both scales (Koedam et al., 2011; Lehmann et al., 2012; Scheltens et al., 1995). It should further be noted that, while most MCI subjects included in this study have a relatively amnestic presentation as defined by the ADNI eligibility criteria (www.adni-info.org/scientists/ADNIGrant/ProtocolSummary.aspx), this group may include MCI subjects with deficits in other cognitive domains.

One potential limitation is the variety of scanners used to obtain MR images. It is unclear how MTA and PA ratings are affected by image differences due to different scanners. However, it has been shown that MTA ratings are comparable using MRI and computed tomography (CT) (Wattjes et al., 2009).

In summary, our study shows that MTA visual ratings are predictive of hazard of conversion to AD in patients with late-onset amnestic MCI, with some evidence that PA ratings are also useful. Furthermore, our results suggest the 2 scales may offer independent and complementary predictive information regarding AD conversion risk. Widespread posterior atrophy is further associated with another marker of neuronal injury: CSF tau, in both MCI and AD. These findings suggest that posterior atrophy should be considered in late-onset MCI patients, in particular in the absence of clear medial temporal lobe atrophy.

Disclosure statement

University College London (UCL) has received payment from Abbott, Eisai, Elan, Eli Lilly, GE Healthcare, IXICO, Janssen, Lundbeck, Pfizer, Sanofi-Aventis, and Wyeth Pharmaceuticals for image analysis services and/or for consultancy by Professor Fox. The remaining authors disclose no conflicts of interest.

Acknowledgements

This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centers funding scheme. The Dementia Research Centre is an Alzheimer's Research UK Co-ordinating Center and has also received equipment funded by the Alzheimer's Research UK. M.L. is supported by an Alzheimer's Research UK Travel Fellowship, E.L.K. is supported by Internationale Stichting Alzheimer Onderzoek (ISAO), J.M.S. is a UK HEFCE Senior Clinical Lecturer, and received grant support from Alzheimer's Research UK; N.C.F. is supported by an MRC (UK) Senior Clinical Fellowship and holds a National Institute for Health Research (NIHR) senior investigator award.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Amorfix Life Sciences Ltd.; AstraZeneca; Bayer HealthCare; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles. This research was also supported by NIH grants P30 AG010129, K01 AG030514, and the Dana Foundation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2012.03.010.

References

Albert, M.S., Dekosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 270–279.

Arai, H., Terajima, M., Miura, M., Higuchi, S., Muramatsu, T., Machida, N., Seiki, H., Takase, S., Clark, C.M., Lee, V.M., 1995. Tau in cerebrospinal fluid: a potential diagnostic marker in Alzheimer's disease. Ann Neurol 38, 649–652.

Blennow, K., Hampel, H., 2003. CSF markers for incipient Alzheimer's disease. Lancet Neurol. 2, 605–613.

Blennow, K., Wallin, A., Agren, H., Spenger, C., Siegfried, J., Vanmechelen, E., 1995. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? Mol. Chem. Neuropathol. 26, 231–245.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259.

Chételat, G., Desgranges, B., de la Sayette, V., Viader, F., Eustache, F., Baron, J.C., 2003. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease? Neurology 60, 1374–1377.

Chiang, G.C., Insel, P.S., Tosun, D., Schuff, N., Truran-Sacrey, D., Raptentsetsang, S.T., Thompson, P.M., Reiman, E.M., Jack, C.R., Jr., Fox, N.C., Jagust, W.J., Harvey, D.J., Beckett, L.A., Gamst, A., Aisen, P.S., Petersen, R.C., Weiner, M.W., Alzheimer's Disease Neuroimaging Initiative, 2011. Impact of apolipoprotein ϵ4-cerebrospinal fluid beta-amyloid interaction on hippocampal volume loss over 1 year in mild cognitive impairment. Alzheimers Dement. 7, 514–520.

de Leon, M.J., DeSanti, S., Zinkowski, R., Mehta, P.D., Pratico, D., Segal, S., Rusinek, H., Li, J., Tsui, W., Saint Louis, L.A., Clark, C.M., Tarshish, C., Li, Y., Lair, L., Javier, E., Rich, K., Lesbre, P., Mosconi, L., Reisberg, B., Sadowski, M., DeBernadis, J.F., Kerkman, D.J., Hampel, H., Wahlund, L.O., Davies, P., 2006. Longitudinal CSF and MRI biomarkers improve the diagnosis of mild cognitive impairment. Neurobiol. Aging 27, 394–401.

Devanand, D.P., Pradhaban, G., Liu, X., Khandji, A., De Santi, S., Segal, S., Rusinek, H., Pelton, G.H., Honig, L.S., Mayeux, R., Stern, Y., Tabert, M.H., de Leon, M.J., 2007. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. Neurology 68, 828–836.

Du, A.T., Schuff, N., Kramer, J.H., Rosen, H.J., Gorno-Tempini, M.L., Rankin, K., Miller, B.L., Weiner, M.W., 2007. Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. Brain 130, 1159–1166.

Dubois, B., Feldman, H.H., Jacova, C., Dekosky, S.T., Barberger-Gateau, P., Cummings, J., Delacourte, A., Galasko, D., Gauthier, S., Jicha, G., Meguro, K., O'Brien, J., Pasquier, F., Robert, P., Rossor, M., Salloway,

S., Stern, Y., Visser, P.J., Scheltens, P., 2007. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 6, 734–746.

Ferri, C.P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., Hall, K., Hasegawa, K., Hendrie, H., Huang, Y., Jorm, A., Mathers, C., Menezes, P.R., Rimmer, E., Scazufca, M., Alzheimer's Disease International, 2005. Global prevalence of dementia: a Delphi consensus study. Lancet 366, 2112–2117.

Fjell, A.M., Walhovd, K.B., Amlien, I., Bjørnerud, A., Reinvang, I., Gjerstad, L., Cappelen, T., Willoch, F., Due-Tønnessen, P., Grambaite, R., Skinningsrud, A., Stenset, V., Fladby, T., 2008. Morphometric changes in the episodic memory network and tau pathologic features correlate with memory performance in patients with mild cognitive impairment. AJNR Am. J. Neuroradiol. 29, 1183–1189.

Fleisher, A.S., Sun, S., Taylor, C., Ward, C.P., Gamst, A.C., Petersen, R.C., Jack, C.R., Aisen, P.S., Thal, L.J., 2008. Volumetric MRI vs clinical predictors of Alzheimer disease in mild cognitive impairment. Neurology 70, 191–199.

Frisoni, G.B., Fox, N.C., Jack, C.R., Jr., Scheltens, P., Thompson, P.M., 2010. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 6, 67–77.

Frisoni, G.B., Pievani, M., Testa, C., Sabattoli, F., Bresciani, L., Bonetti, M., Beltramello, A., Hayashi, K.M., Toga, A.W., Thompson, P.M., 2007. The topography of grey matter involvement in early and late onset Alzheimer's disease. Brain 130, 720–730.

Hampel, H., Blennow, K., Shaw, L.M., Hoessler, Y.C., Zetterberg, H., Trojanowski, J.Q., 2010a. Total and phosphorylated tau protein as biological markers of Alzheimer's disease. Exp. Gerontol. 45, 30–40.

Hampel, H., Bürger, K., Pruessner, J.C., Zinkowski, R., DeBernardis, J., Kerkman, D., Leinsinger, G., Evans, A.C., Davies, P., Möller, H.J., Teipel, S.J., 2005. Correlation of cerebrospinal fluid levels of tau protein phosphorylated at threonine 231 with rates of hippocampal atrophy in Alzheimer disease. Arch. Neurol. 62, 770–773.

Hampel, H., Shen, Y., Walsh, D.M., Aisen, P., Shaw, L.M., Zetterberg, H., Trojanowski, J.Q., Blennow, K., 2010b. Biological markers of amyloid beta-related mechanisms in Alzheimer's disease. Exp. Neurol. 223, 334–346.

Hansson, O., Zetterberg, H., Buchhave, P., Londos, E., Blennow, K., Minthon, L., 2006. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol. 5, 228–234.

Hebert, L.E., Scherr, P.A., Bienias, J.L., Bennett, D.A., Evans, D.A., 2003. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch. Neurol. 60, 1119–1122.

Herholz, K., 2003. PET studies in dementia. Ann. Nucl. Med. 17, 79–89.

Ishii, K., Kawachi, T., Sasaki, H., Kono, A.K., Fukuda, T., Kojima, Y., Mori, E., 2005. Voxel-based morphometric comparison between early- and late-onset mild Alzheimer's disease and assessment of diagnostic performance of Z score images. AJNR Am. J. Neuroradiol. 26, 333–340.

Jack, C.R., Bernstein, M.A., Fox, N.C., Thompson, P., Alexander, G., Harvey, D., Borowski, B., Britson, P.J., L. Whitwell, J., Ward, C., Dale, A.M., Felmlee, J.P., Gunter, J.L., Hill, D.L., Killiany, R., Schuff, N., Fox-Bosetti, S., Lin, C., Studholme, C., DeCarli, C.S., Krueger, G., Ward, H.A., Metzger, G.J., Scott, K.T., Mallozzi, R., Blezek, D., Levy, J., Debbins, J.P., Fleisher, A.S., Albert, M., Green, R., Bartzokis, G., Glover, G., Mugler, J., Weiner, M.W., 2008. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J. Magn. Reson. Imaging 27, 685–691.

Jack, C.R., Jr., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., Petersen, R.C., Trojanowski, J.Q., 2010. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 9, 119–128.

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.

Jicha, G.A., Parisi, J.E., Dickson, D.W., Johnson, K., Cha, R., Ivnik, R.J., Tangalos, E.G., Boeve, B.F., Knopman, D.S., Braak, H., Petersen, R.C., 2006. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. Arch. Neurol. 63, 674–681.

Jones, B.F., Barnes, J., Uylings, H.B., Fox, N.C., Frost, C., Witter, M.P., Scheltens, P., 2006. Differential regional atrophy of the cingulate gyrus in Alzheimer disease: A volumetric MRI study. Cereb. Cortex 16, 1701–1708.

Karas, G., Scheltens, P., Rombouts, S., van Schijndel, R., Klein, M., Jones, B., van der Flier, W., Vrenken, H., Barkhof, F., 2007. Precuneus atrophy in early-onset Alzheimer's disease: A morphometric structural MRI study. Neuroradiology 49, 967–976.

Killiany, R.J., Hyman, B.T., Gomez-Isla, T., Moss, M.B., Kikinis, R., Jolesz, F., Tanzi, R., Jones, K., Albert, M.S., 2002. MRI measures of entorhinal cortex versus hippocampus in preclinical AD. Neurology 58, 1188–1196.

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.

Korf, E.S., Wahlund, L.O., Visser, P.J., Scheltens, P., 2004. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. Neurology 63, 94–100.

Lehmann, M., Koedam, E.L., Barnes, J., Bartlett, J.W., Ryan, N.S., Pijnenburg, Y.A., Barkhof, F., Wattjes, M.P., Scheltens, P., Fox, N.C., 2012. Posterior cerebral atrophy in the absence of medial temporal lobe atrophy in pathologically confirmed Alzheimer's disease. Neurobiol. Aging 33, 627.e1–627.e12.

Likeman, M., Anderson, V.M., Stevens, J.M., Waldman, A.D., Godbolt, A.K., Frost, C., Rossor, M.N., Fox, N.C., 2005. Visual assessment of atrophy on magnetic resonance imaging in the diagnosis of pathologically confirmed young-onset dementias. Arch. Neurol. 62, 1410–1415.

Markesbery, W.R., Schmitt, F.A., Kryscio, R.J., Davis, D.G., Smith, C.D., Wekstein, D.R., 2006. Neuropathologic substrate of mild cognitive impairment. Arch. Neurol. 63, 38–46.

Morris, J.C., Storandt, M., Miller, J.P., Mckeel, D.W., Price, J.L., Rubin, E.H., Berg, L., 2001. Mild cognitive impairment represents early-stage Alzheimer disease. Arch. Neurol. 58, 397–405.

Mosconi, L., Perani, D., Sorbi, S., Herholz, K., Nacmias, B., Holthoff, V., Salmon, E., Baron, J.C., De Cristofaro, M.T., Padovani, A., Borroni, B., Franceschi, M., Bracco, L., Pupi, A., 2004. MCI conversion to dementia and the APOE genotype: a prediction study with FDG-PET. Neurology 63, 2332–2340.

Nestor, P.J., Fryer, T.D., Smielewski, P., Hodges, J.R., 2003. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. Ann. Neurol. 54, 343–351.

Petersen, R.C., Stevens, J.C., Ganguli, M., Tangalos, E.G., Cummings, J.L., Dekosky, S.T., 2001. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 56, 1133–1142.

Price, J.L., Morris, J.C., 1999. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann. Neurol. 45, 358–368.

Scahill, R.I., Schott, J.M., Stevens, J.M., Rossor, M.N., Fox, N.C., 2002. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc. Natl. Acad. Sci. U. S. A. 99, 4703–4707.

Scheltens, P., Launer, L.J., Barkhof, F., Weinstein, H.C., van Gool, W.A., 1995. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. J. Neurol. 242, 557–560.

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 aging—Diagnostic value and neuropsychological correlates. J. Neurol. Neurosurg. Psychiatry 55, 967–972.

Scheltens, P., Pasquier, F., Weerts, J.G., Barkhof, F., Leys, D., 1997. Qualitative assessment of cerebral atrophy on MRI: inter- and intra-observer reproducibility in dementia and normal aging. Eur. Neurol. 37, 95–99.

Schuff, N., Woerner, N., Boreta, L., Kornfield, T., Shaw, L.M., Trojanowski, J.Q., Thompson, P.M., Jack, C.R., Weiner, M.W., Alzheimer's Disease Neuroimaging Initiative, 2009. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. Brain 132, 1067–1077.

Shaw, L.M., Vanderstichele, H., Knapik-Czajka, M., Clark, C.M., Aisen, P.S., Petersen, R.C., Blennow, K., Soares, H., Simon, A., Lewczuk, P., Dean, R., Siemers, E., Potter, W., Lee, V.M., Trojanowski, J.Q., Alzheimer's Disease Neuroimaging Initiative, 2009. Cerebrospinal Fluid Biomarker Signature in Alzheimer's Disease Neuroimaging Initiative Subjects. Ann. Neurol. 65, 403–413.

Shiino, A., Watanabe, T., Kitagawa, T., Kotani, E., Takahashi, J., Morikawa, S., Akiguchi, I., 2008. Different atrophic patterns in early- and late-onset Alzheimer's disease and evaluation of clinical utility of a method of regional z-score analysis using voxel-based morphometry. Dement. Geriatr. Cogn. Disord. 26, 175–186.

Silbert, L.C., Quinn, J.F., Moore, M.M., Corbridge, E., Ball, M.J., Murdoch, G., Sexton, G., Kaye, J.A., 2003. Changes in premorbid brain volume predict Alzheimer's disease pathology. Neurology 61, 487–492.

Sole-Padulles, C., Llado, A., Bartres-Faz, D., Fortea, J., Sanchez-Valle, R., Bosch, B., Antonell, A., Molinuevo, J.L., Rami, L., 2011. Association between cerebrospinal fluid tau and brain atrophy is not related to clinical severity in the Alzheimer's disease continuum. Psychiatry Res. Neuroimaging 192, 140–146.

Strozyk, D., Blennow, K., White, L.R., Launer, L.J., 2003. CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. Neurology 60, 652–656.

Tapiola, T., Alafuzoff, I., Herukka, S.K., Parkkinen, L., Hartikainen, P., Soininen, H., Pirttilä, T., 2009. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch. Neurol. 66, 382–389.

Tapiola, T., Overmyer, M., Lehtovirta, M., Helisalmi, S., Ramberg, J., Alafuzoff, I., Riekkinen, P., Soininen, H., 1997. The level of cerebrospinal fluid tau correlates with neurofibrillary tangles in Alzheimer's disease. Neuroreport 8, 3961–3963.

Tosun, D., Schuff, N., Truran-Sacrey, D., Shaw, L.M., Trojanowski, J.Q., Aisen, P., Peterson, R., Weiner, M.W., Alzheimer's Disease Neuroimaging Initiative, 2010. Relations between brain tissue loss, CSF biomarkers, and the ApoE genetic profile: a longitudinal MRI study. Neurobiol. Aging 31, 1340–1354.

van der Flier, W.M., Pijnenburg, Y.A., Fox, N.C., Scheltens, P., 2011. Early-onset versus late-onset Alzheimer's disease: the case of the missing APOE ϵ4 allele. Lancet Neurol. 10, 280–288.

Vemuri, P., Wiste, H.J., Weigand, S.D., Shaw, L.M., Trojanowski, J.Q., Weiner, M.W., Knopman, D.S., Petersen, R.C., Jack, C.R., Jr., Alzheimer's Disease Neuroimaging Initiative, 2009. MRI and CSF biomarkers in normal, MCI, and AD subjects: predicting future clinical change. Neurology 73, 294–301.

Wattjes, M.P., Henneman, W.J., van der Flier, W.M., de Vries, O., Träber, F., Geurts, J.J., Scheltens, P., Vrenken, H., Barkhof, F., 2009. Diagnostic imaging of patients in a memory clinic: Comparison of MR imaging and 64-detector row CT. Radiology 253, 174–183.

Whitwell, J.L., Josephs, K.A., Murray, M.E., Kantarci, K., Przybelski, S.A., Weigand, S.D., Vemuri, P., Senjem, M.L., Parisi, J.E., Knopman, D.S., Boeve, B.F., Petersen, R.C., Dickson, D.W., Jack, C.R., Jr., 2008a. MRI correlates of neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study. Neurology 71, 743–749.

Whitwell, J.L., Shiung, M.M., Przybelski, S.A., Weigand, S.D., Knopman, D.S., Boeve, B.F., Petersen, R.C., Jack, C.R., 2008b. MRI patterns of atrophy associated with progression to AD in amnestic mild cognitive impairment. Neurology 70, 512–520.