

Original Research Article

# CERAD Neuropsychological Total Scores Reflect Cortical Thinning in Prodromal Alzheimer's Disease

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## Key Words

Alzheimer's disease · Cognition · Cortical thickness · Magnetic resonance imaging · Memory · Neuropsychology · Mild cognitive impairment · AddNeuroMed study

## Abstract

**Background:** Sensitive cognitive global scores are beneficial in screening and monitoring for prodromal Alzheimer's disease (AD). Early cortical changes provide a novel opportunity for validating established cognitive total scores against the biological disease markers. **Methods:** We examined how two different total scores of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery and the Mini-Mental State Examination (MMSE) are associated with cortical thickness (CTH) in mild cognitive impairment (MCI) and prodromal AD. Cognitive and magnetic resonance imaging (MRI) data of 22 progressive MCI, 78 stable MCI, and 98 control subjects, and MRI data of 103 AD patients of the prospective multicenter study were analyzed. **Results:** CERAD total scores correlated with mean CTH more strongly ( $r = 0.34$ – $0.38$ ,  $p < 0.001$ ) than did MMSE ( $r = 0.19$ ,  $p = 0.01$ ). Of those vertex clusters that showed thinning in progressive MCI, 60–75% related to the CERAD total scores and 3% to the MMSE. **Conclusion:** CERAD total scores are sensitive to the CTH signature of prodromal AD, which supports their biological validity in detecting early disease-related cognitive changes.

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## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common memory disorder causing dementia in older age. Atrophy of the hippocampus and entorhinal cortex is a characteristic early brain change in AD that is related to deficits of episodic memory [1, 2]. However, early AD has been shown to also affect distributed cortical areas outside the hippocampus [3, 4], and little is known about the relationship between cortical morphology and established global cognitive scores. Previous studies have mainly focused on the short cognitive scales in the AD population [5–7], and thus the relationship between the neocortical changes and more extensive neuropsychological total scores that are potential measures of global cognitive progression in mild cognitive impairment (MCI) and prodromal AD is largely unknown. A recent study found that cortical thickness (CTH) signatures of neuropsychological domain scores (memory, language, etc.) are applicable in predicting the conversion from MCI to AD; however, they did not analyze those of established global cognitive scores [8].

The Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) [9] was developed to be a reliable and standardized battery for measuring primary cognitive manifestations of AD. The original CERAD-NB included 5 cognitive tests: Verbal Fluency [10], 15-item Boston Naming Test [11], Mini-Mental State Examination (MMSE) [12], 10-item Word List Learning, Recall and Recognition Test, and Constructional Praxis [13]. The CERAD-NB also includes the Constructional Praxis Recall subtest that was later added to the battery in response to concerns about the balance between verbal and visual tests. The CERAD-NB has been shown to be sensitive in detecting MCI and AD in different populations [14–16] and has also been applied as a screening tool for memory disorders in primary health care [17]. Previously, the CERAD-NB results had to be interpreted at the level of single subtests; however, more recently, compound score tabulation methods have been suggested [18–20]. The original CERAD total score [18] has been shown to be accurate in detecting MCI and early AD in several populations [19–21] and has also been found to be a reliable measure of cognitive progression in AD [22]. The primary objective of this study was to examine two raw score-based CERAD total scores and the MMSE in relation to the mean CTH in healthy elderly subjects and MCI patients, and to evaluate their sensitivity to CTH signatures of prodromal AD in a multinational population. Our study hypothesis was that previously described CERAD total scores, which are shown to be sensitive in detecting MCI and AD [18–21], should also reflect the early pathological changes of AD.

## Materials and Methods

### *Participants*

A total of 301 subjects, i.e. 100 MCI subjects (51 females, 49 males; mean age  $73.6 \pm 5.8$  years), 98 age-matched healthy controls (HC) (53 females, 45 males; mean age  $72.2 \pm 6.4$  years) and 103 AD subjects (71 females, 32 males; mean age  $74.6 \pm 5.6$  years) from the magnetic resonance imaging (MRI) part of the multicenter AddNeuroMed biomarker study [23] were analyzed. Ninety-nine percent of the subjects were white European. Twenty-two of the 100 MCI subjects converted to AD during a 1-year follow-up period. MCI subjects were further divided into 22 progressive MCI (PMCI) subjects (9 females, 13 males; mean age  $72.3 \pm 6.5$  years) and 78 stable MCI (SMCI) subjects (42 females, 36 males; mean age  $74.0 \pm 5.6$  years). The AddNeuroMed study was conducted at 6 medical centers across Europe: University of Kuopio, Finland; University of Perugia, Italy; Aristotle University of Thessaloniki, Greece; King's College London, UK; Medical University of Lodz, Poland, and University of Toulouse,

France. The AddNeuroMed MRI substudy initially included 378 participants (130 AD, 131 MCI and 117 HC) [23], of whom 198 MCI and HC subjects had a successful baseline CTH analysis, as well as cognitive and clinical data and follow-up information. In this paper, AD cases could not be included in the final correlative analyses because their cognitive performance was not assessed with the CERAD-NB; however, they were analyzed as an MRI reference group. Altogether 16 HC, 30 MCI and 27 AD subjects were excluded because of incomplete cognitive/clinical data, insufficient quality of their MRI data or unsuccessful CTH analyses. In addition, 3 controls (who progressed to MCI) and 1 MCI subject (who converted to control status) were excluded. Ethics review boards at each clinical and data-coordinating site approved the study protocol. Written informed consent was acquired from all subjects participating in the study. The study was conducted according to good clinical practice and complied with the declaration of Helsinki.

#### *Diagnostic Procedures and Inclusion Criteria*

The clinical centers recruited patients through local hospital and memory clinics and population-based samples. AD diagnosis was based on the *Diagnostic and Statistical Manual of Mental Disorders*, ed 4 (DSM-IV) and the National Institute of Neurologic and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria for probable AD [24]. All MCI subjects presented memory problems in their daily life assessed with a Clinical Dementia Rating Scale [25] (memory subscore of 0.5 or 1), but no specific thresholds in cognitive test performance were used in the initial diagnosis. The MCI subjects were required to meet all the other components of the criteria for amnesic MCI [26], i.e. (a) memory complaint by patient, family, or physician; (b) normal activities of daily living (based on the clinical interview); (c) normal global cognitive function (MMSE score 24–30); (d) Clinical Dementia Rating Scale total score of 0.5, and (e) absence of dementia according to DSM-IV criteria. None of the MCI or AD subjects had another neurological or psychiatric disease, significant unstable systemic illness or organ failure, and alcohol or substance misuse. The controls had no neurological or psychiatric disorders nor did they take psychoactive medication. The Geriatric Depression Scale score [27] for HC and MCI subjects was  $\leq 5$ .

#### *Neuropsychological and Clinical Evaluations*

All study participants underwent neuropsychological and clinical evaluations at baseline and were followed up after 1 year. In the AddNeuroMed study, HC and MCI subjects were assessed with the CERAD-NB and AD subjects with the Alzheimer's Disease Assessment Scale – cognitive subscale [13]. As CERAD data were not available in the AD group, they were analyzed as an MRI reference group. All clinical assessments were performed by appropriately qualified and experienced researchers. The compound scores for CERAD-NB were tabulated according to two previous methods – the original CERAD total score (CERAD-TS1: maximum score 100) [18] and a recent total score modification (CERAD-TS2: maximum score 111) [20]. The latter also includes the Constructional Praxis Recall score, with an additional 11 points measuring praxis memory. The MMSE score is not included in the total scores.

#### *MRI Data Acquisition*

Data acquisition took place using 6 different 1.5-tesla MR systems (4 General Electric, 1 Siemens and 1 Picker). At each site, a quadrature birdcage coil was used for radiofrequency transmission and reception. Data acquisition was designed to be compatible with the Alzheimer's Disease Neuroimaging Initiative [28]. The imaging protocol included a high-resolution sagittal 3-dimensional T1-weighted MPRAGE volume (repetition time = 9–13 ms, echo

time = 3.0–4.1 ms, inversion time = 1,000 ms, flip angle = 8°, voxel size  $1.1 \times 1.1 \times 1.2 \text{ mm}^3$ ) and axial proton density/T2-weighted fast spin echo images (repetition time = 3,000 ms, echo time 1 = 10 ms, echo time 2 = 97 ms, flip angle = 90°, voxel size =  $0.94 \times 0.94 \times 3 \text{ mm}^3$ ). Full brain and skull coverage was required for both of the latter datasets, and detailed quality control was carried out on all MR images [23, 29]. All MR images received a clinical evaluation by an on-site radiologist to exclude any subjects with non-AD-related pathologies.

### Image Analyses

A highly automated structural MR image processing pipeline developed by Fischl et al. [30–32] was utilized for data analysis. The CTH maps produced are not restricted to the voxel resolution of the original data and are thus capable of detecting submillimeter differences between groups. Procedures for the measurement of the CTH have been validated against histological analysis [33] and manual measurements [34]. These procedures show good test-retest reliability across scanner manufacturers and across field strengths [35]. The image analysis pipeline copes well with interindividual differences.

### General Study Design

Relationships between the cognitive total scores and mean global CTH were analyzed in the pooled sample of all MCI and HC subjects ( $n = 198$ ), and separately in the PMCI, SMCI and HC groups. Regional vertex cluster-based CTH values and cognitive scores were studied in the pooled sample (all MCI and HC subjects) as this population presents very mild cognitive impairment on average but still forms a cognitive continuum with enough variation. Next, cortical regions that were found to be related to cognitive total scores were contrasted with cortical areas that presented thinning in progressive MCI as compared with the HC group. Contrasts were built up by comparing surface-based CTH maps that reached statistical significance ( $p < 0.05$ ) in age-, gender- and education-adjusted models.

### Statistical Analyses

**CTH Statistical Analysis.** The CTH data were analyzed using the SurfStat toolbox [36]. A least-squares regression analysis was performed at each vertex in order to calculate the coefficients  $\{a_0, a_1, \dots, a_n\}$  for a user-defined linear model of the form:  $\text{CTH} = a_0 + a_1x_1 + a_2x_2 + \dots + a_nx_n$ , where  $x_1$  is the variable of interest (contrast), and  $\{x_2, x_3, \dots, x_n\}$  are the covariates. Age, gender and years of education were used as covariates, as they have previously been shown to affect CTH [37]. For a comparison between two groups, the model is defined as:  $\text{CTH} = a_0 + a_1(\text{case type}) + a_2(\text{age}) + a_3(\text{gender}) + a_4(\text{years of education})$ , where for example case type = 1 for HC and 0 for PMCI and gender = 1 for male and 0 for female. For correlation with clinical measures such as the MMSE, the model is defined similarly:  $\text{CTH} = a_0 + a_1(\text{MMSE score}) + a_2(\text{age}) + a_3(\text{gender}) + a_4(\text{years of education})$ . A *t* statistic is calculated for the coefficient of the contrast variable at each vertex, and *p* value maps were then created for vertices and for clusters, using the random field theory to correct for multiple comparisons. For comparison between groups and cognitive measures, the *p* value maps generated for the correlation between the CTH and group membership and for the correlation between the CTH and test battery scores were converted to binary masks with a threshold of  $p = 0.05$ . Both masks were then displayed on the same rendered cortical surface. The degree of overlap between the masks was quantified by calculating the percentage of vertices demonstrating a significant difference in CTH between groups that also showed a significant correlation with the test battery score.

**Clinical Data Statistical Analyses.** Statistical analyses of the clinical data were conducted using SPSS version 20 for Windows. Descriptive statistics were used to characterize the study groups. The majority of cognitive test data was not normally distributed, and thus the study

**Table 1.** Baseline demographic and clinical characteristics in the study groups

	PMCI	SMCI	HC	AD
Number	22	78	98	103
Women/men	9/13	42/36	53/45	71/32*
CDR total score	0.5±0*	0.5±0*	0±0	1.1±0.5*
Age, years	72.3±6.5	74.0±5.6	72.2±6.4	74.6±5.6*
Education, years	9.6±4.3	8.9±4.3*	11.0±4.9	8.1±4.1*
MMSE score	26.7±2.0*	27.3±1.6*	29.1±1.2	21.0±4.9*
GDS score	1.5±1.5	2.3±1.4*	1.6±1.7	–
CDR-SB	1.7±1.1*	1.3±0.8*	0.1±0.2	6.3±3.2*

The data are given as number of subjects or as means ± SD. \* p < 0.05 against controls (Pearson  $\chi^2$  or Mann-Whitney U test). CDR = Clinical Dementia Rating Scale; GDS = Geriatric Depression Scale; CDR-SB = CDR Sum of Boxes.

groups were compared with nonparametric independent-samples Kruskal-Wallis and Mann-Whitney U tests for all continuous clinical variables and mean global CTH values. The Pearson  $\chi^2$  test was used for examining the difference in gender ratio. The Spearman correlation analysis was used to examine the relationship between mean CTH and cognitive total scores. The level of statistical significance in all statistical procedures was set to p < 0.05.

## Results

### *Clinical and Cognitive Sample Characteristics*

**Demographics.** Sample characteristics of the study participants are presented in table 1. PMCI, SMCI and HC groups did not differ in age [ $\chi^2(2, n = 198) = 3.02, p = 0.221$ ] or gender ratio [ $\chi^2(2, n = 198) = 1.34, p = 0.512$ ]. However, in the AD group, women were overrepresented as compared with the other study groups ( $\chi^2 > 4.31, p < 0.038$  in all comparisons). Controls were younger than AD subjects (U = 6178, Z = 2.75, p = 0.006), and they were also on average more educated than AD subjects (U = 3330, Z = -4.18, p < 0.001) and SMCI subjects (U = 2951, Z = -2.60, p = 0.009). The PMCI and SMCI groups did not differ in any demographic or clinical variables, except the Geriatric Depression Scale score that was slightly higher in the SMCI group (U = 593, Z = -2.25, p = 0.024). The Geriatric Depression Scale score of the SMCI group was also higher than that of the controls (U = 4994, Z = 3.56, p < 0.001).

**Cognitive Performance.** CERAD-NB results for the different study groups are presented in table 2. HC subjects achieved higher baseline scores than SMCI and PMCI subjects on all CERAD tests, except the Constructional Praxis task in which controls did not differ from PMCI subjects. A significant difference between the PMCI and SMCI subjects was found only for the Constructional Praxis Recall score (U = 599, Z = -2.17, p = 0.030).

### *Analyses of Mean Global CTH*

Mean global CTH values ± standard deviations (in millimeters) of the entire cortical mantle for the different groups were: 2.16 ± 0.12 mm for the HC, 2.10 ± 0.14 mm for the SMCI, 2.06 ± 0.11 mm for the PMCI and 1.98 ± 0.19 mm for the AD group. The HC group had significantly thicker mean CTH than the SMCI (U = 2777, Z = -3.11, p = 0.002), PMCI (U = 550, Z = -3.58, p < 0.001) and AD (U = 2134, Z = -7.07, p ≤ 0.001) groups. The SMCI group also differed from the AD group (U = 2560, Z = -4.17, p < 0.001). However, no significant differences were

**Table 2.** Baseline CERAD-NB data in the study groups

	PMCI	SMCI	HC
Number	22	78	98
Verbal Fluency	16.8±4.6	15.8±4.4	20.4±5.5*
Boston Naming Test	11.0±2.4	12.0±2.3	13.6±1.7*
Word List Learning	14.0±4.2	14.0±3.3	19.8±4.4*
Word List Recall	3.0±2.1	4.1±2.0	6.6±2.1*
Word List Recognition	17.3±2.3	17.7±2.5	19.3±1.1*
Constructional Praxis	10.0±1.6 <sup>†</sup>	9.7±1.6	10.4±1.2*
Constructional Praxis Recall	4.3±3.6**	6.2±3.1	8.5±2.8*
CERAD-TS1 <sup>a</sup>	62.0±10.0	63.0±8.9	79.2±11.0*
CERAD-TS2 <sup>b</sup>	66.3±11.7	69.2±10.7	87.7±12.6*

The data are given as means ± SD. \*  $p < 0.05$ : significant difference (Mann-Whitney U test) vs. SMCI and PMCI in all test scores (exception is marked with a cross). \*\*  $p < 0.05$ : significant difference vs. SMCI.

<sup>a</sup> Total score according to Chandler et al. [18]. <sup>b</sup> Total score according to Seo et al. [20].

found in SMCI versus PMCI ( $U = 687$ ,  $Z = -1.42$ ,  $p = 0.155$ ) and PMCI versus AD ( $U = 877$ ,  $Z = -1.66$ ,  $p = 0.097$ ) comparisons.

#### Analyses of CTH Atrophy Signatures

**SMCI versus HC.** The SMCI subjects had a thinner cortex than the controls in the left temporal pole and left superior temporal and right lingual gyri. Bilateral thinning was seen in parahippocampal gyri, and entorhinal and posterior insular cortices (fig. 1a).

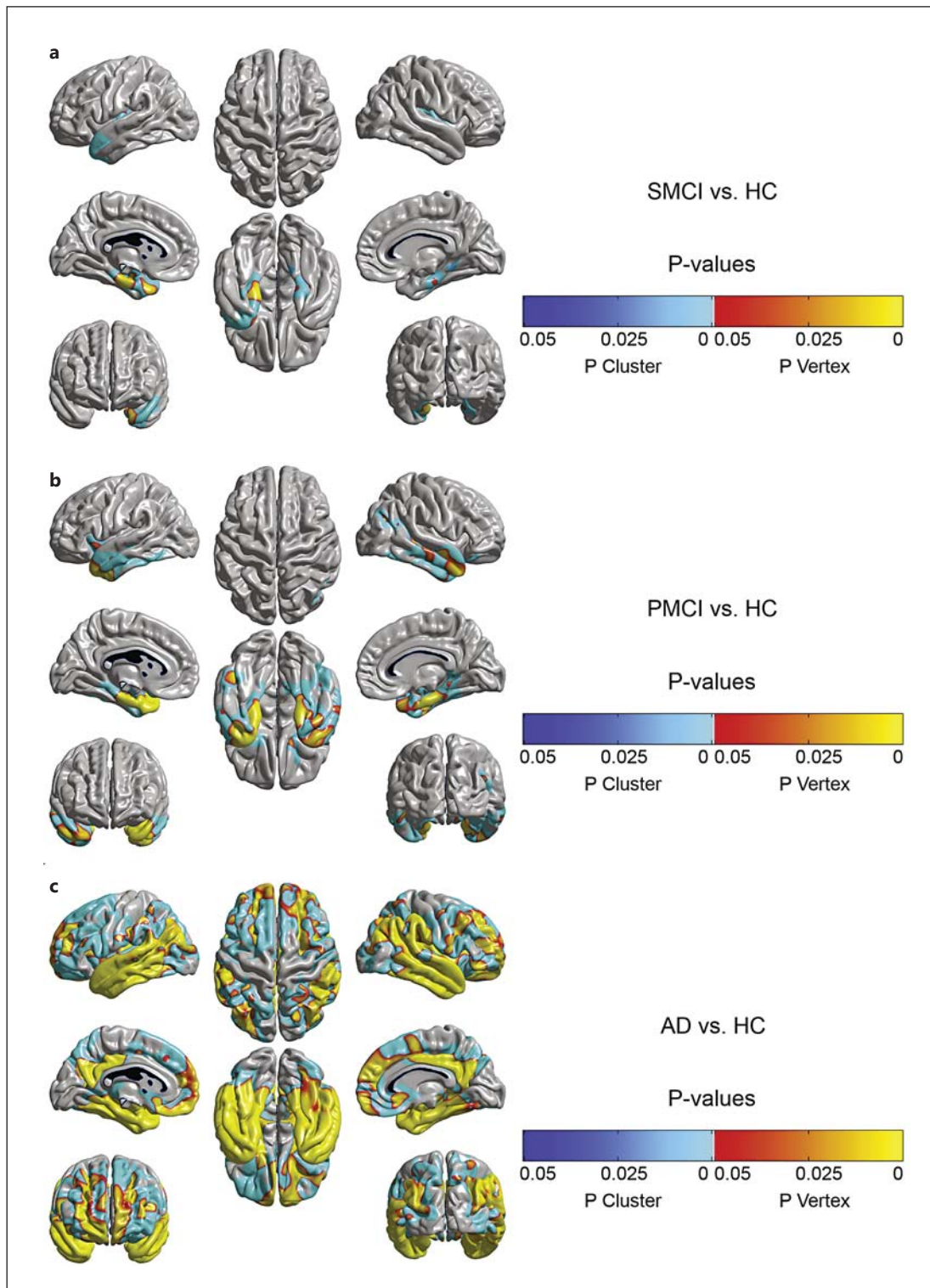
**PMCI versus HC.** In the PMCI group, cortical thinning was visible extensively in temporal lobes and parts of the posterior orbitofrontal cortex and fusiform gyrus bilaterally. In addition, thinning covered the left anterior insula, the right angular gyrus and the interparietal sulcus. The difference between the PMCI and HC groups covered 12.0% of all cortical vertex clusters (fig. 1b). In the SMCI and PMCI groups, cortical thinning patterns did not reach statistical significance in direct comparison. However, PMCI subjects displayed thinning across broader cortical areas compared with SMCI subjects when both were contrasted with controls.

**AD versus HC.** In the AD group, cortical thinning was visible in extensive neocortical areas. The AD subjects had a thinner cortex than the HC subjects in 74.0% of all vertex clusters. The AD signature covered a majority of the temporal lobes, superior and middle frontal gyri, prefrontal and insular cortices, precuneus, cingulate gyri and inferior and superior parietal lobules (fig. 1c).

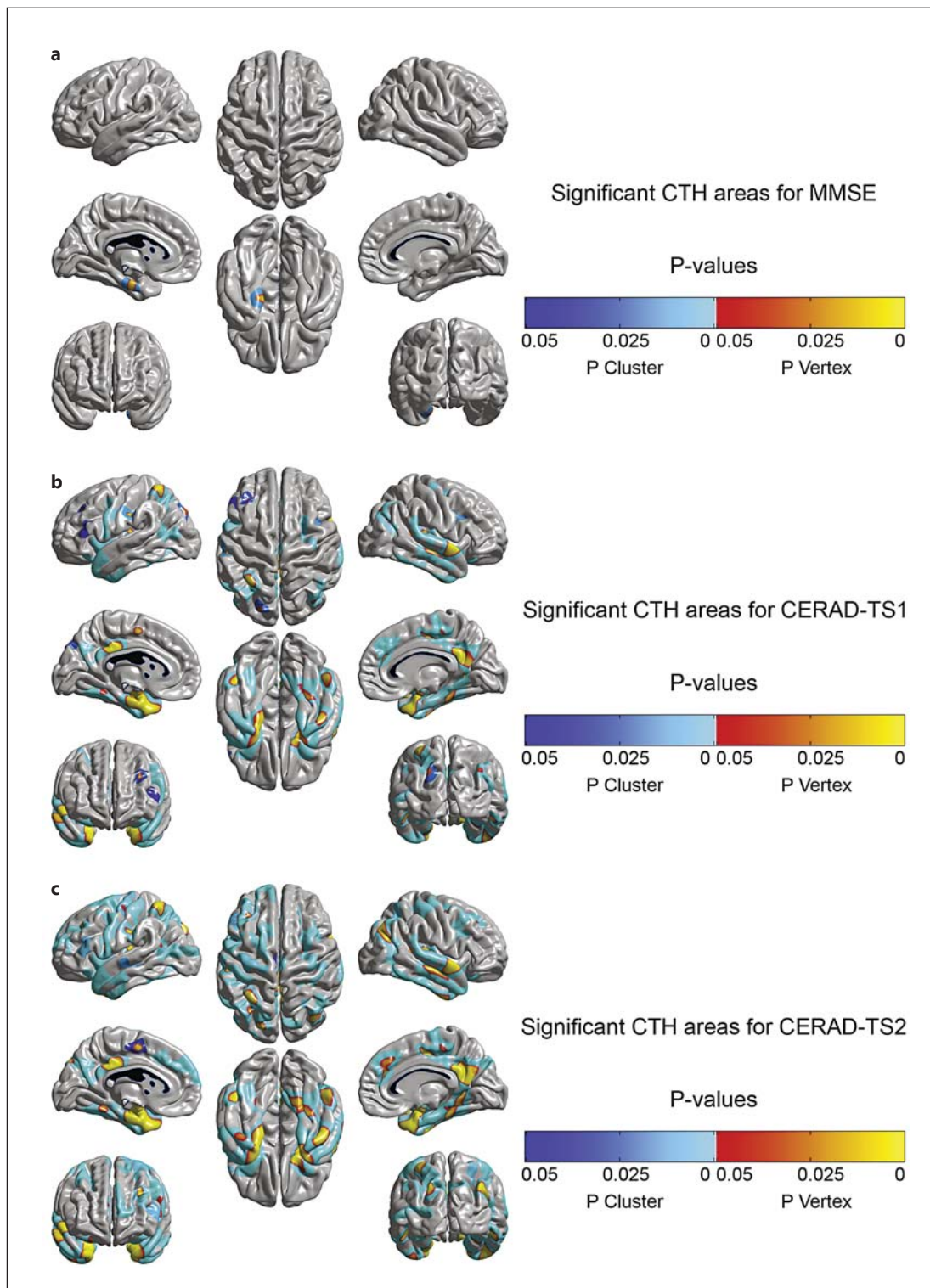
#### CTH and Cognitive Total Scores

The Spearman correlation analysis was conducted to examine the relationship between mean CTH and performance on cognitive total scores in the pooled sample of MCI and HC subjects ( $n = 198$ ), and separately in the HC, SMCI and PMCI groups. In the pooled sample, correlations between mean CTH and test scores were  $r = 0.188$  ( $n = 198$ ,  $p = 0.008$ ) for MMSE,  $r = 0.343$  ( $n = 198$ ,  $p < 0.001$ ) for CERAD-TS1 and  $r = 0.375$  ( $n = 198$ ,  $p < 0.001$ ) for CERAD-TS2.

In the HC group, none of the global scores yielded a significant correlation with mean CTH: MMSE ( $r = -0.101$ ,  $n = 98$ ,  $p = 0.323$ ), CERAD-TS1 ( $r = 0.143$ ,  $n = 98$ ,  $p = 0.160$ ) and TS2 ( $r = 0.170$ ,  $n = 98$ ,  $p = 0.095$ ). In the SMCI group, the correlation between mean CTH and MMSE was still not significant ( $r = 0.038$ ,  $n = 78$ ,  $p = 0.738$ ); however, significant relationships with CERAD-TS1 ( $r = 0.314$ ,  $n = 78$ ,  $p = 0.005$ ) and CERAD-TS2 ( $r = 0.341$ ,  $n = 78$ ,  $p = 0.002$ ) were



**Fig. 1.** Results of the cluster- and vertex-based CTH comparisons. **a** SMCI (n = 78) vs. HC (n = 98). **b** PMCI (n = 22) vs. HC. **c** AD (n = 103) vs. HC. Significance level was set at  $p < 0.05$  in a least-squares regression analysis (age, education and gender adjusted with random field theory multiple testing correction).



**Fig. 2.** Cluster- and vertex-based CTH signatures of cognitive total scores: MMSE (a), CERAD-TS1 (b), and CERAD-TS2 (c) in the pooled sample (n = 198) of HC and subjects with MCI.



found. In the PMCI group, correlations between mean CTH and test scores were  $r = 0.456$  ( $n = 22$ ,  $p = 0.033$ ) for MMSE,  $r = 0.429$  ( $n = 22$ ,  $p = 0.046$ ) for CERAD-TS1, and  $r = 0.543$  ( $n = 22$ ,  $p = 0.009$ ) for CERAD-TS2.

#### *CTH Signatures of Cognitive Total Scores*

In the sample of MCI and HC subjects, both CERAD total scores correlated with the CTH across much broader areas than did MMSE. CERAD-TS1 correlated with 21.3%, CERAD-TS2 with 33.0% and MMSE with 0.3% of all neocortical vertex clusters. The MMSE score correlated with CTH only in part of the left parahippocampal gyrus, while in the same sample, CERAD-TS1 related broadly to medial temporal lobe structures, fusiform and angular gyri, precuneus, and parts of the frontal and parietal lobules. For CERAD-TS2, additional significant relations were seen in frontal, parietal and temporal areas bilaterally (fig. 2).

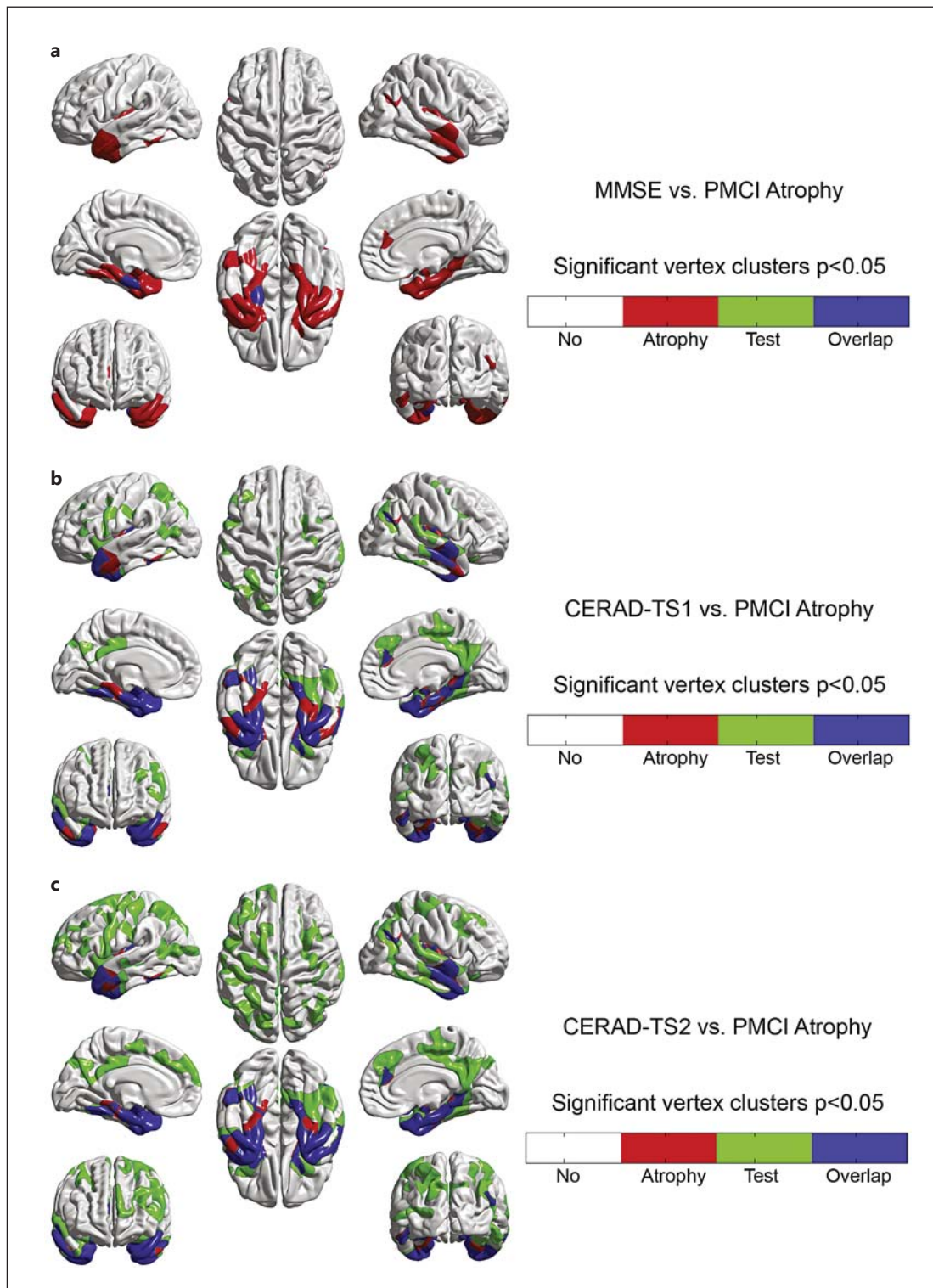
#### *CTH Atrophy Signatures versus Signatures of Cognitive Total Scores*

Of all vertex clusters that presented reduced CTH in the PMCI group, 60.2% were related to CERAD-TS1. CERAD-TS2 yielded an even higher sensitivity, with 75.1% of vertex clusters showing decreased CTH in the PMCI group related to the test score. The corresponding overlap figure for MMSE was 2.9% (fig. 3).

## Discussion

We examined the relationship of two recently developed CERAD composite scores and MMSE with mean CTH and CTH atrophy signature of PMCI (later refers to prodromal AD) in the multinational AddNeuroMed study. We found that in the sample of MCI and HC subjects, CERAD total scores correlated with CTH extensively in the temporal lobes, and also partly in parietal and frontal regions bilaterally, supporting the previous finding indicating that CERAD-NB subtests are associated with several cortical areas [38]. CTH signatures of CERAD total scores (fig. 2) covered the majority of CTH areas that had previously been found to be related to cognitive domain scores of memory and language. Correspondence with the previously detected signatures of executive function/processing speed and visuospatial functions was somewhat weaker [8]. It is nevertheless important to note that the extent of CTH signatures of cognition strongly depends on the applied statistical threshold level and whether vertex- or cluster-based results are presented. Our main finding was that CERAD total scores reflected a CTH atrophy signature in prodromal AD, and correlated with mean CTH already in the SMCI group when the cortical thinning was least prominent. Another important finding was that the CERAD total score including the Constructional Praxis Recall score [20] corresponded more accurately to the mean CTH and CTH signature of prodromal AD as compared to the original CERAD total score [18]. Interestingly, at baseline, the SMCI and PMCI groups differed from each other only on Constructional Praxis Recall performance, indicating that praxis memory may be a relevant single factor predicting progression from MCI to AD.

The relationship between CTH and global cognitive measures has previously been examined in a limited number of studies focusing on the short cognitive scales in AD [5–7]. The MMSE has been suggested to be sensitive to macrostructural brain changes in AD [5]; however, in our study population, the MMSE correlated only with a restricted left medial temporal lobe thickness area. The reason for these different results seems to be that we studied subjects presenting on average very mild cognitive impairment, but a previous study included demented AD subjects [5]. As AD patients demonstrated wide-ranging atrophy of their brain with parallel general cognitive decline, associations in wider areas could be



**Fig. 3.** CTH signatures of cognitive total scores ( $n = 198$ ) displayed with a CTH atrophy signature of PMCI on the same color-coded cortical surface maps. **a** MMSE. **b** CERAD-TS1. **c** CERAD-TS2. Vertex cluster significance level set at  $p < 0.05$  in a least-squares regression analysis (age, education and gender adjusted with random field theory multiple testing correction).

expected. In our nondemented study population, the variation on CERAD total scores was greater than on MMSE; however, no ceiling or floor effects were visible for CERAD total scores.

The extent of the areas suffering from neocortical thinning was found to be in the order HC < SMCI < PMCI < AD. Direct comparisons of regional CTH between SMCI versus PMCI and PMCI versus AD groups did not yield statistically significant differences, presumably due to the small sample size of the PMCI group ( $n = 22$ ) and the conservative statistical methods used. However, differences in the extent of atrophied cortical areas were clearly visible when clinical groups were compared with HC (fig. 1a–c). According to these results, the PMCI group presented a disease stage between the SMCI and AD groups. The PMCI-related cortical thinning pattern in our study generally corresponded to the previously identified CTH signatures of incipient AD [3, 4]. However, some differences were also visible; significant thinning in the supramarginal gyrus, superior parietal lobule, superior frontal gyrus, inferior frontal sulcus and precuneus was not found, even though these areas have been suggested to be affected in incipient and early AD [3, 4].

There are certain limitations to our study. Firstly, we compared the different study groups at baseline, and we do not have information about the sensitivity of different cognitive total scores to cortical thinning when the same subjects were re-evaluated at follow-up. Thus, studies with repeated cognitive and imaging assessments are needed in the future. Secondly, despite the high observed conversion rate (22%), a 1-year follow-up time is relatively short and a longer follow-up would presumably have increased the number of MCI to AD conversions. On the other hand, we found that CERAD total scores reflected mean CTH also in the SMCI group, indicating that scores are sensitive to very early cortical changes among the subjects who may have an increased risk of developing AD. In addition, it would have been informative to run corresponding analyses in the AddNeuroMed AD group; however, this was not possible as there were no CERAD-NB data available for them.

In conclusion, the strength of our study is that we analyzed a large multinational dataset of an established cognitive test battery together with a fully automated MRI pipeline [32], which provided novel information about the relationship between cognitive total scores and cortical changes in prodromal AD. We found that both CERAD total scores were related to CTH in more extensive cortical areas than were the MMSE and reflected CTH signature of prodromal AD. Despite the fact that cortical changes have not been validated as a gold standard for AD pathology, the observed relationships support the biological validity of CERAD total scores when assessing subjects with MCI and prodromal AD. Our results indicate that, in addition to cognitive screening, CERAD total scores could be considered as conceivable outcome measures in therapeutic interventions which are targeted at retarding brain pathology in prodromal AD.

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## Disclosure Statement

The authors report no conflict of interest for this study.

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