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Cortical Thinning in Individuals with Subjective Memory Impairment

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Abstract. Elderly individuals with subjective memory impairment (SMI) report memory worsening, but perform within the age-, gender-, and education- adjusted normal range on neuropsychological tests. Longitudinal studies indicate SMI as a risk factor or early sign of Alzheimer's disease (AD). There is increasing evidence from neuroimaging that at the group level, subjects with SMI display evidence of AD related pathology. This study aimed to determine differences in cortical thickness between individuals with SMI and healthy control subjects (CO) using the FreeSurfer environment. 110 participants (41 SMI/69 CO) underwent structural 3D-T1 MR imaging. Cortical thickness values were compared between groups in predefined AD-related brain regions of the medial temporal lobe, namely the bilateral entorhinal cortex and bilateral parahippocampal cortex. Cortical thickness reduction was observed in the SMI group compared to controls in the left entorhinal cortex ($p = 0.003$). We interpret our findings as evidence of early AD-related brain changes in persons with SMI.

Keywords: Alzheimer's disease, cortical thickness, entorhinal cortex, parahippocampal cortex, subjective cognitive decline, subjective memory impairment

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia [1]. It is characterized by progressive impairment of cognition and competence in daily functioning [2]. Current research aims to characterize early disease stages and define target populations for early interventions. It is assumed that the preclinical neuropathological process of AD begins several years to decades before the onset of dementia [3]. Mild cognitive impairment (MCI) is defined by impairment on cognitive tests but largely intact activities of daily living [4]. MCI is an at-risk condition for AD. Numerous studies have shown biomarker evidence of AD in patients with MCI and about 10–15% of individuals with MCI convert to AD each year [5].

More recently, studies have focused on people with purely subjective cognitive decline (SCD), which is characterized by a subjectively experienced worsening of cognitive performance in the absence of objective cognitive deficits. Recently, a research framework for SCD in the context of preclinical AD has been conceptualized and consented by an international working group [6]. One particular type of SCD is subjective memory impairment (SMI), in which

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the subjects report specifically worsening of episodic memory function. Longitudinal studies have indicated that persons with SMI/SCD are at increased risk of AD [7, 8]. MRI studies have revealed structural volume reduction in medial temporal lobe regions in subjects with SMI in comparison to control subjects, which have been interpreted as signs of very early AD-related atrophy [9–12]. SMI as an early sign of AD is further supported by evidence of reduced glucose metabolism in AD-related brain regions [11, 13]. Moreover, amyloid positron emission tomography (PET) studies and cerebrospinal fluid (CSF) investigation provided evidence for an increased likelihood of amyloid deposition in individuals with SMI [14–17]. Finally, a functional-MRI study showed decreased activation in the hippocampus and increased activation in the frontal cortex during an episodic memory task in persons with SMI, which may indicate a compensatory mechanism [18].

Among other features, AD is characterized by reduction of cortical thickness (CTh) [19, 20]. CTh can be measured by determining the distance between the white/grey matter border and the pial surface [21]. An alternative approach to assess cortical atrophy is voxel-based morphometry (VBM), which aims to detect local differences using grey-matter probability maps [22]. Thus, CTh provides distinct information on grey matter structure of the brain. Standard approaches of CTh measurement have been shown to be reliable [23–26].

Our aim was to study CTh in subjects with SMI in comparison to individuals without SMI in the medial temporal lobe, a region known to show early neuronal damage in AD [19]. As the hippocampus, a core target region for volumetric MRI-studies in AD, is not captured by CTh measurement, we focused on two neighboring brain regions. These regions are the entorhinal cortex and the parahippocampal cortex.

MATERIALS AND METHODS

Subjects

All subjects with SMI ($n = 41$) were recruited via the memory clinic of the interdisciplinary treatment and research center for neurodegenerative disorders (KBFZ) at the University Hospital Bonn. 69 controls (CO) were recruited from the general population by advertisements. The sample reflects pooled data from three studies that were all performed on three 3-Tesla MR-scanners. Pooling was performed to increase statistical power and was guided by the recently suggested sample size of approximately 40 persons per group for the detection of a difference of CTh of 0.25 mm between groups in the medial temporal lobe in at risk stages of AD [27].

The numbers of participants per study included in the present analysis are: study 1:16 SMI (4 females/12 males)/40 CO (16 females/24 males); study 2:16 SMI (5 females/11 males)/19 CO (9 females/10 males); study 3:9 SMI (3 females/6 males)/10 CO (3 females/7 males).

Volumetric analysis of study sample 1 have been published previously [11, 12, 28]. Data from study 2 have also been reported [18]. Data from study 3 have not yet been reported. Inclusion criteria for participants in the SMI group were self-perceived decline in memory and referral to the memory clinic for diagnostic work-up. Confirmation of memory decline was provided by an informant in subjects of study 1 and 2, but not systematically in subjects of study 3. The onset of memory decline had to be within the last 10 years in all studies. The core inclusion criterion for control participants was the absence of SMI (i.e., no concerns regarding decline in memory capacity). Exclusion criteria for all participants were current or past psychiatric or neurological disorders and medical conditions or current medication that may interfere with cognition as well as MRI exclusion criteria. All participants were tested with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery (study 1 and 2) or the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (study 3). The Trail Making Tests A and B (TMT A+B) were applied in all participants. All subjects (SMI and CO) performed within 1.5 SD of the age, gender and education adjusted mean on all subtests of the respective batteries. Subclinical symptoms of depression were assessed with the Beck Depression Inventory (BDI) (Table 1). All studies were approved by the ethical committee of the University of Bonn, Medical Faculty. All participants gave written informed consent to their inclusion in the studies.

Sociodemographic data did not differ between subjects with SMI and controls with the exception of a slightly higher age of the SMI group ($p = 0.049$). The subjects with SMI did not differ from the control subjects on any of the cognitive tests but the SMI group scored higher on average on the BDI ($p < 0.001$). However, none of the participants fulfilled the criteria of a depressive episode according to ICD-10. Slightly higher scores on depression scales in non-depressed individuals with SMI have been observed in other studies [10, 29]. This may be related to particular personality traits or changes in self-perception at the SMI

Table 1
Sample characteristics and results of cortical thickness measures in four predefined regions of interest

	SMI ($n=41$)	CO ($n=69$)	T	Cohen's d	p
Age (years), mean (sd)	68.9 (7.2)	66.1 (6.9)	1.99	0.39	0.049
Education (years), mean (sd)	14.8 (3.5)	14.9 (3.2)	−1.43	−0.03	n.s.
BDI, mean (sd)	7.5 (5.0)	3.9 (3.0)	4.94	0.94	0.000
TMT-A (seconds), mean (sd)	43.6 (21.4)	42.3 (14.5)	0.33	0.08	n.s.
TMT-B (seconds), mean (sd)	110 (62.9)	96 (41.1)	1.27	0.28	n.s.
CERAD - Semantic Fluency (number of items), mean (sd)	23.8 (5.0)	24.6 (6.1)	−0.66	−0.14	n.s.
CERAD - Immediate Recall Wordlist (number of items), mean (sd)	22.3 (3.3)	22.7 (3.8)	−0.52	−0.11	n.s.
CERAD - Delayed Recall Wordlist (number of items), mean (sd)	7.5 (1.7)	8.1 (1.5)	−1.73	−0.39	n.s.
RBANS - Semantic Fluency*, (number of items), mean (sd)	19.6 (0.7)	19.9 (0.3)	−1.12	−0.62	n.s.
RBANS - Immediate Recall Wordlist*, (number of items), mean (sd)	27.9 (3.4)	30.2 (5.7)	−1.09	−0.47	n.s.
RBANS - Delayed Recall Wordlist*, (number of items), mean (sd)	5.6 (2.5)	6.8 (1.8)	−1.26	−0.58	n.s.
			Chi^2		p
gender (females/males)	12/29	28/41	1.42		n.s.
distribution of MR-scanner-types (all 3-Tesla)			3.71		n.s.
Philips Achieva (persons scanned)	16	40			
Siemens Trio (persons scanned)	16	19			
Philips Ingenia* (persons scanned)	9	10			

Abbr.: BDI: Beck Depression Inventory; CERAD: Consortium to Establish a Registry for Alzheimer's Disease (performed in 91 subjects); CO: control subjects; n.s.: not significant; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status (performed in 19 subjects); sd: standard deviation; SMI: subjective memory impairment; TMT A+B: Trail Making Test A and B; *applied in study 3.

stage [30]. We included the BDI-scores as covariate in all analyses. The distribution of SMI and CO subjects investigated on the different MR-scanners was not equal across studies, but these differences were not significant (Table 1).

MRI acquisition

Structural 3D-T1 weighted MRI was performed on three different 3-Tesla scanners with the following MR sequence parameters: Study 1 (3T-Achieva; Philips Healthcare, Best, The Netherlands) TE/TR/Flip: 3.6 ms/7.6 ms/8°, 170 slices, voxel size: $0.8 \times 0.8 \times 0.8 mm^3$; study 2 (3T Trio, Siemens Medical Solutions, Erlangen, Germany) TE/TR/Flip: 3.42 ms/1.57 ms/15°, 160 slices, voxel size: $1 \times 1 \times 1 mm^3$; study 3 (3T-Ingenia; Philips Healthcare, Best, The Netherlands) TE/TR/Flip: 3 ms/8 ms/8°, 140 slices, voxel size: $1 \times 1 \times 1 mm^3$.

Surface reconstruction

All native T1 weighted images were checked visually for image quality before starting the reconstruction process. Cortical reconstruction was performed using the FreeSurfer (FS) image analysis suite, version 5.1.0 (http://surfer.nmr.mgh.harvard.edu). The technical details of these procedures have been described in prior publications [21, 31]. Briefly, the processing includes motion correction, removal of non-brain tissue, Talairach transformation, segmentation, topology correction, surface inflation, and surface based normalization. CTh measures were obtained by calculating the distance between the white matter boundary and the pial surface. All generated images were inspected visually for correct segmentation and surface reconstruction and corrected manually, if necessary. Corrections were mostly related to skull stripping errors or non accurate detection of the white matter boundary.

Statistical analysis

Statistical analyses were performed using SPSS-20. Differences in demographic variables and cognitive measures between both diagnostic groups were tested with independent t-tests for continuous and Chi^2-test for categorical variables, respectively. Mean regional values of the CTh were extracted from four *a priori* defined cortical regions. These regions were the bilateral entorhinal cortex and the bilateral parahippocampus [9, 10, 19]. For region-of-interest (ROI) definition, the automated labeling of FS ROI atlas was used [32]. For comparison of these CTh measures between groups, we performed a MANCOVA analysis with all four ROI as the dependent variables, diagnostic group as the between-subjects factor, and age, education, and BDI-score as continuous covariates, and gender and MR-scanner-type as categorical covariates. Following the MANCOVA analysis, we performed Bonferroni adjusted *post-hoc* tests (alpha level of $0.05/4 = 0.0125$ per test) to test for differences in the individual ROI.

To examine differential relationships between continuous covariates and CTh between diagnostic groups, we performed Pearson correlation analysis separately within each group, and statistically compared correlation coefficients between the diagnostic groups (comparison of correlation coefficients from two independent samples) [33], and performed Bonferroni correction (alpha level of 0.05/4 = 0.0125 per test). In case of significant differences in correlations, we repeated the main analysis with addition of an interaction effect between the respective covariate and diagnostic group. For the categorical covariate MR-scanner-type, we modelled the interaction of diagnosis*MR-scanner-type in an additional MANCOVA with analogous *post-hoc* tests to check for differential effects of this covariate. In addition to this, we repeated our analyses for each MR-scanner-type separately. We report results of these analyses only for significant covariates in those ROI with significant main effects of diagnosis.

Furthermore, we performed two repeated measures ANCOVA analyses for the entorhinal and parahippocampal CTh values, respectively, to test for lateralization of CTh reduction between hemispheres. In these analyses, the left and right ROI of the respective region served as the within (i.e., hemispheric) factor. We then also modelled the interaction effect of hemisphere with diagnostic group to test for specific lateralization effects in the SMI group.

To visualize differences in CTh between groups topographically, a vertex-wise whole brain surface analysis was performed using the GLM-implementation of FS (qdec, $p < 0.005$, uncorrected). This analysis was modelled with age and BDI-score as nuisance factors to control for the influences of these variables, which differed significantly between groups.

RESULTS

Descriptive statistics of the two diagnostic groups (CO, SMI) are listed in Table 1. MANCOVA analysis revealed a significant overall effect of diagnostic group ($F(4,94) = 2.72$, $p = 0.034$, part $eta^2 = 0.104$) on CTh, together with significant overall covariate effects of MR-scanner-type ($F(8,190) = 4.46$, $p < 0.001$, part $eta^2 = 0.158$), age ($F(4,94) = 5.44$, $p < 0.001$, part $eta^2 = 0.188$); and years of education ($F(4,94) = 3.54$, $p = 0.010$, part $eta^2 = 0.131$).

Analysis of the specific ROI with Bonferroni adjusted *post-hoc* tests showed significantly reduced mean CTh values in the left entorhinal cortex ($F(1,97) = 9.52$ $p = 0.003$; part $eta^2 = 0.089$) in the SMI group (Table 2). Significant covariate effects of MR-scanner-type were observed in left ($F(2,97) = 16.31$, $p < 0.001$; part $eta^2 = 0.252$) and right entorhinal cortex ($F(2,97) = 8.35$, $p < 0.001$; part $eta^2 = 0.147$). Significant covariate effects of age were observed in the left ($F(1,97) = 10.442$, $p = 0.002$, part $eta^2 = 0.097$) and right entorhinal cortex ($F(1,97) = 6.61$, $p = 0.012$; part $eta^2 = 0.064$), as well as the left ($F(1,97) = 11.18$, $p < 0.001$; part $eta^2 = 0.103$) and right parahippocampus ($F(1,97) = 11.22$, $p < 0.001$; part $eta^2 = 0.104$). A significant covariate effect of education was observed in the right entorhinal cortex ($F(1,97) = 6.25$, $p = 0.014$; part $eta^2 = 0.061$) and in the right parahippocampus ($F(1,97) = 7.41$, $p = 0.008$; part $eta^2 = 0.071$).

Age and MR-scanner-type were the only covariates with significant effects on CTh in the left entorhinal cortex which was the only significant ROI in the Bonferroni adjusted *post-hoc* analysis. A significant correlation between age and CTh was observed in the SMI group ($r = -0.470$, $p = 0.002$), but did not reach statistical significance in the CO group ($r = -0.064$, $p = 0.6$). The difference in correlation coefficients differed significantly between groups ($z = -2.19$, $p = 0.029$). Because of this significant difference in correlations of age and CTh between groups we repeated the ANCOVA analysis for the left entorhinal cortex and additionally modeled an interaction effect between age and diagnosis. In this analysis we observed a significant interaction effect between diagnosis and age ($F(1,96) = 6.81$, $p = 0.011$;

Table 2
Comparison of cortical thickness values in the SMI vs. CO group (raw data and results of MANCOVA *post-hoc* analyses for each ROI)

	SMI ($n = 41$)	CO ($n = 69$)	F*	part·eta^2*	p*
lh entorhinal cortex (mm), mean (sd)	3.08 (0.4)	3.32 (0.4)	9.516	0.089	0.003
lh parahippocampal cortex (mm), mean (sd)	2.52 (0.4)	2.68 (0.3)	1.680	0.017	n.s.
rh entorhinal cortex (mm), mean (sd)	3.37 (0.4)	3.49 (0.4)	0.865	0.009	n.s.
rh parahippocampal cortex (mm), mean (sd)	2.53 (0.3)	2.65 (0.2)	1.102	0.011	n.s.

Abbr.: CO: control subjects; lh: left hemisphere; mm: millimeter; MANCOVA: Multivariate analysis of covariance; rh: right hemisphere; ROI: region(s) of interest; sd: standard deviation; SMI: subjective memory impairment **post-hoc* analyses are adjusted for covariates (age, gender, education, BDI-score, MR-scanner-type) and for multiple testing (Bonferroni corrected alpha level = 0.0125).

part eta^2 = 0.066) besides the two main effects (diagnosis: F(1,96) = 9.95, p = 0.002; part eta^2 = 0.094; age: F(1,96) = 11.67, p < 0.001; part eta^2 = 0.133). The direction of the interaction effect indicated greater group differences between SMI and CO with increasing age. We observed no diagnosis*MR-scanner-type interaction effect in the entorhinal cortex (or the other ROI). The separate analyses for each MR-scanner-type revealed lower left entorhinal cortical thickness values in the SMI group compared to the control group for each MR-scanner individually. The difference between groups reached significance in case of scanner 2. Mean (SD) CTh values in each group were as follows: scanner 1: SMI, 3.03 mm (0.49), CO, 3.16 mm (0.32), p = 0.402; scanner 2: SMI, 3.22 mm (0.37), CO, 3.68 mm (0.30), p = 0.003; scanner 3: SMI, 2.89 mm (0.33), CO, 3.25 mm (0.28), p = 0.132.

Repeated measures ANCOVA showed a significant effect for the within-subjects-factor hemisphere (F(1,97) = 18.35, p < 0.001; part eta^2 = 0.159), a significant main effect for the between-subjects-factor of diagnostic group (F(1,97) = 5.61, p < 0.020; part eta^2 = 0.055) and an ordinal interaction effect of hemisphere with diagnostic group (F(1,97) = 4.08, p < 0.046; part eta^2 = 0.040) indicating a lateralization effect towards the left entorhinal cortex.

The additional vertex-wise analysis (p < 0.005), adjusted for effects of age and BDI-score, showed cortical thinning in the entorhinal cortex in the left hemisphere, in line with the results of ROI analysis (Fig. 1) and in additional regions. We found no regions with reduced CTh in CO compared to SMI.

DISCUSSION

The aim of this study was to investigate, whether SMI is associated with reduced CTh in brain regions known to show atrophy in early AD. We observed significantly smaller mean CTh values in the left entorhinal cortex in the SMI group. Our results are in agreement with an earlier volumetric study in an independent sample showing reduced volumes of the entorhinal cortex in SMI subjects [9]. Transentorhinal areas including the entorhinal cortex and surrounding areas including the parahippocampal gyrus are considered sites of very early formation of neurofibrillary tangles in AD including early volume loss [34, 35]. Cortical thinning in circumscribed medial temporal lobe areas may thus reflect first alterations relating to AD pathology in the SMI sample of our study.

One recent study did not find significant CTh differences between controls and subjects with subjective cognitive impairment [36], which may be related to a smaller sample size (subjective cognitive impairment, n = 16; controls, n = 21) as compared to our study [27]. In addition, other factors, e.g., SMI/SCD definition and way of recruitment may influence the results within a specific sample. Such factors might have also contributed to discrepant findings between our study and that of Selnes et al. [36]. To achieve a sufficiently large sample, we pooled data across MR-scanners. We treated MR-scanner-type as a covariate. MR-scanner-type had a significant impact on CTh values. However, the effect of diagnostic group remained after controlling for the scanner effect. There was no diagnosis*MR-scanner-type interaction effect, which indicates that there was no significant confounding covariate effect of MR-scanner-type. Also, analyses within each scanner-type revealed smaller measures for left entorhinal cortical thickness in the SMI group as compared to controls. This difference was significant for scanner 2.

In contrast to AD cortical thinning over time in normal aging in regions of the medial temporal lobe, including the parahippocampal area, is relatively spared [37]. One recent study, however, reported that atrophy of the entorhinal cortex is not restricted to AD and is also found in elderly subjects with very low probability of incipient AD [38]. In our study, we found a difference between the diagnostic groups regarding the correlation of age and CTh in the entorhinal cortex. Following this observation we modelled the interaction effect of diagnostic group and age on CTh in the entorhinal cortex in an additional analysis. This analysis revealed stronger group differences (SMI < CO) in CTh with increasing age. This suggests an accelerated effect of age in the SMI group.

Greater CTh reduction in the entorhinal cortex in SMI is also in agreement with Dickerson et al. [19] who found the largest magnitude of cortical thinning in four samples of AD-patients in the medial temporal lobe and with another study that reported the greatest cortical thinning in the medial temporal lobe in MCI patients [39].

The vertex-wise analyses, which we provided for visualization, revealed other areas of cortical thinning beside the medial temporal lobe. We will not interpret these findings, for which no *a priori* hypotheses were formulated and which were observed at an uncorrected statistical threshold.

There are inconsistent reports on lateralization of atrophy in AD [40, 41]. We found an interaction effect between the within-subject factor hemisphere and the between-subject factor diagnostic group in the

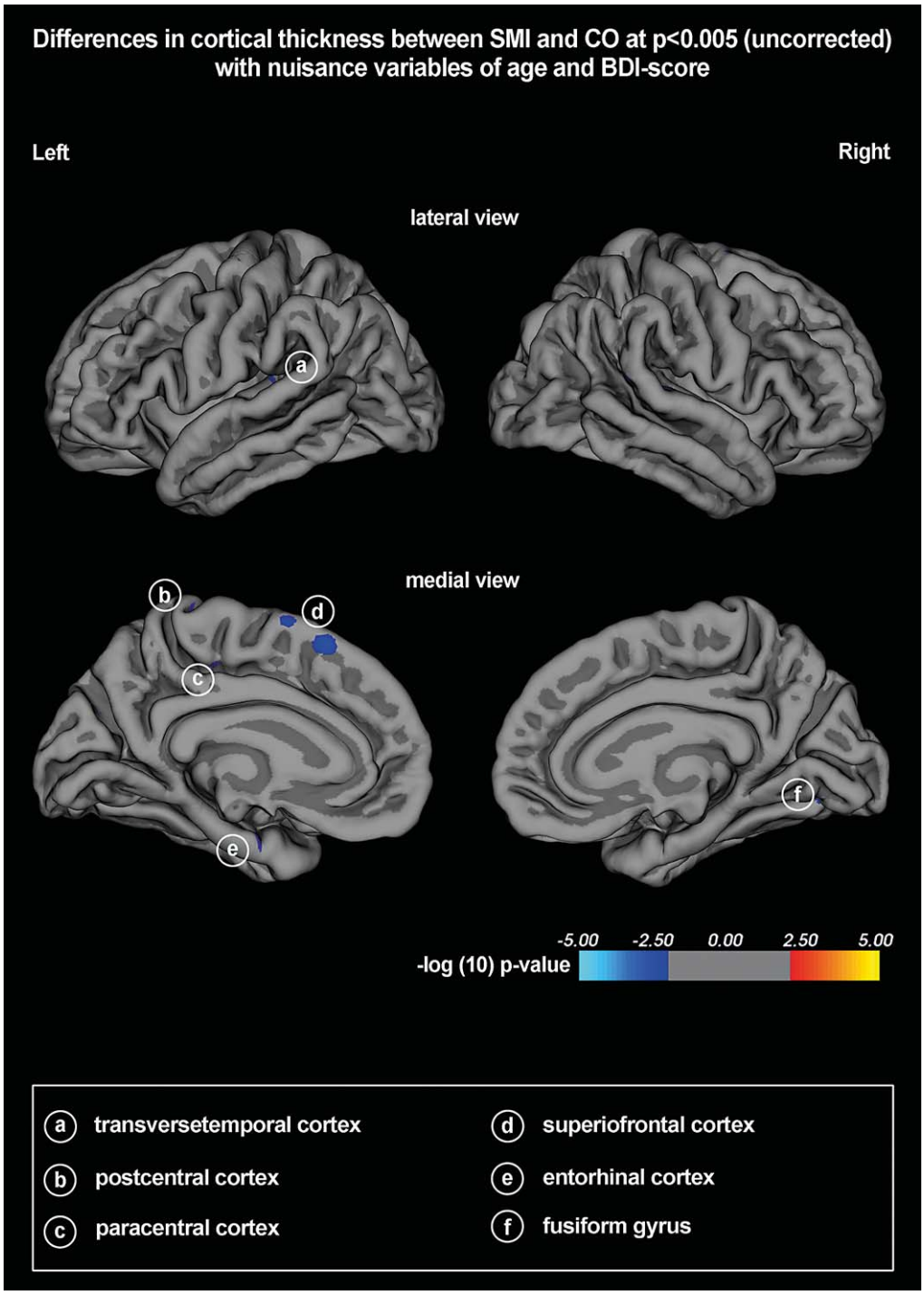

Fig. 1. Visualization of group comparison using qdec (FreeSurfer), showing areas of reduced cortical thickness in blue in subjects with SMI compared to controls in both hemispheres at $p < 0.005$, uncorrected, including age and BDI-score as nuisance variables. Abbr.: SMI: subjective memory impairment; CO: control subjects.

entorhinal cortex. The interaction effect indicated stronger differences between SMI and CO in the left entorhinal cortex.

BDI-scores differed between groups (Table 1). It is important to note that none of the participants in both groups fulfilled the criteria for a depressive episode

according to ICD-10. However, slightly higher scores on depression scales in non-depressed SMI subjects are frequently seen in studies on SMI [10, 29]. These subthreshold symptoms may reflect very early signs of AD. They may also reflect minor effects on the affective state associated with critical self-appraisal of memory worsening. It is necessary in studies on SMI/SCD to apply assessments of the individual's affective state and to further increase the understanding of the relationship of SMI/SCD and depressive symptomatology. In our study, the BDI-score was used as a covariate in all analyses and showed no significant influence on the results in the entorhinal cortex.

Limitations of this study are the absence of additional biomarkers indicating AD pathology like CSF biomarkers or PET-imaging. We also did not investigate the relationship between CTh and SMI, because we did not apply quantitative SMI scales.

In summary, our data indicate the presence of subtle cortical thinning in the left entorhinal cortex in SMI, which may reflect early AD pathology. Our data support the model of SMI as an early symptomatic indicator of AD before the clinical condition of MCI [6].

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