Subjective memory complaints, cortical thinning, and cognitive dysfunction in middle-age adults at risk of AD

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Abstract

Background: Subjective memory complaints (SMCs) represent an individual’s perception of subtle changes in memory in the absence of objective impairment in memory. However, it is not fully known whether persons with SMCs harbor brain alterations related to Alzheimer’s disease (AD) or whether they indeed demonstrate poorer cognitive performance.

Methods: The participants were 261 middle-age adults (mean age 54.30 years) enrolled in the Wisconsin Registry for Alzheimer’s Prevention, a registry of cognitively normal adults at risk of AD. They answered a question pertaining to subjective memory, completed a comprehensive neuropsychological examination, and subsequently underwent a volumetric magnetic resonance imaging scan. Cortical thickness measurements were derived from 10 a priori regions of interest involved in AD. Analyses of covariance were conducted to investigate the group differences in cortical thickness and neuropsychological measures.

Results: Compared with individuals without SMCs, those with SMCs had significant cortical thinning in the entorhinal, fusiform, posterior cingulate, and inferior parietal cortices and significantly reduced amygdala volume. Similarly, those with SMCs had significantly lower test scores on measures of Immediate Memory, Verbal Learning & Memory, and Verbal Ability. Additional adjustment for depressive symptoms (which differed between the groups) attenuated only the findings for the entorhinal cortex (P = .061) and Verbal Ability (P = .076).

Conclusion: At-risk, cognitively healthy individuals with SMCs exhibit cortical thinning in brain regions affected by AD and poorer performance on objective memory tests. These findings suggest that, in some individuals, SMCs might represent the earliest stages of AD.

Keywords: Preclinical AD; Subjective memory complaints; Cortical thickness; Cognition

1. Introduction

Recent years have witnessed an increasing interest in subjective memory complaints (SMCs) as a potential precursor to symptomatic Alzheimer’s disease (AD). Although currently no definition has been universally accepted [1],
SMCs are generally believed to represent subtle changes in memory that fall below the detection thresholds of common cognitive tests [1]. Furthermore, the question of whether individuals with SMCs are a population with an increased risk of progression to AD remains controversial. Some investigators have suggested that SMCs are characteristic of a “worried well” population; hence, the lack of an association between SMCs and memory performance in such studies [2,3]. In contrast, others have found significant relationships between SMCs and objective cognitive performance [4–6]. For example, a recent study [5], found significant correlations between SMCs and decreased performance on objective measures of episodic memory, working memory, and semantic knowledge. In addition, longitudinal studies have shown SMC groups to have a faster rate of decline on immediate recall and related psychometric measures [4,7].

If SMCs represent an individual’s awareness of early, subtle, changes in cognition, a relationship should be expected between the presence of SMCs and specific AD pathologic processes, such as atrophy of the medial temporal lobes and lateral/middle parietal cortices [8–11]. To date, a number of studies have reported evidence for such brain changes. For example, Jessen et al [12] found a decreased entorhinal cortex volume in individuals with SMCs compared with healthy controls. Additionally, a more recent study [13] found gray matter volume reductions in several brain areas, such as the hippocampus, anterior cingulate, and prefrontal cortex, as part of the nonpathologic aging process [18,19]. Taken together, these findings suggest that the memory complaints could reflect actual AD-related brain alterations.

Although brain volume might shrink as a result of either normal aging or a neurodegenerative process such as AD, cortical thinning is believed to be a hallmark feature of AD [16,17]. However, some have reported thinning in the prefrontal cortex as a part of the nonpathologic aging process [18,19]. Although previous studies have examined the relationship between regional brain volume and SMCs, no studies to date have investigated whether SMCs are linked to thinning in AD-sensitive brain regions. Furthermore, most of the studies in this area have focused on cohorts of elderly adults. Thus, it remains unknown whether SMCs in midlife is related to brain and cognitive changes, particularly in an at-risk cohort that might ostensibly be overly sensitive to normal fluctuations in mental function.

Accordingly, in the present study, we examined whether SMCs are associated with thinning of cortical regions involved in AD within a middle-age cohort of cognitively normal individuals with risk factors for AD. Additionally, we also examined how individuals with SMCs perform on objective cognitive tests compared with those without SMCs.

### 2. Methods

#### 2.1. Participants

The data from 261 middle-age adults from the Wisconsin Registry for Alzheimer’s Prevention (WRAP) cohort were used in the present study. WRAP is a longitudinal registry composed of more than 1500 cognitively normal middle-age adults aged 40 to 65 years at study entry [20]. The participants for the present study were selected on the basis of having completed a baseline WRAP visit and a subsequent magnetic resonance imaging (MRI) scan. The sample was enriched for a parental family history of AD (FH; 71.3%) and possession of the e4 allele of the apolipoprotein E gene (APOE4; 42.1%). The methods for determining FH have been described previously [21]. In brief, to verify the diagnosis of AD in the parent, the parental medical records were obtained (including autopsy reports when available) and reviewed by a multidisciplinary diagnostic consensus panel. When these records were not available, the dementia questionnaire [22] was used. The absence of an FH of AD was verified through detailed medical history surveys and telephone interview (including the dementia questionnaire) with the participants. The inclusion in the FH group required that the father had survived to at least age 70 years and the mother to age 75 years, without incurring a formal diagnosis of dementia or exhibiting cognitive deterioration. Women comprised 67.4% of the sample, and the average age at baseline was 54.30 ± 6.44 years (Table 1 provides a summary of

### Table 1

| Variable                        | SMC+ (n = 77) | SMC− (n = 184) | P value |
|---------------------------------|---------------|----------------|---------|
| FH positive (%)                 | 77.9          | 68.5           | .124    |
| APOE4 positive (%)              | 46.8          | 40.2           | .329    |
| Female sex (%)                  | 67.5          | 67.4           | .982    |
| White race (%)                  | 94.8          | 96.2           | .610    |
| Age (y)                         | 54.33 ± 6.10  | 54.41 ± 6.44   | .925    |
| Range                           | 41.89–66.40   | 40.31–67.56    | .763    |
| Education (y)                   | 15.97 ± 2.25  | 16.16 ± 2.33   | .707    |
| Range                           | 12–20         | 12–22          | .001    |
| MMSE score                      | 29.43 ± 0.80  | 29.53 ± 0.88   | <.001   |
| Range                           | 27–30         | 25–30          | .750    |
| CES-D score ≥16                 | 14.5          | 2.7            | <.001   |
| Interval between WRAP visit and MRI (y) | 5.57 ± 1.87 | 5.52 ± 1.81 | .750 |
| Range                           | 0.00–9.00     | 0.00–9.54      |         |

Abbreviations: FH, parental family history of Alzheimer’s disease; APOE4, varepsilon 4 allele of apolipoprotein E gene; MMSE, Mini Mental State Examination; CES-D, Center for Epidemiological Studies Depression Scale (16 is the established cutoff for elevated depressive symptoms [31]); MRI, magnetic resonance imaging; SMC, subjective memory complaint; WRAP, Wisconsin Registry for Alzheimer’s Prevention.

NOTE: All measurements were taken from the baseline visit, except for the MMSE, which was first given at the Wave 2 visit (approximately 4 years after baseline).
logic defects. Our analyses focused on select ROIs known to be affected early in the AD cascade, such as the hippocampus and posterior cingulate (Table 2).

2.4. Cognitive assessment

At their baseline WRAP visit, the participants completed a comprehensive neuropsychological battery that included psychometric measures spanning the traditional cognitive domains of memory, attention, executive function, language, and visuospatial ability. Earlier factor analytic studies [29,30] of these psychometric measures within the larger WRAP cohort showed that these tests map onto six cognitive factors [~N(0,1)]: Immediate Memory, Verbal Learning & Memory, Working Memory, Speed & Flexibility, Visuospatial Ability, and Verbal Ability (each factor’s constituent tests are listed in Table 3). These factor scores were used in our present evaluation of the association between SMCs and cognition. In addition to these cognitive tests, participants also completed the Center for Epidemiological Studies Depression questionnaire (CES-D).

2.5. Statistical analysis

Group differences on baseline demographic measures were tested using the independent samples $t$ test or chi-square analyses, as appropriate. We used analyses of covariance (ANCOVA) to test for group differences (SMC+ versus SMC−) on our a priori ROIs. For the thickness measures, we adjusted for age, sex, and the interval between the cognitive assessment and brain imaging studies. For volumetric measures, the covariates included age, sex, total intracranial volume, and the interval between the cognitive assessment and brain imaging. Similarly, we used an ANCOVA framework to assess for group differences in the neuropsychological measures. The covariates included age, sex, and education. All relevant model assumptions (e.g., normality and homogeneity of variance) were evaluated

| Anatomic                  | SMC+ ($n = 77$) | SMC− ($n = 184$) | $P$ value |
|---------------------------|-----------------|------------------|-----------|
| Hippocampal volume        | 3930.77 ± 384.04| 3970.48 ± 383.88 | .447      |
| Amygdala volume           | 1572.17 ± 195.31| 1636.80 ± 195.26 | .016      |
| Entorhinal                | 3.37 ± 0.26     | 3.45 ± 0.02      | .026      |
| Fusiform                  | 2.62 ± 0.09     | 2.65 ± 0.01      | .044      |
| Parahippocampal           | 2.69 ± 0.26     | 2.71 ± 0.02      | .395      |
| Cingulate isthmus         | 2.51 ± 0.18     | 2.54 ± 0.01      | .265      |
| Posterior cingulate       | 2.58 ± 0.18     | 2.62 ± 0.01      | .043      |
| Precuneus                 | 2.38 ± 0.09     | 2.40 ± 0.14      | .193      |
| Supramarginal             | 2.45 ± 0.09     | 2.46 ± 0.14      | .332      |
| Inferior parietal         | 2.43 ± 0.09     | 2.46 ± 0.14      | .036      |

Abbreviation: SMC, subjective memory complaint.
NOTE: All data presented as estimated mean ± standard deviation. For the thickness measures, statistical adjustment was made for age, sex, and the interval between the cognitive assessment and brain imaging. For the volume measures, the covariates included age, sex, total intracranial volume, and interval between cognitive assessment and brain imaging.
Table 3: Association between SMCs and objective cognitive performance

| Variable                          | SMC+ (n = 77) | SMC− (n = 184) | P value |
|-----------------------------------|---------------|---------------|---------|
| Immediate Memory                  | −0.170 ± 0.97 | 0.174 ± 0.95  | .007    |
| RAVLT Trial 1                     |               |               |         |
| RAVLT Trial 2                     |               |               |         |
| Verbal Learning & Memory          | −0.192 ± 0.97 | 0.108 ± 0.95  | .024    |
| RAVLT Trial 3                     |               |               |         |
| RAVLT Trial 4                     |               |               |         |
| RAVLT Trial 5                     |               |               |         |
| RAVLT Long Delay                  | −0.132 ± 1.05 | 0.126 ± 1.09  | .068    |
| Working Memory                    |               |               |         |
| WAIS Digit Span Forward           |               |               |         |
| WAIS Digit Span                   |               |               |         |
| WAIS Backward                     |               |               |         |
| WAIS Letter-Number                |               |               |         |
| Sequencing                        |               |               |         |
| Speed & Flexibility               | 0.060 ± 0.88  | 0.122 ± 0.95  | .615    |
| Trail Making Test A               |               |               |         |
| Trail Making Test B               |               |               |         |
| Visualspatial Ability             | 0.016 ± 0.88  | 0.216 ± 0.95  | .096    |
| WASI Block Design                 |               |               |         |
| WASI Matrix Reasoning             |               |               |         |
| Benton JLO                        |               |               |         |
| Verbal Ability                    | 0.001 ± 0.79  | 0.239 ± 0.81  | .035    |
| WASI Vocabulary                   |               |               |         |
| WASI Similarities                 |               |               |         |
| Boston Naming Test                |               |               |         |
| WRAT III—Reading                 |               |               |         |

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; WAIS, Wechsler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence; JLO, Judgment of Line Orientation; WRAT III, Wide-Range Achievement Test, 3rd edition.

NOTE: Data presented as estimated mean ± standard deviation. Statistical adjustment was made for age, sex, and education.

and found to be satisfactorily met. The analyses were performed using SPSS, version 20.0 (IBM Corp., Armonk, NY). Only findings with a 2-tailed P value ≤ .05 were considered significant.

3. Results

3.1. Background characteristics

The SMC+ and SMC− groups did not differ significantly on age, sex, FH, APOE4 status, education, or global cognition. Significantly more people with CES-D scores ≥16 (the established cutpoint for elevated depressive symptoms [31]) were in the SMC+ group (n = 11) compared with the SMC− group (n = 5). These results are summarized in Table 1.

3.2. Association between SMCs and brain structure

The ANCOVA used to examine the group differences in brain structure revealed that, compared with the SMC− group, the SMC+ group had a significantly thinner cortex in the entorhinal, fusiform, posterior cingulate, and inferior parietal cortices. In addition, the amygdala volume was significantly lower in the SMC+ group than in the SMC− group. Although the groups did not differ significantly in the other brain regions, a consistent trend was observed, such that the SMC+ group had lower values than the SMC− group. These results are listed in Table 2. When we also adjusted for FH and APOE4 status, the results remained unchanged with the exception that the posterior cingulate finding became marginally significant (P = .085).

3.3. Association between SMCs and objective cognitive function

The results of the comparisons between the SMC+ and SMC− groups on objective cognitive measures are listed in Table 3. The SMC+ individuals had poorer test scores than those in the SMC− group in the Immediate Memory, Verbal Learning & Memory, and Verbal Ability domains. A trend toward a poorer Working Memory (P = .068) and Visuospatial Ability (P = .096) in the SMC+ group was also observed. However, we noted that—consistent with this being a cognitively normal cohort—the mean test scores within the SMC+ group were not lower than 0.2 standard deviation below the mean for any cognitive domain (the typical cutpoint for abnormal cognitive test scores was ≥1.5 standard deviations less than the reference mean). Just as with the brain structure analysis, we also adjusted for FH and APOE4 status in the models. The only change to the initial results was Verbal Ability, which had decreased to a trend (P = .065).

3.4. Secondary analyses

Because the study entry criteria excluded persons with a history of depressive disorders, the observed group difference on the CES-D was not deemed clinically meaningful. However, we opted to perform follow-up sensitivity analyses to determine whether and to what extent our initial findings were driven by elevated depressive symptoms, given emerging evidence that SMCs might be linked to depression [12,32].

We began by running Pearson’s correlations to examine the associations between our brain/cognitive measures and the CES-D scores (dichotomized at ≥16). This was founded on the statistical premise that, if the CES-D scores were not associated with the outcomes, the elevated depressive symptoms could not be the primary underlying reason for the observed associations between SMCs and the outcomes [33]. Next, if any of the brain/cognitive measures were found to correlate significantly with the CES-D, we ran the original ANCOVA analyses again, including CES-D as an additional covariate.

The Pearson’s correlations showed that only Verbal Ability (r = −0.14, P = .024) and entorhinal cortex thickness (r = −0.13, P = .037) were significantly associated with the CES-D scores. When the ANCOVAs were refit,
Of interest, however, the CES-D was not significantly associated with either measure ($P = .290 (\Delta R^2 = .003)$ and $P = .269 (\Delta R^2 = .005)$, respectively) in these refitted ANCOVAs. Because the essence of our original SMC findings persisted on correction for elevated depressive symptoms, it appears those initial findings were not primarily driven by differentials in the depressive symptoms between the 2 groups.

Finally, we repeated these sensitivity analyses using the CES-D scores obtained from the WRAP visit closest to the time of the MRI scan (6.84 ± 6.12 months), to determine whether and to what extent our findings were driven by “MRI-concurrent” depressive symptoms. Pearson’s correlations showed no significant associations ($P > .112$) between these MRI-concurrent CES-D scores and our outcome measures, suggesting that any depressive symptoms at MRI scanning were unlikely to be the underlying reason for the observed associations between the presence of SMCs and the outcomes [33].

4. Discussion

In the present study, we found that middle-age individuals with SMCs have a thinner cortex in AD-vulnerable brain regions, such as the entorhinal, fusiform, inferior parietal, and posterior cingulate cortices and had a reduced amygdala volume compared with their peers without SMCs. In addition, we observed that objective cognitive test scores were decreased in individuals with SMCs compared with those without. Specifically, the measures of Immediate Memory, Verbal Learning & Memory, and Verbal Ability were all significantly lower in those with SMCs.

An increasing number of studies have investigated structural brain changes in SMCs [32,34–36]. In one such study, conducted in a large community-based sample, SMCs were associated with cross-sectional decrements in hippocampal, parahippocampal, and amygdalar volumes [35] and longitudinal hippocampal volume loss 4 years later [36]. Similarly, a study of individuals referred to a memory clinic found that those with SMCs had a significantly smaller right hippocampal volume than did the controls [32]. Additionally, another study [34] found that individuals with SMCs had a smaller hippocampal and parahippocampal volume than did those without SMCs. Our findings of significant cortical thinning of AD-relevant cortices complement these volumetric studies. A previous study [12] had also found that SMC+ individuals exhibited a lower entorhinal cortex volume but not a lower hippocampal volume compared with the SMC− individuals. This is in accord with the known topographic progression of neurodegenerative changes in AD, which starts in the transentorhinal region and then moves to the entorhinal cortex, before affecting the hippocampus [37–39]. This topographic sequence might explain why the extent of entorhinal atrophy has been shown to better identify cognitively normal individuals at risk of developing AD compared with hippocampal atrophy [40–42].

Although we did not directly examine the other imaging biomarkers of AD in the present study, the current hypothetical models of AD pathophysiologic changes suggest that brain structure changes occur later in the AD cascade than alterations in amyloid-β and glucose metabolism [43]. Therefore, our observed group differences in brain structure would suggest that cerebral amyloidosis and/or hypometabolism in AD-related brain regions might be detectable in individuals with SMCs. An increasing number of studies have reported evidence for such disease-related changes [5,7,15,32]. Perrotin et al [15] found that individuals with SMCs had increased fibrillary amyloid deposition in the right posterior cingulate and precuneus, and another study [32] observed hypometabolism in the right parahippocampal gyrus, right hippocampus, and bilateral precuneus in older adults with SMCs. These findings, combined with the findings from our study, provide new neuroimaging evidence of cortical thinning in AD-vulnerable brain regions, adds to the hypothesis that individuals with SMCs might represent a population at increased risk of eventual progression to probable AD [43–47].

Investigations of the link between SMCs and objective cognitive performance are an active area of research, and the emerging evidence has been heterogeneous [4,5,12,32,48]. Congruent with our study, Amariglio et al [5] found SMCs were associated with decreased episodic and working memory. Similarly, Scheef et al [32] found a decline in episodic and immediate verbal memory in a population with SMCs. Another longitudinal study has also provided evidence for a decline in the measures of working memory and perceptual motor skills in individuals with SMCs [4]. Our observation of comparatively decreased performance in Immediate Memory, Verbal Learning & Memory, and Verbal Ability in individuals with SMCs is in accordance with the findings from these previous studies. Similar to medial temporal lobe structural alterations, impairment in episodic memory is an early feature of AD [49]. Therefore, our finding of concomitant decreases in episodic memory and mesial temporal cortical thickness in our SMC+ participants increases the possibility that these individuals might be in the very early stages of the AD cascade. Because the WRAP is an ongoing study, we will be well positioned to investigate the long-term prognostic utility of early subjective complaints.

We observed no significant group differences in APOE4 status, FH, age, education, or sex, indicating that those with these risk factors for AD are not any more likely to report SMCs in midlife than those without these risk factors. This is in agreement with most studies of SMCs [12,15,32,48]. However, the absence of a FH differential
between our SMC groups was rather surprising. Individuals with a FH are typically aware they harbor this risk factor, which is not always the case for other risk factors, such as APOE4 status. This awareness, and the experience of observing the disease course in their affected relatives, often leads to a heightened sensitivity to what might otherwise be normal variability in cognitive functioning [50,51]. Therefore, if SMCs were merely a symptom of a “worried well” population, one would have expected that persons with a FH would disproportionately endorse subjective memory failures [52]. The absence of such an association in our sample suggests that, at least in some contexts, a simple inquiry into SMCs might have clinical validity for identifying the subset of cognitively normal persons who might truly be experiencing objective cognitive difficulties and associated brain changes and thus have a greater risk of future progression to AD.

Our observation of greater depressive symptoms in the SMC+ group parallels reports from other investigators [7,12,32,34,53]. A recent study by Steinberg et al [53] found that scores on a questionnaire pertaining to SMCs were associated with measures of depressive symptoms. Additionally, other investigators [12,32] have found individuals with SMCs to have significantly higher scores on measures of depression compared with controls. In both these latter studies, differences between the SMC— and SMC+ groups for gray matter volume, cerebral glucose metabolism, and cognitive performance persisted even after adjustment for depressive symptoms. Similarly, although we found the CES-D scores to bivariately correlate with two of our outcome measures (Verbal Ability and entorhinal cortex thickness), when we included the CES-D scores in the original multivariable statistical model, it failed to be associated with either of these measures, and the essence of our original SMC findings persisted. When this negative CES-D finding is placed in the context of our study’s entry criteria, which excluded persons with major depression and other major psychiatric disorders, it appears rather improbable that the memory complaints were driven by clinical depression in our study. Although some evidence has shown that mid-to-late-life depressive symptoms are associated with cortical thinning in the parietal and temporal regions [54] and might even be a prodrome for dementing disorders [55]. It would be of future interest to determine whether greater depressive symptoms at baseline are associated with prospective changes in brain health and cognition within our cohort [56].

Our study had some limitations. Although the cross-sectional nature of our study has provided insight into the initial brain and cognitive changes that might be differentially occurring in middle-age individuals with SMCs, longitudinal studies are needed for a full understanding of these initial findings. Given that the WRAP is ongoing, we will have the data to determine whether asymptomatic individuals with SMCs are more likely to transition to the symptomatic stages of the AD cascade. Also, the WRAP cohort is predominantly composed of highly educated, non-Hispanic white individuals. Therefore, it is not known whether our measure of SMCs would be similarly associated with brain structure and objective cognition in a more heterogeneous middle-age sample. Additionally, a single question about subjective complaints, such as that used in the present study, could be easily incorporated into busy clinical practices, with potential to be useful for the early identification of at-risk older adults, especially when used in conjunction with other pertinent health and clinical information. Such individuals might then be potential candidates for clinical trials investigating disease-modifying interventions for AD.

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1. Systematic review: We searched PubMed using the terms: “subjective memory complaint,” “SMC,” “subjective cognitive impairment,” “subjective memory impairment,” “subjective cognitive complaints” and “Alzheimer’s disease,” or “dementia.”

2. Interpretation: Early detection of individuals at increased risk of developing dementia is of major scientific and clinical interest. Our study finds that middle-age, asymptomatic, persons with SMCs have a thinner cortex in brain regions affected by Alzheimer’s disease compared with persons without such subjective complaints. SMCs were also associated with objective cognitive performance in our cohort. These findings support the use of SMCs as a potential method for identifying cognitively normal persons with subtle brain and cognitive changes that might be indicative of incipient Alzheimer’s disease.

3. Future directions: Continued follow-up of our cohort will allow us to determine whether asymptomatic individuals with SMCs will transition into symptomatic stages of the AD cascade.

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