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ORIGINAL ARTICLE

Memory complaints in subjective cognitive impairment, amnestic mild cognitive impairment and mild Alzheimer's disease

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Abstract Memory complaints are a frequent phenomenon in elderly individuals and can lead to opportunistic help-seeking behavior. The aim of this study was to compare different aspects of memory complaints (i.e., prospective versus retrospective complaints) in individuals with subjective cognitive impairment (SCI), amnestic mild cognitive impairment (aMCI), and mild Alzheimer's disease (AD). The study included a total of 115 participants (mean age: 68.82 ± 8.83 years) with SCI ($n = 34$), aMCI ($n = 46$), and mild AD ($n = 35$). Memory complaints were assessed using the Prospective and Retrospective Memory Questionnaire (PRMQ), which consists of 16 items that describe everyday memory failure of both prospective memory (PM) and retrospective memory (RM). For aMCI and AD subjects, informants also completed an informant-rating of the PRMQ. All participants completed detailed neuropsychological tests. Results show that PM complaints were equivalent among the three groups. However, RM complaints differed. Specifically, RM complaints in aMCI were higher than SCI, but similar to AD. Informant-reported memory complaints were higher for AD than aMCI. Our study suggests that RM complaints of memory complaints may be helpful in discriminating between SCI and aMCI, but both PM and RM complaints are of limited value in differentiating aMCI from AD.

Keywords Subjective cognitive impairment · Mild cognitive impairment · Alzheimer disease · Memory complaint

Introduction

Subjective cognitive impairment (SCI), usually defined by subjective memory complaints (SMCs) and cognitive performance in the normal adjusted range [1, 2], is frequent in elderly people. Evidence suggests that SCI is a risk factor for future cognitive decline, as well as for mild cognitive impairment (MCI) and dementia [3–5]. In addition, biomarker studies have demonstrated increased prevalence of Alzheimer's disease (AD)-type pathology in SCI [6–8]. Taken together, these findings suggest that SCI may serve as a symptomatic indicator of preclinical AD [9]. In addition, SMCs are a cardinal feature of amnestic mild cognitive impairment (aMCI), which is considered to be a prodromal phase of AD [10]. Therefore, SCI, aMCI, and AD appear to be on a spectrum of clinical disease [9], and it is clinically important to identify aMCI among older adults with SMCs.

SMCs can be assessed by a single question about whether memory complaints are present or by memory questionnaires. The questions address mostly about episodic memory for past life events, commonly referred to as retrospective memory (RM). Other important aspects of memory have been somewhat underestimated in assessing SMCs, notably prospective memory (PM). To assess SMCs in the current study, we used the Prospective and Retrospective Memory Questionnaire (PRMQ), which rates the frequency of everyday memory failures, including the failure to remember past events (i.e., RM) and to realize future intentions (i.e., PM) to capture different aspects of SMCs [11].

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The aim of this study was to compare memory complaints in individuals with SCI, aMCI, and mild AD. Furthermore, we explored whether group differences exist in PM versus RM complaints.

Methods

Participants

A total of 115 participants took part in the study, including 34 SCI, 46 aMCI, and 34 mild AD patients. All subjects were enrolled from the Memory Disorders Clinic of the Department of Neurology at The Catholic University of Korea, Daejeon St. Mary's Hospital. Subjects underwent a detailed medical history, physical and neurologic examinations, a brain MRI, and a neuropsychological test.

Inclusion criteria for SCI were as follows: (1) SMCs; (2) normal performance on tests of cognitive abilities, including memory (within 1 SD of age- and education-adjusted norms); and (3) stage 2 on the Global Deterioration Scale [12].

The diagnosis of aMCI was based on criteria from Petersen et al. [10], including: (1) memory complaints, preferably corroborated by an informant; (2) memory impairment below at least the 10th percentile (−1.28 SD) of the age- and education-adjusted norms in delayed recall of Seoul Verbal Learning Test (SVLT) or Rey Complex Figure Test (RCFT) from the neuropsychological test battery; (3) preserved general cognitive function; (4) largely intact functional activities; (5) stage 3 on the Global Deterioration Scale; and (6) absence of dementia by DSM-IV criteria [13].

Diagnosis of AD met the criteria for dementia according to the DSM-IV criteria [13] and the criteria for probable AD established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [14]. All of the AD patients were classified as being in the mild stage (stage 4 on the Global Deterioration Scale).

Participants were excluded if they had major neurologic or psychiatric illnesses (e.g., schizophrenia or major depression), history of stroke, history of significant head trauma, unstable medical illness, history of brain surgery, history of alcohol or substance abuse, structural brain abnormalities (e.g., territorial infarction, intracranial hemorrhage, brain tumor, hydrocephalus, or other focal lesions), hearing or vision loss, or illiteracy. Any subjects taking psychoactive medications that could affect cognitive function (e.g., antidepressants, neuroleptics, chronic anxiolytics, or sedative hypnotics) were excluded. In addition, subjects with aMCI and AD were not using cholinesterase inhibitors or memantine at recruitment.

This study was approved by the Institutional Review Boards of The Catholic University of Korea, Daejeon St. Mary's Hospital and the research was completed in accordance with the 1964 Helsinki Declaration and its later amendments.

Subjective memory complaints

SMCs were assessed using the Korean translation [15] of the PRMQ [11]. The PRMQ is a 16-item questionnaire that measures everyday memory failure of both PM (e.g., deciding to do something in a few minutes' time and then forgetting to do it) and RM (e.g., forgetting something that you were told a few minutes before). For each item, participants were asked to rate the frequency of failure on a 5-point Likert-type scale that ranged from 5 (very often) to 1 (never). PRMQ total scores range from 16 to 80 and PM and RM subscores each range from 8–40. Higher scores indicate more memory complaints. Reliability of the PRMQ scale has been found to be acceptable [16]. Reliability of the PRMQ total scale and of the PM and RM subscales in the present study was high (Cronbach's α of 0.91, 0.87, and 0.83, respectively).

Informants for subjects with aMCI and AD completed an informant-rating of the PRMQ. They were asked to record their estimate of how often each type of memory failure happened to the patients on the same 5-point scale. Reliability of the informant-rated PRMQ scale has also been found to be acceptable [17]. Reliability of the informant-rated PRMQ total scale and PM and RM subscales in the present study was also high (Cronbach's α of 0.95, 0.91, and 0.93, respectively). In addition, informant-rating of the PRMQ for subjects with SCI was performed if there were available informants for SCI participants.

Neuropsychological test

Subjects received the Korean version of the Mini-Mental State Examination (K-MMSE) [18] for global cognitive function and Global Deterioration Scale for staging of cognitive impairment [12]. Neuropsychological tests included five cognitive domains: (1) attention: digit span forward; (2) language: Korean version of the Boston Naming Test (K-BNT) [19]; (3) visuospatial: RCFT copy [20]; (4) memory: SVLT (delayed recall) and RCFT (delayed recall) [20]; (5) executive: phonemic Controlled Oral Word Association Test (COWAT) [21] and Stroop Color-Word Test [22]. Raw scores from K-MMSE and each neuropsychological test were transformed into age- and education-adjusted z scores using normative data [20, 23].

Assessment of depression and functional status

Depressive symptomatology was assessed using the Korean version [24] of the Geriatric Depression Scale (GDS)-

Short Form, which includes 15 items. Scores range from 0–15, and higher scores indicate stronger depressive symptoms. Function was assessed using the Barthel Index of activities of daily living (ADL) (range 0–20) [25] and the Korean Instrumental Activities of Daily Living (K-IADL) (range 0–3) [26]. Higher scores reflect lower levels of dependence for basic ADLs and worse IADL performance, respectively.

Statistical analyses

Group differences were assessed with one-way analyses of variance (ANOVA) [post hoc group comparisons with Tukey Honestly Significant Difference (HSD)] or Kruskal–Wallis tests (post hoc group comparisons with nonparametric Steel–Dwass method) for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables.

Analysis of covariance (ANCOVA) was used to compare PRMQ scores across SCI, aMCI, and AD groups while controlling for demographic variables (i.e., age, hypertension, MMSE scores). Because the distribution of PRMQ total and PRMQ-PM scores was skewed in the AD group, values were log-transformed for analysis. Post hoc comparisons were explored using Tukey HSD post hoc tests.

Informant-rated PRMQ scores were compared for AD and aMCI groups using a Mann–Whitney U test. Additional ANCOVA analyses using log-transformed PRMQ total scores were computed to adjust for effects of the demographic variables (i.e., age, hypertension, MMSE scores).

Paired t tests were performed on mean PRMQ-PM and PRMQ-RM subscale scores and on self-reported and informant-reported PRMQ total scores within each group. Spearman's correlations were calculated between each PRMQ score (total, PM, and RM) and cognitive performance.

Statistical analyses were performed using JMP pro 11.0.0 (SAS Inc., Cary, NC, USA) and SPSS software package version 19.0 (SPSS Inc., Chicago, IL, USA). The level of significance was set at $p < 0.05$. All statistical tests were two-tailed.

Results

Demographic characteristics

A total of 115 participants were included in the analysis. The mean age was 68.82 ± 8.83, and the majority were female (69.57 %). Table 1 shows the demographic data and neuropsychological test results of the participants by group (SCI, aMCI, AD).

The three groups were similar on education, sex, and GDS score, but differed on age, K-MMSE score, and K-IADL score ($p < 0.001$) (Table 1). Post hoc analyses (nonparametric Steel–Dwass method) showed that AD subjects were older than SCI and aMCI subjects ($p < 0.001$), and aMCI and SCI subjects were of similar age ($p = 0.563$). On K-MMSE, AD subjects had lower scores than SCI and aMCI subjects ($p < 0.001$), and aMCI subjects had lower scores than SCI subjects ($p < 0.041$). In addition, AD subjects had higher K-IADL scores than SCI and aMCI ($p < 0.001$), and aMCI and SCI subjects had similar scores ($p = 0.477$). Regarding medical illness, the three groups were similar on diabetes, hyperlipidemia, and heart disease, but AD subjects had the highest proportion of hypertension ($p = 0.028$) (Table 1).

Group differences were observed in neuropsychological tests ($p < 0.001$) (Table 1). Post hoc tests (Steel–Dwass method) indicated that AD patients were different from SCI and aMCI across all tests ($p < 0.001$). In addition, post hoc tests revealed that memory domain scores (SVLT and RCFT delayed recall) were different between SCI and aMCI ($p < 0.001$ in both cases) (Table 1).

PRMQ scores

Mean scores of PRMQ total and PM and RM subscale for the entire sample were: 37.58 ± 11.40, 19.11 ± 6.13, and 18.43 ± 5.86, respectively. Table 2 shows PRMQ scores by group (SCI, aMCI, AD). SCI subjects had higher PM scores than RM scores ($t = 5.04$, $p < 0.001$), indicating more complaints in PM, but aMCI and AD subjects showed no difference ($t = -0.08$, $p = 0.94$; $t = -0.47$, $p = 0.64$, respectively).

To assess group differences on PRMQ scores, an ANCOVA was performed with Group (SCI, aMCI, AD) as a between-subject factor and age, hypertension status, and K-MMSE z score as covariates. After adjusting for covariates, ANCOVA revealed group differences on PRMQ-RM [$F(2, 109) = 4.528$, $p = 0.013$]. There were no group differences on PRMQ total (log-transformed) [$F(2, 109) = 2.511$, $p = 0.086$] and PRMQ-PM (log-transformed) [$F(2, 109) = 1.677$, $p = 0.192$]. Post hoc analyses (Tukey HSD) revealed pairwise group differences on PRMQ-RM between SCI and aMCI ($p = 0.018$) and between SCI and AD ($p = 0.036$), but not between aMCI and AD ($p = 0.610$) (Table 2). We assessed group differences on informant-rated PRMQ data, which were available for 43 aMCI and 33 AD individuals. Informants included spouses (aMCI = 65.12 %, AD = 30.30 %), children (aMCI = 32.56 %, AD = 46.05 %), relatives (aMCI = 2.33 %, AD = 2.63 %), and friends (aMCI = 0.0 %, AD = 1.32 %). Subjects with aMCI self-reported more memory complaints (i.e., higher PRMQ total scores)

Table 1 Demographic characteristics and neuropsychological test results for SCI, aMCI, and mild AD

	SCI ($n = 34$)	aMCI ($n = 46$)	AD ($n = 35$)	p value
Age, years	64.71 ± 7.17	66.65 ± 9.08	75.66 ± 5.55	<0.001[†,‡]
Education, years	8.07 ± 4.47	9.52 ± 4.91	7.96 ± 5.34	0.339
Female, *n* (%)	28 (82.35)	29 (63.04)	23 (65.71)	0.15
Hypertension, *n* (%)	16 (47.06)	13 (28.26)	20 (57.14)	0.028
Diabetes, *n* (%)	4 (11.76)	9 (19.57)	9 (25.71)	0.336
Hyperlipidemia, *n* (%)	7 (25)	10 (25.64)	11 (35.48)	0.587
Heart disease, *n* (%)	2 (5.88)	6 (13.04)	3 (8.57)	0.622[a]
GDS	4.56 ± 3.97	4.43 ± 3.48	4.54 ± 3.51	0.971
K-MMSE	27.09 ± 1.75	25.93 ± 1.84	20.17 ± 3.14	<0.001[*,†,‡]
K-IADL	0.18 ± 0.13	0.22 ± 0.14	0.49 ± 0.26	<0.001[†,‡]
Barthel Index of ADL	20 ± 0.0	19.96 ± 0.21	19.71 ± 0.83	0.035
Neuropsychological test				
Digit span forward	7.03 ± 0.97	7.04 ± 1.21	5.91 ± 1.2	<0.001[†,‡]
K-BNT	11.88 ± 1.98	10.89 ± 2.08	7.34 ± 2.83	<0.001[†,‡]
RCFT copy	33.12 ± 3.34	30.87 ± 5.83	22.13 ± 10.56	<0.001[†,‡]
SVLT delayed recall	6.65 ± 1.89	2.91 ± 2.48	0.8 ± 1.39	<0.001[*,†,‡]
RCFT delayed recall	17.47 ± 6.68	9.17 ± 6.42	2.77 ± 3.39	<0.001[*,†,‡]
COWAT (phonemic)	26 ± 10.17	20.8 ± 10.38	10.5 ± 7.18	<0.001[†,‡]
Stroop test	90.79 ± 18.62	78.13 ± 24.6	35.43 ± 20.43	<0.001[†,‡]

Values represent mean ± SD or number (percentage). p values were calculated by Kruskal–Wallis with Steel–Dwass post hoc tests for continuous variables and χ^2 (or Fisher's exact) tests for categorical variables

SCI subjective cognitive impairment, *aMCI* amnestic mild cognitive impairment, *AD* Alzheimer's disease, *GDS* Geriatric Depression Scale, *K-MMSE* Korean version of mini-mental state examination, *K-IADL* Korean Instrumental Activities of Daily Living, K-BNT Korean version of the Boston Naming Test, *RCFT* Rey Complex Figure Test, *SVLT* Seoul Verbal Learning Test, *COWAT* Controlled Oral Word Association Test

$p < 0.05$ by post hoc test: [*] SCI vs. aMCI, [†] SCI vs. mild AD, [‡] aMCI vs. mild AD

[a] Fisher's exact test

Table 2 PRMQ results for SCI, aMCI, and mild AD

	SCI ($n = 34$)	aMCI ($n = 46$)	AD ($n = 35$)	p value[a]
PRMQ total	35.09 ± 10.11	39.11 ± 11.04	38 ± 12.88	0.086
PRMQ-PM	18.85 ± 5.7	19.5 ± 5.66	18.86 ± 7.2	0.192
PRMQ-RM	16.21 ± 4.82	19.54 ± 6.02	19.14 ± 6.13	0.013[*†]
Informant-rated	SCI ($n = 17$)[b]	aMCI ($n = 43$)	AD ($n = 33$)	p value[c]
PRMQ total	27.41 ± 8.86	30.86 ± 10.73	42.45 ± 14.19	<0.001
PRMQ-PM	14.47 ± 5.08	15.86 ± 5.29	20.79 ± 6.82	0.002
PRMQ-RM	12.94 ± 4.22	14.98 ± 5.86	21.64 ± 7.86	<0.001

Values represent mean ± SD. PRMQ total and PRMQ-PM scores were log-transformed

SCI subjective cognitive impairment, *aMCI* amnestic mild cognitive impairment, *AD* Alzheimer's disease, *PRMQ* Prospective and Retrospective Memory Questionnaire, *PM* prospective memory, *RM* retrospective memory

$p < 0.05$ by Tukey HSD post hoc test: [*] SCI vs. aMCI, [†] SCI vs. mild AD

[a] Analysis of covariance, adjusting for age, hypertension status, and K-MMSE z score

[b] Informant-rated PRMQ results are shown for SCI participants with available informants

[c] Mann-Whitney U test between aMCI and AD

Table 3 Correlations between memory complaints and cognitive performance

Cognitive test[a]	Entire group			SCI and aMCI groups		
	PRMQ			PRMQ		
	Total[b]	PM[b]	RM	Total	PM	RM
K-MMSE	0.078	0.189*	−0.046	0.038	0.148	−0.059
Digit span forward	0.111	0.131	0.059	0.087	0.127	0.018
K-BNT	0.042	0.112	−0.029	0.020	0.054	−0.008
RCFT copy	−0.004	0.037	−0.070	0.022	0.049	−0.021
SVLT delayed recall	−0.056	0.080	−0.189*	−0.121	0.008	−0.230*
RCFT delayed recall	−0.054	0.048	−0.157	−0.123	−0.041	−0.199
COWAT (phonemic)	0.019	0.090	−0.072	−0.036	0.015	−0.105
Stroop test	−0.056	0.026	−0.140	−0.209	−0.140	−0.259*

Values are Spearman correlation coefficients (ρ)

SCI subjective cognitive impairment, *aMCI* amnestic mild cognitive impairment, *PRMQ* Prospective and Retrospective Memory Questionnaire, *PM* prospective memory, *RM* retrospective memory, *K-MMSE* Korean version of Mini-Mental State Examination, *K-BNT* Korean version of the Boston Naming Test, *RCFT* Rey Complex Figure Test, *SVLT* Seoul Verbal Learning Test, *COWAT* Controlled Oral Word Association Test

[a] Each score is an age- and education-adjusted z score

[b] Log-transformed PRMQ total and PRMQ-PM scores

* $p < 0.05$

than their informants ($t = 3.23$, $p = 0.003$), but AD subjects had higher informant-rated than self-reported memory complaints ($t = -2.04$, $p = 0.0499$). In addition, AD subjects had higher informant-rated PRMQ total ($p < 0.001$), PRMQ-PM ($p = 0.002$), and PRMQ-RM ($p < 0.001$) scores than those with aMCI (Table 2). When we investigated additional ANCOVA analyses using log-transformed PRMQ total scores, the results remained marginally significant after adjusting for age, hypertension status, and K-MMSE z score ($t = 9.78$, $p = 0.05$). In addition, informant-rated PRMQ data for SCI were available from 17 subjects with SCI. The results are included in Table 2. Regarding informant-rated PRMQ results among three groups, there were group differences on each informant-rated PRMQ score ($p < 0.001$ for each PRMQ score with Kruskal–Wallis tests). Post hoc analyses (nonparametric Steel–Dwass method) showed that AD subjects were higher informant-rated PRMQ scores than SCI and aMCI subjects ($p < 0.001$ for PRMQ total and PRMQ-RM scores; $p < 0.01$ for PRMQ-PM score), and aMCI and SCI subjects had similar scores.

Correlations between memory complaints and cognitive performance

The association between memory complaints and cognitive test performance was computed across all of the groups. PRMQ total score was not correlated with K-MMSE score or any cognitive test score. However, PRMQ-PM and -RM scores correlated with K-MMSE ($p = 0.043$) and SVLT delayed recall ($p = 0.044$), respectively. When only SCI and aMCI subjects were analyzed, PRMQ-RM correlated with SVLT delayed recall ($p = 0.04$) and Stroop Test ($p = 0.02$) (Table 3).

Discussion

In the present study, different aspects of SMCs (PM and RM complaints) were compared across individuals with SCI, aMCI, and mild AD. As shown in Table 2, PM complaints were similar across groups. RM complaints were higher in aMCI than SCI, but showed no difference between aMCI and AD. These findings suggest that RM complaints of SMCs may be helpful in discriminating aMCI from SCI, but SMCs (both PM and RM complaints) are of limited value in differentiating AD from aMCI.

Regarding SMCs in MCI and SCI, our finding of more RM complaints in aMCI than SCI supports prior research showing more SMCs in MCI than controls [27]. However, other studies show no difference in SMCs between MCI and healthy controls or subjects with SMCs [28, 29]. These discrepant findings could be due to differences in methods of assessing SMCs and in study populations. With respect to SMCs in MCI and AD, present results show no difference of SMCs between aMCI and AD, consistent with prior reports [27, 29]. Lack of awareness of declining memory problems in AD could lead to decreased SMCs in this group. Figure 1 shows means of PM versus RM complaints across group. Notably, individuals with SCI report more PM complaints than RM complaints. This could be explained by greater awareness of PM failures because PM

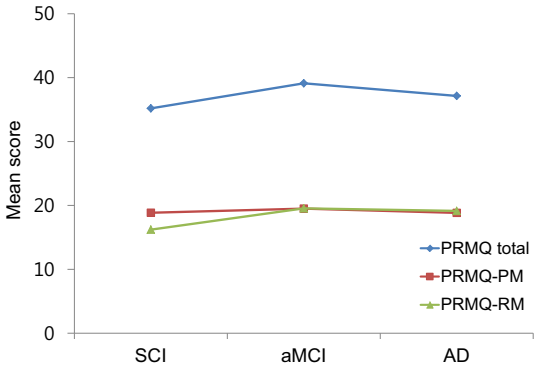

Fig. 1 Mean PRMQ scores in SCI, aMCI, and mild AD. PM complaints are similar across group. RM complaints are higher in aMCI than SCI, but no difference between aMCI and mild AD. *SCI* subjective cognitive impairment, *aMCI* amnestic mild cognitive impairment, *AD* Alzheimer's disease, *PRMQ* Prospective and Retrospective Memory Questionnaire, *PM* prospective memory, *RM* retrospective memory

tasks involve more self-initiated (executive) processing, making them more sensitive to evaluation [30]. On the other hand, individuals with aMCI show more RM complaints than those with SCI, while there being no differences of PM complaints. These findings suggest that PM complaints may be a cardinal feature of SMCs in SCI and RM complaints may serve as a clinical indicator of MCI among older adults with SMCs. Figure 1 also shows that both PM and RM complaints are of limited value in differentiating aMCI from AD. However, informants reported more memory complaints for individuals with AD than aMCI (Table 2), and this results remained marginally significant ($p = 0.05$) after adjusting for age, hypertension status, and K-MMSE z score. These findings align with other studies [29, 31, 32], suggesting the importance of incorporating an informant in studies of AD and other diseases with anosognosia.

In regard to cognitive measures, PRMQ-RM score was related to SVLT delayed recall (Table 3). Prior research has generally demonstrated little consistent results concerning cognitive correlates of SMCs [27, 29, 33]. Therefore, these issues remains to be elucidated in future studies with a larger sample.

This was a small, cross-sectional, retrospective study of participants enrolled from a Memory Disorders Clinic. This sample, therefore, is not representative of the general population. Furthermore, MCI is a heterogeneous group, so we included subjects with aMCI to be considered as a prodromal phase of AD. However, our MCI group was not validated by cerebrospinal fluid or amyloid Positron Emission Tomography biomarker of AD-type pathology. Therefore, MCI subjects with other conditions could be included in this study. Larger, longitudinal, prospective studies with biomarker study will be important to replicate these results and determine their long-term clinical significance.

Conclusions

Taken together, our results suggest that RM complaints of SMCs specifically can help to discriminate SCI and aMCI, but both PM and RM complaints are of limited value in discriminating aMCI from AD. These findings underscore the importance of clinical evaluation of memory complaints in older adults.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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