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Differences in quantitative methods for measuring subjective cognitive decline – results from a prospective memory clinic study

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ABSTRACT

Background: Cognitive complaints occur frequently in elderly people and may be a risk factor for dementia and cognitive decline. Results from studies on subjective cognitive decline are difficult to compare due to variability in assessment methods, and little is known about how different methods influence reports of cognitive decline.

Methods: The Subjective Memory Complaints Scale (SMC) and The Memory Complaint Questionnaire (MAC-Q) were applied in 121 mixed memory clinic patients with mild cognitive symptoms (mean MMSE = 26.8, SD 2.7). The scales were applied independently and raters were blinded to results from the other scale. Scales were not used for diagnostic classification. Cognitive performances and depressive symptoms were also rated. We studied the association between the two measures and investigated the scales' relation to depressive symptoms, age, and cognitive status.

Results: SMC and MAC-Q were significantly associated ($r = 0.44$, $N = 121$, $p = 0.015$) and both scales had a wide range of scores. In this mixed cohort of patients, younger age was associated with higher SMC scores. There were no significant correlations between cognitive test performances and scales measuring subjective decline. Depression scores were significantly correlated to both scales measuring subjective decline. Linear regression models showed that age did not have a significant contribution to the variance in subjective memory beyond that of depressive symptoms.

Conclusions: Measures for subjective cognitive decline are not interchangeable when used in memory clinics and the application of different scales in previous studies is an important factor as to why studies show variability in the association between subjective cognitive decline and background data and/or clinical results. Careful consideration should be taken as to which questions are relevant and have validity when operationalizing subjective cognitive decline.

Key words: subjective cognitive decline, subjective memory complaints, assessment, dementia, mild cognitive impairment

Introduction

Subjective cognitive decline is defined as perceptions of cognitive decline but with no objective signs of cognitive impairment. Cognitive complaints such as recalling recent events or names of people occur frequently in elderly people and have attracted interest as a risk factor for dementia and cognitive decline. Studies with long follow-up intervals (more than three years) have indicated that reports of cognitive decline may be an important risk factor for future dementia or cognitive decline (Reid and Maclullich, 2006). Recently, the working group of the Subjective Cognitive Decline Initiative has published research criteria for subjective cognitive decline in mild cognitive impairment (MCI)/preclinical Alzheimer's disease (AD) (Jessen *et al.*, 2014) and subjective cognitive impairment may be an important marker for AD because subjective cognitive decline is correlated with AD biomarkers such as gray matter volume loss (Saykin *et al.*, 2006), cerebral hypometabolism (Scheef *et al.*, 2012), cerebrospinal fluid markers (Visser *et al.*, 2009) and amyloid accumulation (Perrotin *et al.*, 2012).

Systematic interview on subjective cognitive complaints may contribute to the diagnostic evaluation of patients referred to a memory clinic (Salem *et al.*, 2015). However, findings between

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subjective cognitive complaints and cognitive functioning in memory clinic settings are conflicting (Jonker *et al.*, 1996; Vestberg *et al.*, 2007). Some studies suggest that subjective cognitive complaints are related to cognitive performance (Lam *et al.*, 2005; Jessen *et al.*, 2007). Others have not found such a relationship (Reid and Maclullich, 2006). This may be explained by different methodological approaches in relation to clarifying the complaints by a single question or a scale (Abdulrab and Heun, 2008) and whether the complaints are solicited or volunteered. Some studies used a dichotomous variable approach (and group differences were assessed), whereas a continuous variable was used in other studies (and correlations were investigated). The types of questionnaires used to measure subjective decline are different. Some measure memory, others measure subjective cognition in general. Importantly, reports of cognitive impairment may be related to factors other than cognitive impairment including affective symptoms, certain personality traits and a high level of physical morbidity (Jonker *et al.*, 2000; Jessen *et al.*, 2007; Elfgren *et al.*, 2010; Montejo *et al.*, 2011; Singh-Manoux *et al.*, 2014).

The aim of this study was to investigate the association between two scales for subjective cognitive decline in a mixed memory clinic population. Further, we aimed to investigate the association between age, cognitive impairment, and depressive symptoms on each of the scales for subjective cognitive impairment.

Methods

Patients

Patients were recruited from the Copenhagen University Hospital Memory Clinic at Rigshospitalet, which is a combined secondary and tertiary outpatient clinic based in a neurology setting. The clinic offers diagnostic evaluation and treatment of cognitive disorders and dementia, and receives primary, secondary, and tertiary referrals from general practitioners, private consultants in neurology and psychiatry and other hospitals. Patients with rare (such as genetic disorders) or uncertain etiology are referred from other Danish regions. All patients underwent the following investigations: Detailed medical history was obtained; cognitive functions were assessed with the Mini-Mental State Examination (MMSE) and the Danish version of Addenbrooke's Cognitive Examination (ACE) (Stokholm *et al.*, 2009). Physical and neurological examination, routine laboratory tests, and ECG were performed. Structural CT or MRI of the brain was also performed. Other supplemental tests were performed if clinically relevant (fludeoxyglucose positron emission tomography (^{18}FDG-PET), examination of cerebrospinal fluid, electroencephalography, psychiatric evaluation, neuropsychological assessment). After completion of the initial study program, the multidisciplinary staff established a standardized consensus report for each patient. The consensus report contained a classification of the cognitive profile, the primary underlying cause, and concomitant conditions.

The patients included in this study came from study on subjective cognitive complaints in 307 patients from a mixed memory clinic (Salem *et al.*, 2015*)*. Inclusion criteria were as follows: (1) referral to the Copenhagen Memory Clinic for diagnostic evaluation of cognitive or behavioral symptoms; (2) a diagnostic conclusion was available; (3) the patient was native Danish speaking; (4) assessment of depressive symptoms with the Major Depression Inventory (MDI) (Bech *et al.*, 2001). (In some patients — exact number not known — MDI was not administered due to time constraints); (5) MMSE score above 12.

Procedures

At the first visit in the clinic, the SMC (Schmand *et al.*, 1996) was applied by a specialist nurse (in interview-format) at the beginning of the interview with the patient. The SMC includes ten items concerning difficulties in daily-life memory tasks, with total scores (*SMC total*) ranging from 0 (no complaints) to 21, see Table 1. The SMC scale measures memory as well as non-amnestic complaints and was originally designed to investigate subjective cognitive complaints in a population-based study on cognitive decline and dementia. The specialists who later examined the patients were blinded to the results of the SMC scale and the SMC results were not used for diagnostic classification.

The MAC-Q (Crook, III *et al.*, 1992) is a short memory scale consisting of six items where the participant answers questions comparing the current memory functioning as compared to when they were young (in this study they were asked to compare to when they were 20 years old). The items are shown in Table 2. Each item is rated on a 5-point Likert scale from "*much better now*" to "*much worse now.*" Scores are summed (MAC-Q total), with double weighting for the final item (a comparison of general memory abilities). The score range is 7–35; higher scores indicate greater self-reported decline. This scale was originally developed to assess age-related memory decline and validated in persons meeting diagnostic criteria for age-associated memory impairment.

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Table 1. Items of the subjective memory complaints scale (Schmand *et al.*, 1996)

	ITEM NUMBER	SCORE RANGE
1.	Do you have any complaints concerning your memory?	0–3
2.	Do other people find you forgetful?	0–2
3.	Do you ever forget names of family members or friends?	0–3
4.	Do you often forget where things are left?	0–3
5.	Do you often use notes to avoid forgetting things?	0–2
6.	Do you ever have difficulties in finding particular words?	0–1
7.	Do you ever lose your way in your neighborhood?	0–1
8.	Do you think more slowly than you used to?	0–2
9.	Do your thoughts ever become confused?	0–2
10.	Do you have concentration problems?	0–2

Table 2. Items of the Memory Complaint Questionnaire (Crook, III *et al.*, 1992)

	MUCH BETTER NOW (1)	SOMEWHAT BETTER NOW (2)	ABOUT THE SAME (3)	SOMEWHAT POORER NOW (4)	MUCH POORER NOW (5)
1. Remembering the name of a person just introduced to you					
2. Recalling telephone numbers or zip codes that you use on a daily or weekly basis					
3. Recalling where you have put objects (such as keys) in your home or office					
4. Remembering specific facts from a newspaper or magazine article that you have just finished reading					
5. Remembering the item(s) you intended to buy when you arrive at the grocery store or pharmacy					
6. In general, how would you describe your memory as compared to when you were in high school?	(2)	(4)	(6)	(8)	(10)

The MAC-Q was administered to all patients who were examined by a neuropsychologist. The MAC-Q was applied at the neuropsychological examination (typically two weeks after the first visit) before any tests had been administered. The neuropsychologist was blinded to the results from SMC. Neuropsychological assessment is usually done in all patients with MMSE score $\geq$ 22 on initial visit in the clinic, but patients with lower MMSE scores may be examined if relevant.

Assessment of depressive symptoms

Depression was assessed by the MDI which was applied at the initial visit to the clinic. The physician administering MDI was blinded to SMC results. The MDI consists of 12 items answered by choosing one of six response options from "At no time" (=0) to "All the time" (=5). When using the MDI as a depression rating scale 10 of the 12 items are used for the total score. Only the highest score on the items 8a and 8b and items 10a and 10b is included. Subsequently, a sum score is formed ranging from 0 to 50. Scores on this scale could lead to the following classification of depression: "no depression" (score of 0–19), "mild depression" (score of 20–24), "moderate depression" (score of 25–29), and "severe depression" (score of 30–50) (Bech *et al.*, 2001). A diagnosis of depression was based on clinical evaluation and fulfillment of international criteria for depression and not solely based on MDI score. However, the MDI score (as opposed to results from measures on subjective cognitive decline) was included as part of the diagnostic process.

A total of 121 patients were included in the study (full data set for the subjective cognitive scales), and these were classified in four diagnostic categories

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to investigate if some of these were driving the associations in the total group:

1. Dementia

Patients in this group had significant impairment in instrumental activities of daily living (IADL) and significant impairment in at least two cognitive domains. For the specific dementia diseases, international consensus criteria were used, with the most common being dementia due to AD (McKhann *et al.*, 2011), vascular dementia (Roman *et al.*, 1993), dementia with Lewy bodies (McKeith *et al.*, 2005), dementia in Parkinson's disease (Emre *et al.*, 2007), and frontotemporal dementia (McKhann *et al.*, 2001).

2. MCI, amnestic, or non-amnestic

MCI patients met the criteria described by Petersen (2004). Patients (or informants) described cognitive decline, but patients did not meet the criteria for dementia and had essentially normal functional activities. Amnestic MCI was defined when the patient's memory domain score was below −1.5 SD, whereas performances in other cognitive domains were above −1.5 SD. Non-amnestic MCI was defined as an impairment in one cognitive other than memory (defined as domain scores below −1.5 SD).

3. Affective disorders

Patients in this group had diseases in the affective spectrum (mild/moderate depression, bipolar affective disorder, reaction to severe stress, adjustment disorder, or anxiety disorder). All patients were diagnosed according to ICD-10 criteria, many by a specialist in psychiatry.

4. No cognitive impairment

Patients in this group had no significant cognitive impairment on either cognitive screening tests or neuropsychological examination, and there were no other investigations indicating possible cognitive disorders. Some of these patients were healthy worriers while others could have other neurological disease. None of these patients had affective disorders.

Ethics

The research project was approved by the Danish Data Protection Agency and the National Board of Health (j.nr. 2007-58-0015). Approval of the study was not required by the Ethical Committee of Copenhagen County (j.nr. 2011–296).

Statistical analysis

The level of significance in group by group comparisons was investigated with independent sample *t*-test for quantitative variables with normal distribution. One way analysis of variance (ANOVA) with *post hoc* Bonferroni corrected group comparisons was used to investigate the significance of differences between the diagnostic groups. Associations between variables were investigated using Pearson product-moment correlations. Lastly, two stepwise linear regression analyses were used with MAC-Q total and SMC total as dependent variables. Age and scores on MDI, MMSE, and ACE were independent variables. Plots of residuals were used as model control. The level of significance was set at $p \leq 0.05$.

Results

Background data and diagnostic classification

Background data and results from clinical variables are shown in Table 3. The mean MMSE was 26.8 (SD = 2.7); 22.3% scored below 25 and 58.7% had scores of 27 or above. A wide range of scores was also found for MDI (see Table 3). In this mixed memory clinic cohort, 55 patients met the criteria for dementia, the criteria for MCI were met in 25 patients, 30 had affective disorders, and 11 were classified in the group without cognitive impairment. The frequencies of underlying diseases in the dementia group were: 31 AD, 12 vascular dementia, 8 unspecified dementia, 2 frontotemporal dementia, 1 dementia with Lewy bodies, 1 normal pressure hydrocephalus. The patients with affective disorders were significantly younger ($M = 59.8$, SD = 11.4) than patients with MCI or dementia ($M = 72.7$, SD = 8.9).

SMC and MAC-Q results and correlations with clinical variables

Both SMC total and MAC-Q total are shown for all patients in Table 3. The overall correlation between SMC total and MAC-Q total was statistically significant but moderate ($r = 0.44$, $N = 121$, $p = 0.015$). In general, wide distributions of results were found for both scales tapping subjective cognitive decline in this mixed memory clinic population. There were no significant group differences for gender for SMC total (t (119) = 0.48, $p = 0.63$) or MAC-Q total (t (119) = −0.61, $p = 0.54$).

The correlations between results from the measures on subjective cognitive impairment and age, MDI scores, MMSE scores, and ACE scores are shown in Table 4. Based on the results from all 121 patients, there were no significant correlations between cognitive test performances (MMSE/ACE) and subjective cognitive scales. There was a significant effect of age on SMC total, but age and MAC-Q total were not significantly correlated. Thus, SMC total decreases with age

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Table 3. Background data and test results. Results are presented as mean (SD), unless stated otherwise

	MEMORY CLINIC PATIENTS N= 121
Age (years)	69.0 (11.1) Range 39–92
Sex	60 % female 40% male
Mini-Mental State Examination (MMSE) score	26.8 (2.7) Range 19–30
Addenbrooke's cognitive examination (ACE) score	80.3 (11.6) Range 51–100
Major depression inventory (MDI) score	11.3 (9.0) Range 0–37
Subjective memory complaints scale (SMC) score	9.2 (4.0) Range 0–20
Memory complaint questionnaire (MAC-Q) score	28.0 (4.1) Range 18–35

Table 4. Pearson product moment correlations coefficients between subjective memory results and clinical variables

	SUBJECTIVE MEMORY COMPLAINTS SCALE (SMC) SCORE N=121	MEMORY COMPLAINT QUESTIONNAIRE (MAC-Q) SCORE N=121
Age	− 0.24*	− 0.08
Major depression inventory (MDI) score	0.39**	0.22*
Mini-Mental State Examination (MMSE) score	0.10	0.13
Addenbrooke's cognitive examination (ACE) score	− 0.01	0.06

*Significant correlation ($p < 0.05$).
**Significant correlation ($p < 0.005$).

in a mixed memory clinic population. MDI scores were significantly correlated to both SMC total and MAC-Q total, demonstrating that subjective memory problems increase with an increase in depressive symptoms.

To assess which clinical variables (age, MDI scores, MMSE score, ACE score) had the highest association with the two scales measuring subjective cognitive decline, stepwise linear regression models were used. MDI had a significant impact on the variance in SMC total [$r^2 = 0.15$, F (1,117) = 20.9, $p < 0.001$] and on the variance in MAC-Q [$r^2 = 0.05$, F (1,117) = 5.8, $p = 0.02$]. Other variables (age, MMSE score and ACE score) did not have an additional significant contribution on the variance in the subjective memory measures to that of MDI. Thus, depressive symptoms had the highest association with degree of subjective complaints.

Association between subjective cognitive decline and clinical variables in diagnostic subgroups

In the subgroup of patients categorized with dementia ($N = 55$) there was a significant correlation between SMC total and MAC-Q total ($r = 0.29$, $p = 0.03$) but none of the scales were significantly correlated to age, MDI score, or cognitive performances (MMSE/ACE) in this subgroup of patients (data not shown). For MCI patients ($N = 25$), the same pattern was found: an overall correlation of $r = 0.36$ between the two subjective memory scales, but probably due to the smaller number of patients this result did not reach statistical significance ($p = 0.07$). The scales were not significantly correlated to age, MDI score, or cognitive performances (MMSE and ACE) (data not shown) in this subgroup of patients. For patients with affective disorders, a significant correlation was found between the two scales measuring cognitive decline ($r = 0.36$, $p = 0.049$), and none of these scales were significantly correlated to age or cognitive test results (data not shown). For the patients with affective disorders ($N = 30$), a significant correlation was found between SMC total and MDI score ($r = 0.37$, $p = 0.04$), whereas MDI scores and MAC-Q total were not significantly correlated ($r = 0.21$, $p = 0.26$). For the small group of patients categorized with no cognitive impairment ($N = 11$), a significant correlation was found between MAC-Q total and age ($r = 0.62$, $p = 0.04$) but not between age and SMC total ($r = 0.37$, $p = 0.27$). In this subgroup, the two scales measuring subjective decline were not significantly correlated, and none of the scales were

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significantly correlated to MDI scores or cognitive test results.

Discussion

This study investigated whether different methodological approaches may affect the measurement of subjective cognitive decline in a mixed memory clinic population. Two commonly used scales for measuring subjective cognitive impairment were only moderately correlated in this patient group and age had different impact on the level of subjective cognitive decline depending on the selected scale for assessment. Thus, different scales measuring subjective complaints are not interchangeable when used in memory clinic cohorts.

The degree of depressive symptoms was the factor in this study which contributed the most to the variance in subjective cognitive decline, and age and cognitive status did not have additional association with results from subjective memory scales, when depressive symptoms were accounted for. A strong relation between subjective cognitive complaints and depressive symptoms has been established in several studies (Abdulrab and Heun, 2008; Lehrner et al., 2013) and a significant correlation between younger age and depressive symptoms in memory clinic patients has previously been found (Knapskog et al., 2014). Previously, we have shown that in patients referred to our memory clinic young patients with an affective disorder had the highest level of subjective cognitive complaints (Salem *et al.*, 2015).

Overall, a wide range of scores was found on both SMC and MAC-Q and results from both scales were not associated with the degree of cognitive impairment on testing. This implies that in a mixed memory clinic cohort, the intensity of cognitive complaints by itself is not helpful information in reaching a diagnosis. An important finding from a previous study investigating different approaches to assessing subjective cognitive decline is that results from questionnaires with fixed questions were not associated with performances on memory tests but that an open-ended questions approach may be predictive of actual impairment (Mattos *et al.*, 2003). In a recent population-based study, it was found that participants reported more cognitive complaints when filling out questionnaires relative to spontaneous reports and that structured assessments may overlook some subjective complaints that people find even more distressing than items typically assessed by questionnaires (Burmester *et al.*, 2015). From these studies it seems that questionnaires are relevant to use when merely investigating the presence of subjective cognitive impairment but that spontaneous reports may be more relevant when examining which complaints have the highest impact on daily functioning (Apolinario *et al.*, 2013).

In this mixed memory clinic cohort lower age was significantly associated to higher subjective scores as opposed to findings from population-based studies where subjective symptoms increase with age (Bassett and Folstein, 1993; Montejo *et al.*, 2011). Two factors seem important here. The first is the inclusion of younger patients with depression (which was the group of patients with most complaints may explain this result). Second, the reliability of self-reported memory problems in patients with dementia is questionable, because some patients have impaired insight of memory problems, and this may affect ratings of subjective memory problems (Salem *et al.*, 2015).

Subgroup analysis showed that the significant correlation between MDI and SMC could only be found in patients with affective disorders but not in patients with MCI or dementia. Patients with affective disorders were much younger than patient with MCI or dementia, and the MAC-Q may be more "age-resistant" because it requires the patients to compare their memory to a time when they were young (20 years). This may not change significantly with age for patients over 60 years (the majority of included patients were older than 60 years). Further, the items in MAC-Q only taps memory related issues, whereas a broader spectrum of cognitive complaints are examined with the SMC (including concentration problems, slow thinking, prospective memory), which are cognitive deficits more commonly found and reported in depression. Thus, the subsample with affective symptoms and the highest degree of complaints may have a particular effect on SMC results because this scale may be more sensitive to cognitive complaints in depression (Glodzik-Sobanska *et al.*, 2007). Further, when comparing the nature of the scales the MAC-Q appears more "situation based" and specific whereas the SMC asks about "concentration problems" in general and invokes more individual understanding and application of this concept.

Comparison of different scales is difficult because if applied directly after one another, the patient may be biased when answering the scale administered last. The timing between the administration of the two scales is an important limitation in this study, since the time gap may have affected the patients' answers (and thereby the reliability). Another key limitation to this study is that different interviewers administered the scales (in interview format), and the inter-rater reliability of the scales is not known.

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Also the study could have profited from inclusion of measures for lack of insight and also from other types of measures for subjective cognitive decline (e.g. spontaneous reports).

Relating to some issues, results from scales measuring subjective cognitive impairment are comparable, but the results from this study to some degree raise more questions than they provide answers. The major issue raised by this study is whether it will be possible to identify specific subjective perceptions of cognitive change that will have a high diagnostic validity in the assessment of AD and (also potentially) other neurodegenerative dementia diseases. An important issue will therefore be to refine which questions to ask when assessing subjective cognitive decline and to investigate to what degree information from caregivers could be helpful. Careful consideration to these issues should be taken when operationalizing subjective cognitive decline in clinical practice and research e.g. as in the recently published research criteria for subjective cognitive decline in MCI/preclinical AD (the working group of the Subjective Cognitive Decline Initiative) (Jessen *et al.*, 2014) and in the criteria for Subjective Cognitive Impairment (Reisberg and Gauthier, 2008; Reisberg *et al.*, 2008).

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Description of authors' roles

AV was responsible for conceptualization, design, data analysis, and writing the paper. LCS and BBA were responsible for the implementation of the SMC scale in the diagnostic workup and gave valuable suggestions that helped in conceptualizing the paper. GW contributed to the study design and reviewed the paper. All authors have read and approved the manuscript.

Conflict of interest

None.

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