Patterns of subjective memory impairment in the elderly: association with memory performance

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ABSTRACT

Background. The association of subjective memory impairment (SMI) with cognitive performance in healthy elderly subjects is poor because of confounds such as depression. However, SMI is also a predictor for future dementia. Thus, there is a need to identify subtypes of SMI that are particularly related to inferior memory performance and may represent at-risk stages for cognitive decline.

Method. A total of 2389 unimpaired subjects were recruited from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe), as part of the German Competence Network on Dementia. Clusters of SMI according to patterns of response to SMI questions were identified. Gender, age, depressive symptoms, apolipoprotein E (apoE) genotype, delayed recall and verbal fluency were included in a Classification and Regression Tree (CART) analysis to identify discriminators between the clusters.

Results. We identified three clusters. Cluster 1 contained subjects without memory complaints. Cluster 2 contained subjects with general memory complaints, but mainly without memory complaints on individual tasks of daily living. Cluster 3 contained subjects with general memory complaints and complaints on individual tasks of daily living. Depressive symptoms, as the first-level discriminator, distinguished between clusters 1 and 2 versus cluster 3. In subjects with only a few depressive symptoms, delayed recall discriminated between cluster 1 versus clusters 2 and 3.

Conclusions. In SMI subjects with only a minor number of depressive symptoms, memory complaints are associated with delayed recall. As delayed recall is a sensitive predictor for future cognitive decline, SMI may be the first manifestation of future dementia in elderly subjects without depression.

INTRODUCTION

Subjective memory impairment (SMI), defined by memory complaints with normal age-, gender- and education-adjusted cognitive performance, is a frequent phenomenon in elderly people.

Many cross-sectional studies have attributed SMI to depression (O’Connor et al. 1990; Ponds et al. 1997; Riedel-Heller et al. 1999; Jorm et al. 2004a; Jungwirth et al. 2004), personality traits (Hanninen et al. 1994; Ponds et al. 1997; Jorm et al. 2004a) and physical morbidity (Jorm et al. 2004a), while the association with memory test performance in these studies has been mostly poor.
The majority of longitudinal studies, however, have identified SMI as a predictor for future cognitive decline (Jonker et al. 2000; Reid & MacLullich, 2006). Based on these longitudinal data, a recent consensus conference concluded that SMI precedes cognitive deterioration to mild cognitive impairment (MCI) and dementia by up to 15 years (Gauthier et al. 2006).

Post-mortem studies have identified Alzheimer’s disease (AD)-related pathology in non-demented subjects with cognitive impairment (Riley et al. 2002; Markesbery et al. 2006) and in subjects with memory complaints, including mildly impaired individuals (Jorm et al. 2004b; Barnes et al. 2006). In a recent study, very mild cognitive dysfunction in subjects who still performed within the age-adjusted normal range on neuropsychological tests, and were not rated as impaired, has also been associated with AD pathology (Bennett et al. 2006). It may be speculated that this minor subthreshold cognitive dysfunction is related to subjective memory impairment at least in subjects who are sensitive to changes in their own cognitive ability. In this case, subjects with SMI should perform slightly worse on memory tests compared with non-complaining elderly individuals.

One reason for the failure to find an association between SMI and cognitive performance in many cross-sectional studies might be insufficient statistical power. The sample size needs to be large for two reasons: (1) the variation in cognitive performance is small and the group difference between complainers and non-complainers is minor, if the analysis is restricted to cognitively healthy subjects, and (2) confounding factors such as depression have a great impact. Accordingly, large studies with sufficient power observed an association of SMI with cognitive performance, independent of depression (e.g. Gagnon et al. 1994; Jonker et al. 1996).

A second reason for the frequent lack of association between SMI and cognitive performance might be variation in definition and broad assessment of memory complaints. Different profiles of complaints may be differentially associated with either memory performance or other factors such as depression. These complex patterns are frequently not investigated and might not be identifiable by standard statistical approaches, such as logistic regression models.

In the present report, we aimed to address the issues that might prevent the identification of memory impairment in SMI. To achieve an adequate statistical power, the study was performed in a large sample of 2389 cognitively unimpaired subjects above 75 years of age, recruited from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe), which is part of the German Competence Network on Dementia. The AgeCoDe study is a general practice-based longitudinal project on risk factors for cognitive decline in the elderly.

To identify those SMI subgroups that show inferior memory performance, we first applied a cluster analysis based on a set of questions on self-perception of memory. Second, we used a Classification and Regression Tree (CART) analysis (Breiman et al. 1984) to identify variables that differentiate between these clusters. The CART analysis is capable of detecting complex interactions of variables that might be missed by standard statistical approaches. As independent variables, we included gender, age, number of depressive symptoms, apolipoprotein E (apoE) genotype, verbal delayed recall and verbal fluency. Delayed verbal recall indicates medial temporal lobe (MTL) function and is the most sensitive neuropsychological indicator for future cognitive decline (Bäckman et al. 2001), while verbal fluency is an indicator of executive frontal brain function (Alvarez & Emory, 2006).

We tested the hypotheses that different clusters of SMI can be identified and aimed at identifying the respective discriminators.

METHOD
Study population
The cohort consisted of subjects participating in the AgeCoDe study. The participants were recruited at six centres by 19–29 general practitioners (GPs) per site (138 in total). Inclusion criteria for potentially eligible patients were 75–89 years of age, absence of dementia according to the judgement of the GP, and at least one contact with the GP within the past 12 months. Exclusion criteria were consultations
only by home visits, severe illness, insufficient knowledge of German language, deafness or blindness, and lack of capability for informed consent. Of the eligible patients \(n=10,850\), 6,619 randomly selected patients were contacted by mail. Of these, 3,292 subjects either refused or did not respond to the letter, and 3,327 gave informed consent to the GP for participation. The participants were then contacted by the study centres for the assessment by a trained interviewer at the subjects’ homes. Eighty-five subjects were excluded after the interview because of the presence of dementia \(n=41\), age below 75 \(n=39\) or grossly incomplete data \(n=5\). A total of 3,242 subjects formed the database for the AgeCoDe study.

### Assessment of subjective memory impairment

In the initial phase of the interview, the following questions to assess subjective memory impairment were asked: ‘Do you feel like your memory is becoming worse?’ Possible answers were: ‘no’, ‘yes, but this does not worry me’ and ‘yes, this worries me’.

All subjects were additionally asked the following questions, which were derived from the Subjective Memory Decline Scale (Jorm et al. 2001): (1) ‘Do you have trouble remembering things that have happened to you recently?’, (2) ‘Are you worse at remembering where belongings are kept?’, (3) ‘Do you have trouble recalling conversations a few days later?’ and (4) ‘Do you have more trouble remembering appointments and social arrangements?’ The choices of answers were the following: (1) no, not much worse; (2) yes, a bit worse; (3) yes, a lot worse.

### Neuropsychological battery and clinical interview

Neuropsychological and clinical assessment was based on the Structured Interview for Diagnosis of Dementia of Alzheimer type, Multi-infarct dementia and dementia of other aetiology according to DSM-IV and ICD-10 (SIDAM; Zaudig & Hiller, 1996). The SIDAM contains (1) a neuropsychological test battery and (2) a 14-item scale for the assessment of activities of daily living (SIDAM-ADL-Scale). The cognitive battery covers 55 items (SIDAM cognitive score, SISCO) including the Mini-Mental State Examination (MMSE; Folstein et al. 1975). A SISCO below 34 indicates dementia (Zaudig, 1992). German age-, gender- and education-specific norms of the SISCO are available (Busse et al. 2002). In addition, the semantic verbal fluency test and the verbal memory test (10-item word list) of the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) were administered (Morris et al. 1989). The free delayed recall score was used in the present analysis.

Depressive symptoms were assessed with the 15-item version of the Geriatric Depression Scale (GDS; Yesavage et al. 1982). A score of \(\geq 6\) is indicative for clinically relevant depression. Scores below 6 indicate single sub-threshold depressive symptoms.

### Definition of the sample for the analysis

The present study focused on participants with unimpaired cognition. Therefore, MCI subjects were excluded from this analysis. MCI was defined according to the consensus criteria proposed by the International Working Group on Mild Cognitive Impairment (Winblad et al. 2004). The criteria include: (1) absence of dementia according to DSM-IV or ICD-10, (2) self- or informant-reported cognitive decline, (3) impairment on cognitive tasks, and (4) preserved ADL or only minimal impairment in complex instrumental functions.

These criteria were checked by the following procedures. Dementia according to DSM-IV was excluded with the SIDAM (see above). Subjective memory complaints were checked with the question: ‘Do you feel like your memory has become worse?’ (see above). Objective cognitive impairment was defined by the SISCO according to the German age-, gender- and education adjusted normative database (Busse et al. 2002, 2006). A score of 1 standard deviation (s.d.) below the mean was defined as impairment. ADL was assessed with the SIDAM-ADL-Scale, which includes 14 items. According to SIDAM criteria, a score of 2 or higher is considered to reflect ADL impairment (Zaudig & Hiller, 1996).

In addition, subjects without memory complaints who were cognitively impaired (e.g. scoring below 1.0 s.d. on the SISCO) were excluded.
Of the 3242 subjects in the AgeCoDe database, 818 were excluded according to the above procedure. Thirty-five participants had incomplete data regarding the SMI questions and were also excluded. Of the 2389 subjects who constituted the sample for the present analyses, 1529 (64%) were female and 860 (36%) were male. The mean age was 80·1 years (s.d. = 3.52). apoE genotyping was performed according to standard procedures (Hixson & Vernier, 1990). For 90 subjects, either DNA was not available or the apoE genotype could not be determined. Of the remaining subjects, 14 (0·6%) were homozygote apoE4 carriers, 456 (19·8%) were heterozygote apoE4 carriers and 1829 (79·6%) did not carry an apoE4 allele.

**Statistical analyses**

To find groups of participants with similar patterns of SMI, a cluster analysis using the method of Partitioning Around Medoids (PAM; Kaufman & Rousseeuw, 2005) with the adaptation for large datasets was performed. For a given number of groups, the algorithm computes the representative objects, called medoids, and then each object is assigned to the nearest medoid. The representative objects should minimize the sum of the dissimilarities of all objects to their nearest medoid. To determine the most appropriate number of groups, the resulting silhouette plots were compared. Compared to the well-known k-means algorithm, the method of PAM is more robust to outliers. For the cluster analysis, the SMI questions were grouped in the following manner: With regard to the first general question, subjects were either classified as ‘no’ or as ‘yes’, with ‘yes’ combining subjects with and without worries. The questions addressing specific areas of everyday memory were also grouped as ‘no’ or ‘yes’, with ‘yes’ including ‘a bit worse’ and ‘a lot worse’.

To identify factors that can discriminate between the identified clusters, a CART analysis with the cluster membership as response variable was performed. The CART method is based on recursive partitioning analysis (Breiman *et al*. 1984); the aim is to form prediction rules by constructing binary trees. Splitting rules are used as criteria to select the best split at each node, for example the Gini index of diversity as a measure of node impurity. A 10-fold cross-validation was used to accurately assess its goodness of fit. CART analysis has several advantages over traditional statistical methods, including logistic regression models. It is non-parametric; no assumptions are made regarding the underlying distribution of values of the discriminator with respect to predictor variables. It can handle numerical data that are highly skewed or multimodal and categorical predictors with either an ordinal or a non-ordinal structure. CART is often able to uncover complex interactions or patterns between predictors that may be difficult or impossible to uncover using traditional multivariate techniques. CART also produces trees that are relatively simple for non-statisticians to interpret.

To test for the presence of the apoE effect (i.e. healthy apoE4 carriers performing worse compared with non-carriers on memory tests), delayed recall and verbal fluency were compared between apoE4 carriers and non-carriers within each cluster by the Mann–Whitney U test.

For the cluster analysis, S-Plus version 7.0 was used. The CART analysis was performed with CART version 5.0 (Salford Systems, San Diego, CA, USA). For all other statistical tests, SPSS version 14.0 (SPSS Inc., Chicago, IL, USA) was used.

**RESULTS**

The cluster analysis identified three groups of subjects according to the pattern of memory complaints. Cluster 1 contained subjects who denied any memory problems in the general question and mostly in all other questions. Cluster 2 contained subjects who reported memory problems but mostly denied any impairment on the specific questions. Cluster 3 identified subjects with general memory complaints and frequent impairment in individual tasks. Table 1 lists the demographic data for subjects within each cluster. Tables 2 and 3 list the frequency of responses to the questions in each cluster, including the grading questions (worries/no worries; a bit impaired/a lot impaired).

The CART analysis with gender, age, site, apoE status, depression score, verbal fluency and delayed recall as independent predictors yielded a classification tree with four terminal nodes, as depicted in Fig. 1.
At the first level, the tree analysis identified a cut-off of 4 points on the GDS as the major discriminator. Clusters 1 and 2 were more likely to score below or equal to 4, while in cluster 3 a larger portion scored higher. At the second level, those scoring below or equal to 4 on the GDS were discriminated by a GDS score of 0. The portion of subjects with a GDS score of 0 was greatest in cluster 1 and smallest in cluster 3. At the third level, those scoring between 1 and 4 on the GDS were discriminated by a verbal delayed recall score of 4 (of 10) items. The portion of subjects recalling more than four words was greatest in cluster 1 and smallest in cluster 3.

These results indicate that the number of depressive symptoms is the most relevant factor to discriminate between memory complainers and non-complainers. In those with low depression scores, verbal delayed recall discriminates between memory complainers and non-complainers. Gender, age, education, site, apoE genotype and verbal fluency did not discriminate between the clusters.

Within each cluster, verbal fluency and delayed verbal recall were compared between apoE4 carriers and non-carriers. The only significant difference of all comparisons was observed for verbal delayed recall in cluster 2 (apoE4 carriers: mean 5·3, s.d. = 2·15; apoE4 non-carriers: mean 5·7, s.d. = 2·17; p = 0·008).

DISCUSSION

The aim of this study was to identify types of SMI that are related to memory performance. We identified three clusters of memory complaints. The first cluster contained subjects who did not complain about memory impairment, and the second cluster contained subjects who reported a general memory complaint but mainly did not report impairment on individual memory tasks. The third cluster contained subjects with a general memory complaint and with frequent subjective impairment on individual tasks of daily living.

The number of depressive symptoms was the major discriminator between complainers and non-complainers. A large number of depressive symptoms were particularly over-represented in SMI subjects, with several complaints in individual tasks of daily living. This finding is in agreement with many cross-sectional studies that reported depressive symptoms to be associated with memory complaints (O’Connor et al. 1990; Ponds et al. 1997; Riedel-Heller et al. 1999).

However, in subjects with only a minor number of depressive symptoms, verbal delayed recall discriminated between SMI subjects and non-complainers. These data are in agreement with large population-based studies (Gagnon et al. 1994; Jonker et al. 1996) showing that memory performance in SMI subjects is inferior compared with non-complainers after controlling for depression.

Verbal fluency did not discriminate between non-complainers and complainers, indicating that cognitive impairment in SMI subjects is not

Table 1. Demographics, apoE genotype, depressive symptoms and cognitive performance of the clusters

<table>
<thead>
<tr>
<th></th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td>333 (33·5)</td>
<td>402 (36·8)</td>
<td>176 (58·5)</td>
</tr>
<tr>
<td>Male</td>
<td>662 (66·5)</td>
<td>691 (63·2)</td>
<td>125 (41·5)</td>
</tr>
<tr>
<td>Female</td>
<td>79·91 (3·39)</td>
<td>80·13 (3·49)</td>
<td>80·86 (3·91)</td>
</tr>
<tr>
<td>Age, mean (s.d.)</td>
<td>1·73 (2·00)</td>
<td>2·16 (2·15)</td>
<td>3·31 (2·9)</td>
</tr>
<tr>
<td>apoE4 status, n (%)</td>
<td>186 (19·4)</td>
<td>207 (19·7)</td>
<td>63 (21·9)</td>
</tr>
<tr>
<td>No apoe4</td>
<td>5 (0·5)</td>
<td>6 (0·6)</td>
<td>3 (1·0)</td>
</tr>
<tr>
<td>Number of depressive symptoms, mean (s.d.)</td>
<td>5·97 (2·11)</td>
<td>5·61 (2·17)</td>
<td>5·24 (2·18)</td>
</tr>
<tr>
<td>GDS (max. = 15)</td>
<td>20·20 (5·15)</td>
<td>20·19 (5·22)</td>
<td>19·45 (5·29)</td>
</tr>
<tr>
<td>Cognition, mean (s.d.)</td>
<td>20·19 (5·22)</td>
<td>24 (21·4)</td>
<td>148 (49·2)</td>
</tr>
</tbody>
</table>

GDS, Geriatric Depression Scale (Yesavage et al. 1982).

Table 2. Distribution of general memory complaints within the three clusters of subjective memory impairment

<table>
<thead>
<tr>
<th></th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No complaints, n (%) of cluster</td>
<td>995 (100)</td>
<td>0</td>
<td>14 (4·7)</td>
</tr>
<tr>
<td>Complaints, n (%) of cluster</td>
<td>0</td>
<td>859 (78·6)</td>
<td>139 (46·2)</td>
</tr>
<tr>
<td>No worries</td>
<td>0</td>
<td>234 (21·4)</td>
<td>148 (49·2)</td>
</tr>
<tr>
<td>Worries</td>
<td>0</td>
<td>234 (21·4)</td>
<td>148 (49·2)</td>
</tr>
<tr>
<td>Total</td>
<td>995</td>
<td>1093</td>
<td>301</td>
</tr>
</tbody>
</table>

At the first level, the tree analysis identified a cut-off of 4 points on the GDS as the major discriminator. Clusters 1 and 2 were more likely to score below or equal to 4, while in cluster 3 a larger portion scored higher. At the second level, those scoring below or equal to 4 on the GDS were discriminated by a GDS score of 0. The portion of subjects with a GDS score of 0 was greatest in cluster 1 and smallest in cluster 3. At the third level, those scoring between 1 and 4 on the GDS were discriminated by a verbal delayed recall score of 4 (of 10) items. The portion of subjects recalling more than four words was greatest in cluster 1 and smallest in cluster 3.

Patterns of subjective memory impairment
of a general nature. While verbal fluency is associated with frontal brain function (Alvarez & Emory, 2006), delayed verbal recall is highly dependent on MTL integrity (Moscovitch et al., 2006). The neurodegeneration in AD starts in the MTL (e.g. Braak & Braak, 1991) and delayed verbal memory has been identified as an early and sensitive indicator of future cognitive decline (e.g. Bäckman et al., 2001). Thus, the inferior performance on delayed verbal memory in those SMI subjects with only a minor number of depressive symptoms may point to MTL damage and AD-related neuronal dysfunction. This hypothesis is supported by recent neuroimaging studies, indicating volume reductions of the hippocampus (van der Flier et al., 2004; Saykin et al., 2006) and the entorhinal cortex (Jessen et al., 2006) in SMI.

ApoE4 is a well-established genetic risk factor for AD (Rubinsztein & Easton, 1999). Healthy middle-aged and elderly apoE4 carriers perform worse on memory tasks than healthy non-carriers (Mayeux et al., 2001; Nilsson et al., 2006) and are at increased risk for cognitive decline (Blair et al., 2005; Heun et al., 2006). Furthermore, apoE4 carriers show more AD-related neuropathology than non-carriers, irrespective of the cognitive status (Ghebremedhin et al., 2001; Riudavets et al., 2006). The inferior performance of apoE4 carriers on verbal delayed recall in cluster 2 (general memory complaint, rarely complaints on individual tasks) reflects the expected apoE effect and makes the presence of confounding factors with major effects on memory unlikely.

There was no apoE effect in cluster 1, which contained subjects without memory complaints. Longitudinal studies show that not all apoE4 carriers develop dementia. At the age of 90, 40% of heterozygote apoE carriers do not have dementia, suggesting that these subjects carry unknown protective factors (Khachaturian et al., 2004). Subjects with these protective factors might be over-represented in the group of elderly non-complainers in our study, which would explain the lack of the apoE effect in this group and the best memory performance of all clusters.

The lack of the apoE effect on memory in the SMI subjects of cluster 3 (general complaint and complaints on individual tasks of daily living) might be related to the presence of depressive symptoms, which may cover the apoE effect. In addition, severe memory complaints may be related to personality traits and other factors that have not been assessed in detail in the present

| Table 3. Distribution of complaints about change in specific areas of everyday memory within the three clusters of subjective memory impairment |
|-------------------------------------------------|------------------|------------------|------------------|
| Do you have trouble remembering things that have happened to you recently? | Cluster 1 | Cluster 2 | Cluster 3 |
| No | 903 (90.8) | 752 (68.8) | 22 (7.3) |
| Yes, a bit | 91 (9.1) | 336 (30.7) | 222 (73.8) |
| Yes, a lot | 1 (0.1) | 5 (0.5) | 57 (18.9) |
| Are you worse at remembering where belongings are kept? | No | 864 (86.8) | 768 (70.3) | 46 (15.3) |
| Yes, a bit | 130 (13.1) | 319 (29.2) | 196 (65.1) |
| Yes, a lot | 1 (0.1) | 6 (0.5) | 59 (19.6) |
| Do you have trouble recalling conversations a few days later? | No | 945 (95) | 890 (81.4) | 59 (19.6) |
| Yes, a bit | 50 (5) | 203 (18.6) | 213 (70.8) |
| Yes, a lot | 0 (0) | 0 (0) | 29 (9.6) |
| Do you have more trouble remembering appointments and social arrangements? | No | 961 (96.6) | 966 (88.4) | 116 (38.5) |
| Yes, a bit | 34 (3.4) | 127 (11.6) | 157 (52.2) |
| Yes, a lot | 0 (0) | 0 (0) | 28 (9.3) |

Values are given as n (% of cluster).
To summarize, our data suggest that general memory complaints in non-depressed subjects are associated with reduced performance in delayed recall, which may be an indicator for the presence of AD.

Our study is limited by not including more cognitive variables. Because of the high age of the population and the application of clinical investigation (Hanninen et al. 1996; Jorm et al. 2004a).

Fig. 1. Classification and Regression Tree (CART) analysis, identifying discriminators between the three clusters. Depicted are the number of cases within each cluster and the separation of the cluster into subgroups according to the identified discriminator. The Geriatric Depression Scale (GDS) discriminates at the first and second levels. At the third level verbal delayed recall discriminates among subjects with a GDS between 1 and 4 points. Here, SMI subjects (clusters 1 and 2) are more likely to score below 4 on verbal delayed recall than non-complainers.
instruments, the number of cognitive measures was limited. However, delayed recall is a sensitive measure of MTL function, while verbal fluency is mainly subserved by frontal lobe function. Thus, these two tasks are representative for two distinct neuronal systems, of which delayed recall is particularly sensitive for early AD.

We are not able to define the predictive power of the different SMI subtypes with regard to cognitive deterioration in this cross-sectional study. However, all participants are followed up longitudinally, which will eventually reveal whether different types of SMI predict different rates of cognitive decline.

APPENDIX

Further members of the AgeCoDe study group: Heinz-Harald Abholz, Matthias Angermeyer, Cadja Bachmann, Martin Dichgans, Ulrich Finckh, Anja Frenzen, Sandra Gorfer, Franziska Haller, Teresa Kaufeler, Melanie Luppa, Manfred Mayer, Heinz-Peter Romberg, Hagen Sandholzer, Hendrik van den Bussche, Michael Wagner, and Anja Wollny.


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DECLARATION OF INTEREST

None.
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