The Predictive Value of Memory Strategies for Alzheimer’s Disease in Subjects with Mild Cognitive Impairment


Abstract

Subjects with Alzheimer’s disease (AD) show impaired learning strategies. Whether impaired learning strategies are already present in subjects with prodromal AD remains unknown. The aim of the present study was to investigate the predictive accuracy of learning strategies for AD in subjects with Mild Cognitive Impairment (MCI). Subjects with MCI (n = 202) were selected from the Maastricht Memory Clinic. Subjects were reassessed over a period of 10 years. Fifty-five of the 202 subjects converted to AD. Learning strategies investigated were subjective organization and serial clustering. Lower scores of subjective organization were associated with a higher risk for AD (OR = 2.1, p = .002). Serial clustering did not predict AD. Prodromal AD is characterized by a decreased use of effortful learning strategies. This finding may have implications for the early detection of AD in MCI subjects and for the development of cognitive training programs.

Keywords: Mild cognitive impairment; Alzheimer’s disease; Learning strategies; Predictors

Introduction

Mild Cognitive Impairment (MCI) is common among the elderly, with prevalence rates ranging from 11% to 17% (Mariani, Monastero, & Mecocci, 2007), and incidence rates ranging from 9 to 26 per 1000 person-years depending on cohort source and MCI definition (Larrieu et al., 2002; Tervo et al., 2004). MCI is a relevant healthcare problem because it reduces the quality of daily living and because a subgroup of subjects with MCI shows a progressive course and will develop Alzheimer’s disease (AD) in the future (Visser, Kester, Jolles, & Verhey, 2006). However, it remains difficult to differentiate between subjects with MCI who will develop AD and those who will not. This would be important because drugs that have the potential to modify the disease progression are supposed to be most effective in the early stage of the disease.

One of the primary cognitive features of AD is impairment in encoding and retrieval of new information (Bennett, Golob, Parker, & Starr, 2006; Visser et al., 2000). Encoding is facilitated by the use of learning strategies (Saan & Deelman, 1986; Sternberg & Tulving, 1977), and there is evidence that subjects with AD do not use learning strategies efficiently (Delis et al., 1991). Previous studies reported that, when compared with healthy controls, subjects with AD showed significantly lower levels of clustering (Carlesimo et al., 1998; Perri, Carlesimo, Serra, & Caltagirone, 2005) and did not benefit from the semantic relatedness of the presented stimuli (Carlesimo et al., 1998). Also subjects with MCI less often used semantic clustering as a learning strategy compared with control subjects (Perri et al., 2005; Ribeiro, Guerreiro, & De Mendonca, 2007).

The aim of this study is to investigate whether impaired learning strategies of subjective organization and serial clustering could predict AD in subjects with MCI. Subjective organization refers to constancies in the order of responses that develop over
a series of free recalls. Subjective organization requires an active reorganization of the presented words (Bousfield & Bousfield, 1966; Saan & Deelman, 1986; Sternberg & Tulving, 1977). In contrast, serial clustering is an automatic, more passive strategy in which the words are recalled in the same order as they were offered (Delis, Kramer, Kaplan, & Ober, 1987). Because subjective organization requires more effort and is less automatic than serial clustering, we hypothesized that subjective organization would be predictive for AD at follow-up, whereas serial clustering would not be.

Materials and Methods

Subjects

Subjects were selected from an ongoing, longitudinal study of non-demented subjects referred to the Maastricht Memory Clinic, an outpatient clinic at the Maastricht University Hospital in the Netherlands (Verhey et al., 1993; Visser et al., 2006). Subjects were referred to the memory clinic for evaluation of their cognitive complaints and were consecutively enrolled at the time of the first visit to the memory clinic. Inclusion criteria were age 40 years or older and a score of 2 or 3 on the Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982). Exclusion criteria were dementia at baseline (discussed subsequently), and an apparent cause for their cognitive impairment, such as cerebrovascular disorders, brain trauma, endocrine disorders, or psychiatric disorders other than mild affective disorders at baseline (Visser et al., 2000). For the present study, we selected: Subjects with MCI which was defined as an impaired score (at least 1.5 SD below the average score of healthy control subjects) on at least one neuropsychological test (discussed subsequently). In addition, we selected subjects with the same Dutch version of the 15-item Auditory Verbal Learning Task (AVLT, discussed subsequently; Brand & Jolles, 1985; Van der Elst, van Boxtel, van Breukelen, & Jolles, 2005) and who had been eligible for the first follow-up visit. The baseline characteristics of the study sample (n = 202) are shown in Table 1. The study was approved by the medical ethics Committee at the Maastricht University Hospital. After the study was explained to the subjects, all subjects gave their written informed consent.

Clinical Assessment and Diagnosis at Baseline

At baseline, all subjects underwent a standardized assessment, which included a detailed history of the subject, a psychiatric, neurological, and physical examination, the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), assessment using the GDS (Reisberg et al., 1982), Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), and the Blessed Dementia Rating Scale (BDS; Blessed, Tomlinson, & Roth, 1968), appropriate laboratory tests, a neuropsychological assessment including tests covering the domains of memory (AVLT; Brand & Jolles, 1985), attention (Stroop card I & II [Stroop, 1935], Trail Making Test (TMT) card A [Reitan, 1958]), executive functioning (Stroop card III [Stroop, 1935]; TMT card B [Reitan, 1958]), and language (fluency animals [Van der Elst, van Boxtel, van Breukelen, & Jolles, 2006]), and CT or MRI as described elsewhere (Verhey et al., 1993). The diagnosis of dementia and AD was made by a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Not demented (n = 147)</th>
<th>AD (n = 55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M ± SD</td>
<td>56.5 ± 9.4</td>
<td>67.9 ± 8.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, % man</td>
<td>59</td>
<td>48</td>
<td>.141</td>
</tr>
<tr>
<td>Education, % low/moderate/high</td>
<td>17/47/36</td>
<td>27/45/28</td>
<td>.200</td>
</tr>
<tr>
<td>MMSE, M ± SD</td>
<td>28.3 ± 1.6</td>
<td>26.5 ± 2.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDRS, M ± SD</td>
<td>11.2 ± 6.1</td>
<td>8.0 ± 5.8</td>
<td>.001</td>
</tr>
<tr>
<td>BDS, M ± SD</td>
<td>1.5 ± 1.4</td>
<td>1.9 ± 1.5</td>
<td>.12</td>
</tr>
<tr>
<td>GDS, M ± SD</td>
<td>2.4 ± 0.5</td>
<td>2.7 ± 0.5</td>
<td>.002</td>
</tr>
<tr>
<td>Learning, raw score, M ± SD</td>
<td>38.0 ± 9.6</td>
<td>26.7 ± 6.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Delayed recall, raw score, M ± SD</td>
<td>7.5 ± 3.1</td>
<td>2.8 ± 2.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Learning, z-score, M ± SD</td>
<td>-0.95 ± 1.2</td>
<td>-1.9 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Delayed recall, z-score, M ± SD</td>
<td>-0.84 ± 1.2</td>
<td>-2.3 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Subjective organization, M ± SD</td>
<td>1.1 ± 0.8</td>
<td>0.6 ± 0.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serial clustering, M ± SD</td>
<td>3.0 ± 1.6</td>
<td>2.6 ± 1.5</td>
<td>.144</td>
</tr>
</tbody>
</table>

M = mean; SD = standard deviation; MMSE = Mini Mental State Examination; HDRS = Hamilton Depression Rating Scale; GDS = Global Deterioration Scale; BDS = Blessed Dementia Rating Scale; AD = Alzheimer’s disease.

*aMean over the learning trials.
multidisciplinary team according to the DSM-IV and NINCDS-ADRDA criteria (American Psychiatric Association, 1994; McKhann et al., 1984).

Clinical Assessment and Diagnosis at Follow-Up

After baseline at 2, 5, and 10 years, subjects were invited to participate in a follow-up assessment. Because enrolment was continuous, and not all subjects had completed all follow-up assessments. None of the subjects received a cholinesterase inhibitor during the course of the study. The follow-up assessment included a standardized questionnaire about medical history and cognitive complaints, the MMSE, GDS, BDS, HDRS, and a neuropsychological assessment comparable to baseline. Subjects who refused to come for the follow-up assessment were assessed via a telephone interview, which included a standardized questionnaire about medical history and cognitive complaints, and the Telephone Interview for Cognitive Status (Brandt, Spencer, & Folstein, 1988). The diagnosis of dementia and AD was made using the same criteria as at baseline and was made independently by both a neuropsychiatrist and a neuropsychologist. Both professionals were blinded to the baseline results. If disagreement on the diagnosis occurred, a consensus meeting was held. When disagreement about the diagnosis remained, the subject was classified as not demented.

Memory Strategies

Memory strategies were tested using the AVLT (Van der Elst et al., 2005). Fifteen unrelated monosyllabic words were presented five times, and after each presentation, the subject was asked to recall as many words as possible. After 20 min, during which non-verbal tests were performed, delayed recall was tested. The strategies of subjective organization and serial clustering were investigated using the five learning trials of the AVLT.

Subjective organization. Subjective organization refers to the consistencies in response order that develop over a series of free recalls (Bousfield & Bousfield, 1966; Tulving, 1962). On the basis of the output order in which the words from two successive trials are listed by the subject, combinations (clusters) of words that are recalled together in these two successive trials are identified. These combinations are based on the organization schema developed by the individual subject and are not dependent on prespecified categorization based on semantic relationships, which is used in several word learning tests such as the California Verbal Learning Test (Delis et al., 1987).

A bidirectional inter-trial repetition (ITR) measure (Sternberg & Tulving, 1977) was used as described in detail elsewhere (Ramakers et al., 2008). In short, the bidirectional ITR corrects for clusters that occur by chance with the following formula (Sternberg & Tulving, 1977): Subjective organization = Observed (ITR) − Expected (ITR) (Ramakers et al., 2008). An outcome of zero indicated that the number of observed ITRs is equal to the number of expected ITRs. A score higher than zero indicates more use of subjective organization than expected by chance. Unless specified otherwise, we used the average level of subjective organization over the four learning trial pairs.

Serial clustering. Serial clustering refers to the number of word pairs that are reproduced in the same order as they were presented (Delis, Freeland, Kramer, & Kaplan, 1988; Kramer, Delis, Kaplan, O’Donnell, & Prifitera, 1997). Serial clustering was measured based on an adapted version of the formula from Mulder, Dekker, and Dekker (1996) as described elsewhere (Ramakers et al., 2008). The total number of observed serial clusters is divided by the number of clusters that are expected based to occur on chance (Bouma, Mulder, & Lindeboom, 1996; Mulder et al., 1996; Ramakers et al., 2008; Saan & Deelman, 1986). A score higher than zero indicates that the subjects reported more clusters than that would be expected generated by chance. Unless specified otherwise, we used the average level of serial clustering over the five learning trials.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Macintosh, version 16. To analyze differences between converters and non-converters, independent t-tests were conducted for continuous variables and chi-square tests for categorical variables. The predictive accuracy was analyzed using a discrete-time survival analysis model and implemented using logistic regression and an appropriately adjusted data set (Hosmer & Lemeshow, 1999). The outcome group included all subjects with AD at follow-up. The reference group included subjects without dementia at follow-up. Analyses were done with adjustment for age, sex, and education. Two-factor repeated measures ANOVAs were performed, with group as a between factor, trial as a within factor, and age, education, and sex as covariates, to analyze the change in
the use of learning strategies across the five learning trials of the AVLT. All tests were two-tailed, and the significance level was set at .05.

Results

Of the 202 subjects included in the study, 19 subjects (9%) had amnestic MCI single domain, 78 (39%) had amnestic MCI multiple domain, 54 (27%) subjects had non-amnestic MCI single domain, and 51 (25%) subjects had non-amnestic MCI multiple domain. Fifty-five subjects (27%) had developed AD within the follow-up period up to 10 years, of which 28 (51%) had AD after 2 years, 18 (33%) after 5 years, and 9 (16%) after 10 years. Three subjects with a non-AD type dementia at follow-up were excluded from the analyses. Table 1 shows the baseline characteristics of the subjects who developed AD and those who did not. Subjects with AD at follow-up had a significantly lower baseline MMSE score, a higher GDS score, a lower HDRS score, and lower scores on the immediate and delayed recall test of the AVLT, and were older than those without AD at follow-up. Sex distribution and level of education were comparable in both groups.

The average score of the strategies used in the five learning trials of the two groups are presented in Table 1. Converters had significantly lower mean levels of subjective organization. Serial clustering was comparable in both groups.

Two-factor GLM repeated measures ANOVA analyses showed a significant main effect of group on subjective organization (\(F = 11.1; df = 1; p = .001\)), indicating that converters had lower scores of subjective organization across the learning trials than non-converters (Fig. 1A). The main effect for trial and the interaction effect between group and trial were not statistically significant. For serial clustering, the main effects for group and trial and the interaction effect between group and trial were not statistically significant (Fig. 1B).

Survival showed that lower levels of subjective organization were associated with an increased risk for AD (OR = 2.1, 95% CI = 1.3–3.5, \(p = .002\)). Serial clustering was not predictive for AD at follow-up (\(p = .170\)). Results were comparable after correction for baseline HDRS and GDS scores. If the delayed recall score was added as covariate in the survival analysis, subjective organization was no longer predictive for AD, but the delayed recall score was.

Findings were similar in subjects aged 40–59 (OR = 3.1, 95% CI = 0.97–9.9, \(p = .055\)) and in subjects aged 60–85 (OR = 1.6, 95% CI = 1.01–2.5, \(p = .046\)). Serial clustering was not predictive for AD in either age group.

In order to investigate whether subjective organization was associated with progression to AD at the short term or long term, we performed separate analyses for subjects who were diagnosed with AD after 2, 5, and 10 years. The OR for AD after 2 years (28 subjects with AD) was 2.6 (95% CI: 1.3–5.0, \(p = .006\)), for AD after 5 years (18 subjects with AD) 1.7 (95% CI: 0.8–3.5, \(p = .18\)), and for AD after 10 years (9 subjects with AD) 3.3 (95% CI: 1.0–11.2, \(p = .055\)).

There was a significant moderately high correlation between subjective organization and delayed recall performance (\(r = .46, p < .001\)), but not with serial clustering, using the Pearson correlation analyses.

![Fig. 1. Average levels of learning strategies in converters and non-converters to AD. (A) Subjective organization and (B) serial clustering. The black line represents the converters and the grey line the non-converters.](image-url)
Discussion

Less use of subjective organization was associated with an increased risk for AD. Use of serial clustering was not predictive for AD. This is in line with our hypothesis. Serial clustering is a passive, low-level approach to recall, which does not involve any new transformation or organization of the presented information (Glosser, Gallo, Clark, & Grossman, 2002). Subjective organization, on the other hand, requires more effort and an active reorganization and consumes a greater portion of a person’s limited mental resources (Bjorklund & Douglas, 1997), which seems to be problematic for subjects with MCI who later convert to AD.

Our findings are consistent with the findings of a cross-sectional study of Carlesimo and colleagues (1998), which suggested that memory aspects that require more processing resources can be used to differentiate normal from pathological aging. Lower scores of subjective organization were associated with an increased risk for AD both at the short term and at the long term, indicating that impairments in subjective organization are a very early symptom of AD. Why subjective organization was not predictive for AD after 5 years is not clear and may be a chance finding.

Subjective organization depends on the active reorganization of the incoming information and may therefore be related to prefrontal lobe functioning and executive functioning (Fletcher, Shallice, & Dolan, 1998; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998; Kramer et al., 2005; Savage et al., 2001). We did not find, however, that the effect of subjective organization on AD was mediated by impairment in executive function as after correction for a variety of executive function tests, results remained similar (data not shown).

Subjective organization was associated with the delayed recall performance at baseline. This suggests that subjective organization improves learning and subsequent retrieval from long-term memory. Alternatively, both learning and retrieval may not be causally correlated with each other, but share a common underlying mechanism.

Implications

The finding that subjective organization is already impaired in prodromal AD gives new insights in the cognitive mechanisms that underlie memory dysfunction in subjects with prodromal AD. In clinical practice, subjective organization scores may help to identify subjects with MCI who progress to AD. Still, the predictive accuracy was less than that of the delayed recall as subjective organization was no longer a significant predictor for AD after correction for this variable. The correlation between subjective organization and delayed recall performance suggests that subjects with MCI could benefit from using these cluster strategies to improve their everyday memory. This supports the use of cognitive training in subjects with MCI (Belleville, 2008) and early-stage dementia (Clare et al., 2003). Indeed, preliminary results confirmed that the use of memory strategies leads to increased performances and concluded that strategy-based cognitive rehabilitation might be beneficial in patients with MCI (Hampstead, Sathian, Moore, Nalisnick, & Stringer, 2008). Because of the role of learning strategies in prodromal AD, the type of word list used to assess memory function may be important for the ability to detect subjects with AD. Word lists that include semantically related words might be less useful to identify subjects with prodromal AD, because active reorganization of the presented material is less needed. Word list learning tests in which the order of the presented words varies over the learning trials, such as the word learning test of the Consortium to Establish a Registry for AD (Welsh et al., 1994) or the cognitive part of the AD Assessment Scale (Rosen, Mohs, & Davis, 1984), might make it more challenging for subjects to apply subjective organization or serial clustering strategies and might be sensitive for early AD.

This study has some points of attention. It is possible that the use of strategies is related to the number of recalled words after each learning trial. However, we corrected the cluster scores for the total number of words remembered in each learning trial. We did not investigate the course of memory strategies over time. The results of this study can be applied to subjects from a memory clinic, but may not be generalizable to other settings.

In summary, we found that the ineffective use of effortful strategies was associated with an increased risk for AD. This finding may help to identify subjects with prodromal AD in subjects with MCI and gives more insight in the underlying mechanisms of memory dysfunction in subjects with prodromal AD. These findings could be used in the development of cognitive training programs.

Conflict of Interest

None declared.
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References


