Topographical recognition memory sensitive to amnestic mild cognitive impairment but not to depression

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SUMMARY

Objective Amnestic mild cognitive impairment (aMCI) involves episodic memory. The person who presents aMCI has a high risk of developing Alzheimer’s disease (AD). However, prediction of deterioration to dementia in cases of aMCI can be confounded with depression due to lack of specificity on selective memory tests. Finding a test sensitive to aMCI but not to depression would be potentially most useful to subsequent longitudinal studies researching the neuropsychological markers of preclinical AD. We hypothesized that the performance on a topographical memory task would be sensitive to the aMCI condition, while depression would not influence such a performance.

Participants and Methods A group of 137 community-dwelling French-speaking subjects between 55 and 70 years old was administered a topographical recognition memory task. Based on aMCI and depression criteria, 45 subjects were selected and divided into four groups: 11 patients with aMCI without depression, nine depressive patients with aMCI, ten depressive patients without cognitive impairment and 15 control subjects. The remaining non-selected participants did not belong to any of the previous interest groups.

Results The ‘aMCI’ factor had a significant effect on the topographical recognition memory task scores, while the ‘depression’ factor did not. The aMCI patients performed worse than the non-aMCI.

Conclusion Although these results were found with relatively small groups, deficits in topographical recognition memory were observed in aMCI patients and did not seem to be sensitive to depression. Further longitudinal studies are needed to examine whether deficits in topographical recognition memory are a neuropsychological marker of preclinical AD.

INTRODUCTION

Mild cognitive impairment (MCI) is defined as one or more cognitive deficit(s) not of sufficient severity to constitute a dementia but greater than that of healthy individuals of same age and education level (Petersen et al., 2001). When the cognitive deficit concerns memory, it is called amnestic mild cognitive impairment (aMCI). Although aMCI presents a high risk of developing Alzheimer’s disease (AD) (Petersen et al., 2001), this category both includes patients who will develop AD (termed as ‘evolving’ aMCI) and others who will never convert (termed as ‘stable’ aMCI). Distinguishing evolving aMCI from stable aMCI in order to prescribe appropriate treatment as quickly as possible in the evolution of AD is a primary objective of aMCI research.

Prediction of deterioration to dementia in cases of aMCI may be confounded with other disorders by lack of specificity on selective memory tests. In particular, delayed free recall considered to be the most sensitive task to detect patients in the early phase of dementia (Welsh et al., 1991), is also vulnerable to depression (Portella et al., 2003), among other disorders. This suggests that some cases may be erroneously labelled as incipient dementia. Moreover, this problem is further confounded by the fact that late-life depression...
and incipient dementia are not mutually exclusive: there is an over-representation of depressive symptoms in early dementia (Baquero et al., 2004). Tests sensitive to AD but not to depression would thus be potentially most useful to orient longitudinal studies researching on neuropsychological markers of preclinical AD.

Whereas depression is generally associated with prefrontal cortex dysfunction (e.g. Kalayam and Alexopoulos, 1999), the parahippocampal gyrus (PHG) is reported to be a structure early impaired in evolving MCI (Dickerson et al., 2004; de Toledo Morell et al., 2004). This latter structure has been found to be activated among other conditions, during building recognition memory task (Ekstrom et al., 2003), which refers to topographical recognition memory. Complementarily, topographical recognition memory was found to be impaired in an evolving aMCI patient (Godbolt et al., 2005), who was tested by means of the Topographical Recognition Memory Test (TRMT; Warrington, 1996).

The fact that the PHG seems to be vulnerable in an early stage in the process leading to AD, together with its role in topographical recognition memory and bearing in mind that the PHG does not appear to be associated with depression, led us to hypothesize that aMCI patients would show impaired performance on the TRMT and that this performance would be insensitive to depression. Therefore, we examined topographical recognition memory in aMCI patients, with or without depression, and in single-depression patients.

METHODS

Subjects

A pool of 137 French-speaking subjects between 55 and 70 years old, educated for at least nine years was recruited from retired associations and from the lecture-attending retired population at Strasbourg’s university in Alsace. Inclusion criteria to participate in the present study were a Mini Mental Status Examination (MMSE; Folstein et al., 1975) score being equal or superior to 26/30 (for norms see Crum et al., 1993) and absence of known neurological and/or psychiatric conditions other than depressive symptoms screened by Goldberg’s depression scale (GDS; Goldberg et al., 1988). Additionally, participants who had had heart attack, fainting fits, hypoxia, prolonged headaches, severe general illnesses or subjects being under antidepressant were also excluded from the study.

Diagnosis of aMCI and depression

The subjects were diagnosed as presenting aMCI according to Petersen et al.’s criteria (2001): (1) Subjective memory complaint (‘Do you sometimes have memory problems?’); (2) Memory performances < −1.5 SD of age-and education-adjusted norms based on the results of the verbal delayed-recall task (the cut-off was 3/12 correct responses for nine years of education and 4/12 for more than nine years); (3) Normal general cognitive functioning evaluated by the MMSE and the Salpêtrière complementary scale (see Appendix); (4) Normal activities of daily living assessed by the four-item version of the IADL; (5) Absence of

Tests

The neuropsychological examination was conducted in a single session lasting 90–120 min. The entire battery was given to all the 137 subjects. aMCI was diagnosed (for criteria see the following section) by assessing the following domains: Global cognitive functioning using the MMSE and a complementary scale (Dubois and Pillon, unpublished, Salpêtrière Hospital, Paris; see Appendix); verbal (Similarities subtest from the French version of Wechsler Adult Intelligence Scale—Revised, 1989) and nonverbal reasoning (Advanced Progressive Matrices; Raven, 1965) and a premorbid verbal IQ estimation (Beauregard, 1971). A task sensitive to frontal lobe dysfunction (a phonological fluency task; Benton, 1968) and a verbal anterograde memory test also guided diagnosis. Concerning the latter, it includes 12-unrelated word list immediate- and delayed-recall tasks. During the learning task, three presentations of the list were given, each followed by an attempted recall where subjects were asked to give as many words as possible. The total score of the immediate recall task was the mean of the two higher scores. Delayed free recall was tested 30 min after the third trial. Finally, we added a four-item version of the Instrumental Activities of Daily Living Scale (IADL; Lawton and Brody, 1969), which included the most sensitive items (telephone use, use of transport, responsibility for medication intake, and budget management; Barberger-Gateau et al., 1993).

The TRMT was used for research purposes. During the learning phase of the test subjects were requested to watch each of the 30 colour photographs of places for 3 sec. Recognition memory was tested immediately afterwards using a three-choice format (each stimulus item being paired with two very similar distracter items). The test takes about 7 min.
dementia: the aMCI patients obtained a score of the MMSE of 26/30 or higher and they had no deficits in cognitive domains other than verbal anterograde memory. GDS that comprises four screening questions and five probe questions was used to detect cases of depression. The probe questions were used only if there was at least one positive screening response. For a score higher than 2 out of 9, the sensitivity to major depressive disorder (APA, 1980) was 85% and the specificity was 96%. Therefore, we considered individuals to be depressed if their score was higher than 2. According to aMCI criteria, 20 aMCI patients and 25 individuals without cognitive impairment were selected. After depression screening for both groups, we identified nine aMCI-depressive patients (amnMCI + DEP; two men), eleven aMCI-non-depressive patients (amnMCI; five men), ten non-aMCI-depressive patients (DEP; one man) and 15 non-aMCI-non-depressive or normal control subjects (NC; six men; see Table 1). The remaining non-selected participants did not belong to any of the previous interest groups. The NC and the DEP obtained normal scores in all the tests. Age, education levels and the MMSE scores were not significantly different between the groups, and DEP and amnMCI + DEP patients’ depressive scores were similar (see Table 1).

Data analyses

For each test, inter-group differences were analysed by a series of ANOVAs, with one inter-subject variable, the ‘group’ factor (i.e. amnMCI, amnMCI + DEP, DEP and NC groups). If significant main effects were shown ($p < 0.05$), pairwise group differences were analysed by Student-Newman-Keuls post-hoc test.

RESULTS

Analyses of variance

Table 2 shows the mean scores of the TRMT for each group. The ‘aMCI’ factor but not the ‘depression’ factor had a significant effect on the TRMT scores ($F[3,41] = 4.57; p = 0.007$). A posteriori analysis (Student-Newman-Keuls test) revealed that both the amnMCI and amnMCI + DEP patients exhibited significantly inferior performances than the NC ($p < 0.03$ and $p < 0.02$ respectively). Furthermore, the NC’s TRMT scores were not significantly different from the DEP ($p = 0.23$). Likewise, the aMCI groups (amnMCI and amnMCI + DEP) obtained TRMT scores, which did not yield significant differences ($p = 0.69$). Although there was an overlap between aMCI patients and cognitively intact DEP patients, ANOVA showed that depression had no effect on the TRMT. The overlap was due to three DEP patients, who presented with an isolated deficit of topographical recognition memory not associated with depression (see below for specificity of the TRMT).

Sensitivity and specificity

On the one hand, cut-off score of 1.5 SD below the mean of the NC subjects for scores on the TRMT correctly classified 72% of the non-aMCI individuals (73.3% of the NC subjects and 70% of the DEP) and 65% of the aMCI patients (63.6% of the amnMCI and 66.8% of the amnMCI + DEP). On the other hand, a

<table>
<thead>
<tr>
<th>Table 1. Demographic data of the different groups</th>
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<tbody>
<tr>
<td><strong>Group</strong></td>
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<td>-----------</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Age Range: 55–70</td>
</tr>
<tr>
<td>Years of education</td>
</tr>
<tr>
<td>MMSE</td>
</tr>
<tr>
<td>GDS/9</td>
</tr>
</tbody>
</table>

Note: amnMCI + DEP, depressive patients with amnestic mild cognitive impairment; amnMCI, patients with amnestic mild cognitive impairment without depression; NC, Control subjects; DEP, depressive patients without cognitive impairment; GDS, Goldberg’s depression scale; MMSE, Mini Mental Status Examination. Values are expressed as means with standard deviations in parentheses.
cut-off score of 1.5 SD below the mean of NC subjects for scores on the word list immediate-recall task correctly classified 92% of the non-aMCI individuals (93.3% of the NC subjects and 90.0% of the DEP) but only 30.0% of the aMCI patients (36.4% of the amnMCI and 22.2% of the amnMCI + DEP). These results showed a reliable sensitivity only for the TRMT. By contrast, TRMT’ specificity was inferior to that of the word list test. Moreover, no other test besides the TRMT distinguished aMCI from non-aMCI individuals (see Table 2).

**DISCUSSION**

We were able to document that the aMCI group performed significantly more poorly on the TRMT than the non-aMCI group and that depression was not related to this deficit. aMCI deficit in topographical recognition memory confirms Godbolt et al.’s (2005) study, in which their evolving aMCI patient presented with deficit on the TRMT. Although this type of recognition memory has not been tested in depressed patients, to the best of our knowledge, its independence of depression agrees with the general observation that recognition memory is not altered by depression (for review, see Austin et al., 2001).

In the present work, 65% of the aMCI patients were impaired on the TRMT. Barbeau et al.’s study (2004) reported that 78% of the aMCI failed on the DSM 48, a visual recognition memory test. Whereas our aMCI patients were selected on Petersen et al.’s criteria (2001) from retired associations and from lecture-attending retired population, Barbeau et al.’s were drawn from a memory clinic where biological and medical neuroimagery data had been performed. This guaranteed their sample homogeneity and, probably, the increased percentage of failure on the DSM 48.

Our aMCI patients who failed the TRMT are likely to have medial temporal lobe or PHG dysfunction. Indeed, the right PHG seemed to be specific to topographical recognition memory since it was selectively involved in this type of material unlike the non-topographical stimuli recognition (Maguire et al., 2001; Cippolotti and Maguire, 2003; Ekstrom et al., 2003). As some studies showed that the PHG was also specifically altered in evolving MCI (Dickerson et al., 2004; De Toledo Morell et al., 2004), our aMCI patients impaired on the TRMT may thus be at higher risk of developing AD. However, the posterior end of the right PHG would not be necessary for topographical recognition memory: patients with damage in this area were in the normal range when testing the TRMT (Epstein et al., 2001). This result suggests that the more anterior portion of the PHG could be altered in aMCI patients who failed the TRMT. This suggestion is in accordance with Braak

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Table 2. Mean scores and standard deviations of the neuropsychological tests in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Non-aMCI</th>
<th>aMCI</th>
<th>Analysis of Variance (ANOVA)</th>
<th>Followed by Newman-Keuls Tests (if p &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NC (N = 15)</td>
<td>DEP (N = 10)</td>
<td>amnMCI (N = 11)</td>
<td>amnMCI + DEP (N = 9)</td>
</tr>
<tr>
<td>TRMT/30</td>
<td>26.8 (2.51)</td>
<td>25.1 (3.11)</td>
<td>23.0 (2.86)</td>
<td>22.4 (4.69)</td>
</tr>
<tr>
<td>Verbal immediate-recall task/12</td>
<td>8.63 (1.30)</td>
<td>8.30 (1.44)</td>
<td>7.41 (1.43)</td>
<td>7.33 (1.30)</td>
</tr>
<tr>
<td>Verbal delayed-recall task/12</td>
<td>6.87 (1.77)</td>
<td>6.70 (2.21)</td>
<td>2.73 (1.62)</td>
<td>2.78 (1.09)</td>
</tr>
<tr>
<td>Attention/15</td>
<td>12.9 (1.16)</td>
<td>13.0 (2.16)</td>
<td>13.1 (0.94)</td>
<td>13.0 (0.87)</td>
</tr>
<tr>
<td>Phonological fluency task “P” for one minute</td>
<td>14.8 (5.58)</td>
<td>15.9 (4.43)</td>
<td>11.8 (4.17)</td>
<td>13.8 (3.83)</td>
</tr>
<tr>
<td>Raven/12</td>
<td>8.13 (2.03)</td>
<td>7.90 (1.85)</td>
<td>8.91 (1.92)</td>
<td>7.44 (2.65)</td>
</tr>
<tr>
<td>Similarities/28</td>
<td>20.6 (2.56)</td>
<td>21.8 (3.97)</td>
<td>20.2 (3.22)</td>
<td>21.1 (3.37)</td>
</tr>
<tr>
<td>Premorbid verbal IQ</td>
<td>120.1 (8.42)</td>
<td>123.1 (5.88)</td>
<td>118.6 (11)</td>
<td>122.6 (5.94)</td>
</tr>
</tbody>
</table>

*Note:* amnMCI + DEP, depressive patients with amnestic mild cognitive impairment; amnMCI, patients with amnestic mild cognitive impairment without depression; DEP, depressive patients without cognitive impairment; NC, normal control subjects; TRMT, Topographical Recognition Memory Test. Values are expressed as means with standard deviations in parentheses.
et al.’s (1999) conclusion concerning the beginning of AD where early lesions were found in the transentorhinal and entorhinal cortices.

Unlike neuroimagery studies in healthy subjects, there is a paucity of clinical studies about cognitive effects of PHG lesions. The few available studies point out that PHG patients show deficits in spatial location recall of environmental landmarks. A study demonstrated that a patient with right PHG lesion was deficient in locating landmarks, while he could recognize and recall environmental landmarks (Luzzi et al., 2000). In the TRMT, the distracters are either photographs taken from different points of view or in different temporal periods. In order to perform successfully the TRMT subjects normally locate salient items (e.g., a restaurant notice, a basket) relative to other items on the photograph (right, bottom, left...). Therefore, additionally to landmark or item spatial location impairment in the latter study, aMCI patients’ deficit may arise from an inability to memorize the place of the salient objects on the photograph. A previous study using a computerized spatial memory task where participants had to recall the original place of patterns on the screen, showed that this task was sensitive to cognitive decline of questionable AD patients (Swainson et al., 2001). Further studies of topographical recognition memory with shifted-view and object-moved photograph recognition tasks are needed to determine which topographical recognition memory component is altered in aMCI.

METHODOLOGICAL ISSUES

Our study has some shortcomings: the small sample size may have lowered the sensitivity of the statistical tests, and the memory complaint was self-evaluated although Petersen et al. (2001) recommended memory complaints preferably corroborated by an informant. This means we could have overestimated the number of patients with aMCI. However, Busse et al. (2003) indicated that subjective memory impairment did not seem to be very useful for the prediction of dementia if objective data on cognitive performance were available.

CONCLUSIONS

This study showed that the TRMT was sensitive to the aMCI condition but not to depression. Although further studies with larger samples are required, the TRMT could be useful for longitudinal studies researching neuropsychological markers of aMCI evolving towards AD.

ACKNOWLEDGEMENT

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APPENDIX

Global cognitive functioning: MMSE and the complementary scale (Salpêtrière Hospital)

Total scores are in parentheses: attention (/15) was scored by summing Attention subtest of the MMSE (/5) and forward (/6) and backward (/4) digit spans of the Salpêtrière scale; spatial and temporal orientation (/10) was assessed with the MMSE; language (/18) was composed of Naming, Repetition, 3-stage command, Reading and Writing of the MMSE and Naming of the Salpêtrière scale (ten drawings of objects (eg. Racket) or animals (eg. Camel)) (/10); praxies in the Salpêtrière scale required the subject to copy gestures without meaning (/4); visuo-constructive activities were evaluated by copying a circle and a diamond (/1), two intersecting pentagons (MMSE, /1), and by reproducing block designs (Salpêtrière scale, /3).

REFERENCES


