Cognitive Decline From Estimated Premorbid Status Predicts Neurodegeneration in Alzheimer’s Disease

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This study investigated the relationship between premorbid and current cognitive function with respect to the clinical features of patients with various types of neurodegeneration in the form of Alzheimer’s disease (AD), mild cognitive impairment (MCI), and subjective cognitive impairment (SCI), as compared to a healthy control group (C). Clinical features (MMSE, cognitive and depressive symptoms), genetics (apolipoprotein E: APOE) and measures of neurodegeneration (Aβ42, t-tau, and p-tau) were examined, as well as present cognitive function. Various methods of assessing premorbid cognitive function were compared, including a Swedish NART-analogous test (Irregularly Spelled Words; ISW), a Swedish lexical decision test (SLDT), a Hold test (Information in WAIS–R), Best current performance test, and combined demographic characteristics. Results showed that cognitive decline (premorbid minus current cognitive function) based on SLDT and ISW was a significant predictor for MMSE and Aβ42, whereas corresponding associations for present cognitive function and decline measures based on other methods were less powerful. Results also showed that specific verbal abilities (e.g., SLDT and ISW) were insensitive to AD and that these abilities indicated premorbid cognitive function in retrospect. In conclusion, cognitive decline from premorbid status reflects the disease processes.

Keywords: premorbid function, cognitive function, Alzheimer’s disease

It is a challenge for clinical neuropsychology to find appropriate methods for evaluating the clinical status of patients. A main question is whether measures of present cognitive function or measures of cognitive decline should be used. Measures of premorbid cognitive function are required to reliably assess decline. Recently, two methods for assessing premorbid cognitive function have been published in Sweden: One is an analogue of the New Adult Reading Test (NART; Nelson & McKenna, 1975), called the Test of Irregularly Spelled Words (ISW; Tallberg, Wennerborg, & Almkvist, 2006) and the other is the Swedish Lexical Decision Test (SLDT; Almkvist, Adveen, Henning, & Tallberg, 2007). These methods have been evaluated on healthy individuals and in relation to measures of present cognitive function, as assessed by the Full Scale IQ (FSIQ) of the Wechsler Adult Intelligence Scale—Revised version (WAIS–R; Wechsler, 1981; see also Bartfai, Nyman, & Stegmann, 1994). The predictive power of both the ISW and the SLDT has been found to be in agreement with similar and other methods, as reported in previous research (for a review, see Franzen, Burgess, & Smith-Seeemiller, 1997). However, it is necessary to evaluate these methods not only in relation to healthy subjects, but also in relation to patients with various diseases, because it is important to find out whether the assessment of premorbid function may be possible in retrospect in patients who have already begun to deteriorate in cognitive function.

As mentioned earlier, not only have specific tests of premorbid function been utilized to estimate premorbid cognitive function, but other methods have been utilized as well, such as the Hold test, which investigates semantic knowledge (e.g., vocabulary or information in WAIS), the Best current performance test, and combinations of these methods. However, these methods have not reached the same predictive power as tests specifically designed for assessing premorbid cognitive function, such as the NART (Franzen, Burgess & Smith-Seeemiller, 1997), although these methods are frequently used in clinical neuropsychology. It has been common to use imprecise methods not only to assess premorbid cognitive status but also to neglect the problem by using current cognitive dysfunction, which is often reduced compared with known population values in clinical applications, as a reflection of disease and disturbance. This procedure implies that the population mean is used as a premorbid function estimate, which is far from true in the majority of patients.

The present study concerns a group of patients who were referred to a memory clinic from their primary care or hospital units after displaying cognitive symptoms that were suspected to be connected with the development of dementia. These patients exhibited the whole spectrum of cognitive functions relating to diagnosed dementia, most often Alzheimer’s disease (AD), as well as a borderline condition, mild cognitive impairment (MCI; Petersen et al., 1999), and a condition characterized by unverified cognitive impairment (despite cognitive symptoms), here denoted as subjective cognitive impairment (SCI; Jorm et al., 1997; Kliegel, Zimprich, & Eschen, 2005; Winblad et al., 2004). The clinical status of patients in memory clinics is commonly characterized by clinical features (e.g., cognitive and emotional symptoms, cognitive screening), a genetic marker (APOE; Corder et al., 1993), and cerebrospinal fluid (CSF) indices of neurodegeneration (e.g., Aβ42, t-tau, and p-tau; Sunderland, Hampel, Takeda, Putnam, &...
Cohen, 2006). These characteristics are used in the present study as markers of dementia, which have to be predicted in a validation study of cognitive measures. The CSF measures may indicate the disease process of AD, as they are linked to the degeneration of neurons, unlike clinical characteristics, which represent indirect features that are associated with both the disease and psychological reactions to the possible disease.

The primary purpose of the present study was to validate two Swedish tests for assessing premorbid cognitive function (ISW and SLDT) in relation to various clinical features associated with the disease process. These specific tests were compared with other commonly used methods (Hold test, Best current performance, and combined demographic characteristics) in terms of predictive power. A second purpose was to examine the effectiveness of measures of cognitive decline compared with current cognitive function in disease prediction; that is, to investigate whether cognitive change is more powerful than present status.

Method

Subjects

Patients (about every 10th patient during a 2-year time period, selected randomly, n = 112) from the memory clinic at Karolinska University Hospital in Huddinge, Stockholm, participated in the study. They were categorized according to their diagnoses: For AD, n = 39; for MCI, n = 31; and for SCI, n = 26. Dementia diagnoses other than AD (i.e., vascular dementia, Lewy body dementia, frontotemporal dementia, and corticobasal dementia) were excluded because they were very few. Control subjects (C; n = 16) were recruited from among the spouses of patients. The demographic characteristics (age, gender, and years of education) for the four subject groups are presented in Table 1. The groups (AD, MCI, SCI, and C) were comparable with regard to demographic characteristics, as is demonstrated by the nonsignificant group effects (F[3, 108] = 1.73, p > .10; F[3, 108] = 2.24, p > .10; and F[3, 107] < 1, p > .10, respectively) found for mean age, gender distribution, and mean years of education, according to one-way (group) analyses of variance (ANOVAs).

Procedure

All patients were examined according to a standard protocol that included their medical history; their clinical status as assessed by the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and the Cornell Depression Index (Cornell; Alexopoulos, Abrams, Young, & Shanoian, 1988); a report on their symptoms given by a close informant using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Jorm, 2004); brain imaging (MRI); analyses of blood, urine, and CSF (routine laboratory analyses as well as measurement of Aβ42, t-tau, and p-tau; discussed later); and an assessment of their cognitive function (discussed later). The control subjects were screened for health problems and included in the study if no complaints were found (Sullivan, Karlsson, & Ware, 1995). We also examined them with regard to their cognitive function, using the same procedure as that for the patients, as discussed later.

CSF Analyses

CSF was obtained by lumbar puncture and analyzed according to the standard ELISA procedure, which has been described in previous research (for Aβ1–42, see Andreasen et al., 1999; for t-tau and p-tau, see Blennow, Wallin, Ågren, Spenger, & Vanmechelen, 1995). According to clinical praxis, standard cutoff values for these measures are used to indicate abnormality, whereas t-tau values >400, p-tau values >60, and Aβ values <450 are considered to be indicative of neurodegenerative disease, despite not being included in standard diagnostic procedures.

APOE Genotyping

DNA samples for APOE were extracted from peripheral white blood cells in accordance with previously published methods (Hixon & Vernier, 1990).

Assessments of Cognitive Function

Present global cognitive function was estimated on the basis of five subtests (Information, Digit Span, Similarities, Block Design,
and Digit Symbol) from the WAIS–R (Bartfai et al., 1994; Wechsler, 1981). The sum of scaled scores from the three verbal tests was multiplied by 2 to estimate the full verbal scaled score. Similarly, the sum of scaled scores from the two performance tests was multiplied by 2.5 to estimate the full performance score. Then the current age-related FSIQ (Bartfai et al., 1994; Wechsler, 1981) could be found.

In addition, the Rey–Osterrieth Test (Lezak, Howieson, & Loring, 2004) was used to evaluate copying performance, and the Trailmaking Test (Lezak et al., 2004) was used to evaluate aspects of attention, cognitive speed, and executive function. We evaluated episodic memory using three scores: The first two were based on the patient’s total learning and retention after a 30-min delay, using the Rey Auditory Verbal Learning Test (RAVL; Lezak et al., 2004), and the third was the retention score of the Rey–Osterrieth Test (Lezak et al., 2004). For evaluation purposes, the neuropsychological test results were separated into three categories to correspond to the diagnostic procedure: dementia, MCI, and no dementia/MCI.

Two measures were used to assess premorbid cognitive function, which were based on a NART-like Swedish test: the ISW (Tallberg et al., 2006) and the SLDT (Almkvist et al., 2007). In the ISW, subjects were presented with a series of cards; each showed a word that was to be read aloud without any time restriction. A total of 38 words, representing words of varying frequencies in Swedish, were presented one at a time. The pronunciations were evaluated as being either correct or incorrect, on the basis of the rules of a specified pronunciation manual (Garlen, 2003). Estimated premorbid FSIQ was calculated according to the number of correct pronunciations along with the demographic data is described in detail in a previous study (Tallberg et al., 2006). In the SLDT, subjects were presented with a form showing 58 “words” (33 real words and 25 pseudowords). The format was forced choice with no time restrictions, and the subjects had to decide whether each “word” was real. There were no orthographic differences between the real words and the pseudowords. The number of correct real words and incorrect pseudowords and the demographic data were used to estimate premorbid FSIQ (Almkvist et al., 2007). In this way, two estimates of premorbid FSIQ were obtained, premorbid FSIQ\textsubscript{ISW} and FSIQ\textsubscript{SLDT}. Accordingly, cognitive decline was defined separately for the ISW and SLDT as estimated premorbid FSIQ and current FSIQ, respectively. In addition, premorbid cognitive function was assessed by means of a Hold test (the WAIS–R Information subtest); the Best test result in the current assessment, as suggested by Lezak et al. (2004); and combined demographic data based on a previous study (Almkvist et al., 2007). In doing so, three estimates of premorbid FSIQ were obtained and three measures of cognitive decline were defined (premorbid FSIQ–current FSIQ).

**Ethics**

The study protocol was approved by the Ethics Committee of Karolinska University Hospital, Huddinge (394/02, 400/02, and 442/02).

**Results**

**Clinical Features, APOE, and Indices of Neurodegeneration**

The clinical features (MMSE, IQCODE, and Cornell), APOE, and biomarkers (t-tau, p-tau, and A\textsubscript{\textbeta42} for the diagnostic groups are presented in Table 2. One-way (group) ANOVAs on each clinical feature showed that there were no reliable differences between the groups with regard to reported symptoms (predominantly cognitive symptoms), as evaluated with the IQCODE. However, significant group effects were obtained regarding screened cognitive function on the MMSE; this was due to cognitive deficits in AD patients, compared with both the SCI and MCI patients, according to Scheffe\textsuperscript{h} post hoc\textit{t} tests (ps < .05). A significant group effect was obtained with respect to emotional status, as assessed by the Cornell test. It is interesting that the effect was caused by marked depressive symptoms in the SCI group, compared with the MCI and AD groups (ps < .05). The APOE gene dose (0, 1, or 2 e4 alleles) was significantly different across groups because the e4 alleles were clearly more abundant in the AD group than in the other groups (ps < .05). For all three biomarkers, one-way ANOVAs showed significant group differences. All groups differed according to the pairwise Scheffe\textsuperscript{h} post hoc \textit{t} test for A\textsubscript{\textbeta42} (ps < .05). For t-tau and p-tau, SCI and MCI patients did not differ (ps > .1), but both these groups differed in comparison with AD patients (ps < .05).

**Cognitive Function**

The neuropsychological test results for premorbid cognitive function (assessed by the SLDT, ISW, Hold test, Best test, and demo-

Table 2: Clinical Characteristics for Healthy Controls, as Well as SCI, MCI, and AD Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>C</th>
<th>SCI</th>
<th>MCI</th>
<th>AD</th>
<th>F</th>
<th>p</th>
<th>\eta^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>30.0 ± 0.0</td>
<td>28.8 ± 1.2</td>
<td>28.6 ± 1.5</td>
<td>25.8 ± 3.2</td>
<td>F(2, 90) = 18.03</td>
<td>&lt;.001</td>
<td>.29</td>
</tr>
<tr>
<td>IQCODE score</td>
<td>—</td>
<td>11.1 ± 7.6</td>
<td>8.0 ± 4.9</td>
<td>13.6 ± 12.6</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornell score</td>
<td>—</td>
<td>9.0 ± 4.7</td>
<td>3.9 ± 3.4</td>
<td>5.1 ± 3.4</td>
<td>F(2, 43) = 6.77</td>
<td>&lt;.01</td>
<td>.24</td>
</tr>
<tr>
<td>APOE, e4 dose</td>
<td>—</td>
<td>0.50 ± 0.67</td>
<td>0.77 ± 0.22</td>
<td>1.25 ± 0.70</td>
<td>F(2, 59) = 9.51</td>
<td>&lt;.01</td>
<td>.18</td>
</tr>
<tr>
<td>A\textbeta42 in ng/L</td>
<td>—</td>
<td>876 ± 133</td>
<td>713 ± 222</td>
<td>424 ± 181</td>
<td>F(2, 70) = 38.57</td>
<td>&lt;.001</td>
<td>.52</td>
</tr>
<tr>
<td>t-tau in ng/L</td>
<td>—</td>
<td>265 ± 36</td>
<td>278 ± 33</td>
<td>542 ± 42</td>
<td>F(2, 72) = 16.13</td>
<td>&lt;.001</td>
<td>.31</td>
</tr>
<tr>
<td>p-tau in ng/L</td>
<td>—</td>
<td>52 ± 21</td>
<td>51 ± 23</td>
<td>76 ± 21</td>
<td>F(2, 68) = 11.80</td>
<td>&lt;.001</td>
<td>.26</td>
</tr>
</tbody>
</table>

**Note.** C = control; SCI = subjective cognitive impairment; MCI = mild cognitive impairment; AD = Alzheimer’s disease; MMSE = Mini-Mental Status Examination; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; ns = nonsignificant; Cornell = Cornell Depression Index; APOE = apolipoprotein E.
graphics), global cognition (assessed by the FSIQ), verbal ability (assessed by the WAIS–R Information and Similarities subtests), spatial function (assessed by the Block Design and Rey–Osterrieth copy), short-term memory ( Digit Span forward and backward), episodic memory (RAVL total learning, RAVL retention, and Rey–Osterrieth retention), and cognitive speed ( Digit Symbol and Trailmaking Tests A & B) are presented in Table 3. There was no significant effect on premorbid tests based on SLDT, ISW, and demographic data. However, in all of the other tests of current performance, except Digit Span forward, the groups differed significantly according to the one-way ANOVAs, which included FSIQ_{Hold}, FSIQ_{Best}, FSIQ, Information, Similarities, Block Design, Rey–Osterrieth copy, Digit Span backward, RAVL total learning, RAVL retention, Rey–Osterrieth retention, Digit Symbol, and Trailmaking Tests A and B. Scheffé post hoc t tests showed that AD patients performed more poorly than the other three groups in all tests except the MMSE, Similarities, and Rey–Osterrieth copy ( p < .05); that the MCI group performed more poorly than the SCI and C groups in RAVL learning and retention ( p < .05); and that the SCI and C groups did not differ in any test ( p > .1).

Comparison of Methods for the Assessment of Premorbid Function in the Prediction of Disease

Cognitive decline was calculated as the difference between an estimate of premorbid function (based on five methods) and current cognitive function. Both SLDT and ISW were used to assess premorbid cognitive function, and among the other commonly used methods (Lezak et al., 2004), the Information subtest in the WAIS–R was utilized as a Hold test, along with the Best current result in all tests, which was used in the current neuropsychological examination (maximum z score out of all 12 neuropsychological tests used). Moreover, a combination of demographic variables (a linear regression-based multiple correlation of age, gender, and years of education), based on previous data (Almkvist et al., 2007), was also used. The decline measure for the Hold and Best test methods was based on z-transformations of all of the test scores and was based on the same reference sample of carefully screened healthy individuals as that used for all of the tests (Bergman, Blomberg, & Almkvist, 2007; Bergman, Johansson, Lundberg, & Almkvist, 2008). All decline measures were expressed according to the FSIQ, which required transforming some of the z scores into FSIQ scores when necessary. The five measures of estimated cognitive decline are presented in Table 4. These measures differed significantly between groups according to the one-way ANOVAs on each measure (see Table 4). Scheffe’s post hoc t test demonstrated that the AD group differed significantly compared with the other three groups on the SLDT, the ISW, and demographic methods, as well as on the Hold method when compared with controls ( p < .05). No pairwise comparisons were significant for the Best test method ( p > .1). It is interesting that the mean cognitive decline was considerable for AD patients as verified by all five measures. In addition, four of five measures indicated close to zero decline.

Table 3
Neuropsychological Test Results for Healthy Controls as Well as SCI, MCI, and AD Patients

<table>
<thead>
<tr>
<th>Domain/test</th>
<th>C</th>
<th>SCI</th>
<th>MCI</th>
<th>AD</th>
<th>F</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ_{SLDT} score</td>
<td>98.8 ± 13.9</td>
<td>97.9 ± 12.2</td>
<td>99.5 ± 15.0</td>
<td>100.3 ± 12.7</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ_{Raw} score</td>
<td>103.5 ± 11.0</td>
<td>107.4 ± 6.5</td>
<td>105.7 ± 12.3</td>
<td>101.1 ± 9.8</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ_{Hold} test score</td>
<td>96.1 ± 16.9</td>
<td>101.7 ± 14.1</td>
<td>95.0 ± 16.2</td>
<td>82.6 ± 14.5</td>
<td>F(3, 104) = 8.88</td>
<td>&lt;.001</td>
<td>.20</td>
</tr>
<tr>
<td>FSIQ_{Best} test score</td>
<td>119.5 ± 11.3</td>
<td>120.1 ± 6.6</td>
<td>111.9 ± 11.9</td>
<td>100.9 ± 13.4</td>
<td>F(3, 104) = 18.28</td>
<td>&lt;.001</td>
<td>.34</td>
</tr>
<tr>
<td>FSIQ_{Demographics} score</td>
<td>100.4 ± 11.4</td>
<td>103.7 ± 8.3</td>
<td>105.3 ± 13.6</td>
<td>104.7 ± 11.3</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present global cognitive function</td>
<td>100.0 ± 17.3</td>
<td>99.1 ± 17.3</td>
<td>89.3 ± 22.1</td>
<td>72.4 ± 17.9</td>
<td>F(3, 101) = 13.53</td>
<td>&lt;.001</td>
<td>.28</td>
</tr>
<tr>
<td>Verbal (raw scores)</td>
<td>20.6 ± 4.7</td>
<td>22.2 ± 4.0</td>
<td>20.3 ± 4.6</td>
<td>16.8 ± 4.1</td>
<td>F(3, 104) = 8.88</td>
<td>&lt;.001</td>
<td>.20</td>
</tr>
<tr>
<td>Similarities</td>
<td>21.7 ± 4.9</td>
<td>21.3 ± 4.2</td>
<td>19.2 ± 4.6</td>
<td>16.8 ± 4.8</td>
<td>F(3, 106) = 8.86</td>
<td>&lt;.001</td>
<td>.16</td>
</tr>
<tr>
<td>Spatial (raw scores)</td>
<td>29.5 ± 8.1</td>
<td>29.5 ± 8.2</td>
<td>24.3 ± 10.8</td>
<td>12.9 ± 8.7</td>
<td>F(3, 105) = 22.84</td>
<td>&lt;.001</td>
<td>.39</td>
</tr>
<tr>
<td>Block Design</td>
<td>34.3 ± 2.5</td>
<td>33.5 ± 3.0</td>
<td>31.7 ± 6.3</td>
<td>28.0 ± 9.0</td>
<td>F(3, 83) = 3.56</td>
<td>&lt;.05</td>
<td>.11</td>
</tr>
<tr>
<td>Rey–Osterrieth copy</td>
<td>6.4 ± 1.8</td>
<td>6.0 ± 1.1</td>
<td>6.0 ± 1.1</td>
<td>5.5 ± 1.3</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term memory (raw scores)</td>
<td>5.8 ± 1.3</td>
<td>5.2 ± 1.0</td>
<td>4.5 ± 1.3</td>
<td>3.6 ± 1.0</td>
<td>F(3, 105) = 16.75</td>
<td>&lt;.001</td>
<td>.32</td>
</tr>
<tr>
<td>Digits backward</td>
<td>52.1 ± 7.3</td>
<td>48.7 ± 7.5</td>
<td>38.3 ± 11.0</td>
<td>30.5 ± 11.2</td>
<td>F(3, 100) = 25.51</td>
<td>&lt;.001</td>
<td>.43</td>
</tr>
<tr>
<td>RAVL retention</td>
<td>10.9 ± 2.5</td>
<td>10.4 ± 3.3</td>
<td>7.6 ± 3.6</td>
<td>3.7 ± 2.9</td>
<td>F(3, 100) = 30.46</td>
<td>&lt;.001</td>
<td>.47</td>
</tr>
<tr>
<td>Rey–Osterrieth retention</td>
<td>19.3 ± 11.7</td>
<td>19.1 ± 5.3</td>
<td>12.6 ± 6.9</td>
<td>4.9 ± 4.9</td>
<td>F(3, 83) = 31.12</td>
<td>&lt;.001</td>
<td>.52</td>
</tr>
<tr>
<td>Cognitive speed</td>
<td>50.4 ± 11.7</td>
<td>44.8 ± 8.9</td>
<td>36.0 ± 15.8</td>
<td>24.7 ± 15.7</td>
<td>F(3, 103) = 17.82</td>
<td>&lt;.001</td>
<td>.34</td>
</tr>
<tr>
<td>TMT A, in seconds</td>
<td>31.6 ± 14.7</td>
<td>35.4 ± 9.8</td>
<td>51.4 ± 27.0</td>
<td>94.4 ± 69.5</td>
<td>F(3, 102) = 22.84</td>
<td>&lt;.001</td>
<td>.27</td>
</tr>
<tr>
<td>TMT B, in seconds</td>
<td>83.6 ± 30.2</td>
<td>84.1 ± 24.1</td>
<td>121 ± 71</td>
<td>196 ± 86</td>
<td>F(3, 99) = 19.45</td>
<td>&lt;.001</td>
<td>.37</td>
</tr>
</tbody>
</table>

Note. C = control; SCI = subjective cognitive impairment; MCI = mild cognitive impairment; AD = Alzheimer’s disease; FSIQ = Full Scale IQ test of the Wechsler Adult Intelligence Scale—Revised; ns = nonsignificant; SLDT = Swedish Lexical Decision Test; ISW = Irregularly Spelled Words test; RAVL = Rey Auditory Verbal Learning test; TMT A and B = Trailmaking Tests A and B.
for the control group. The exception was the Best test method, which showed relatively little variation between groups in estimated cognitive decline. Strangely enough, the Best test method resulted in an estimated considerable decline also in the control group, which most probably is false.

In Table 5, the Pearson correlation coefficients for the cognitive decline and present status (clinical features, APOE gene dose, and markers of neuronal degeneration) of the patients are presented. Cognitive decline based on both the SLDT and ISW was clearly associated with the MMSE, a screening measure cognitive function, in such a way that the larger the decline was, the lower the MMSE score was. The size of the correlation coefficient was larger both for SLDT- and ISW-based methods versus MMSE compared with those of the other methods using z tests with a Fisher transformation of the correlation coefficients

\[ z = 1.86, r_p < .05; z = 2.29, r_p < .01; z = 3.57, r_p < .001; \text{Hold, Best current test and Demographics, respectively}. \]

Also, the correlation between ISW and Aβ42 was larger compared to those of the other methods, although it did not reach statistical significance, a scatterplot showing the estimated decline in FSIQ, based on SLDT’s relation to beta-amyloid, is presented in Figure 1. The SLDT was also significantly correlated to other markers of disease besides the MMSE and Aβ42; that is, IQCODE, ApoE gene dose, t-tau; and p-tau, respectively. A second observation was that the predictive power of the three other methods (Hold test, Best current test, and demographics) was comparable and that they were associated with the MMSE and Aβ42, but not significantly with the other markers of disease. The fourth observation was that the demographic variables were of minor importance, as was demonstrated by the weak but significant correlations found between gender and APOE and between age and Aβ42. Finally, it was evident that depression, as evaluated by the Cornell test, could not be predicted by any of the methods (ps > .1).

**Comparison of Cognitive Decline and Current Cognitive Status in the Prediction of Disease**

The correlation between current cognitive function, as evaluated by the FSIQ, and present status was significant for the MMSE (r = .32, p < .001).

### Table 4

<table>
<thead>
<tr>
<th>Basis of premorbid function</th>
<th>C</th>
<th>SCI</th>
<th>MCI</th>
<th>AD</th>
<th>F</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLDT</td>
<td>-1.2</td>
<td>-1.1</td>
<td>10.2</td>
<td>27.3</td>
<td>6.73</td>
<td>&lt;.001</td>
<td>.46</td>
</tr>
<tr>
<td>ISW</td>
<td>4.6</td>
<td>8.2</td>
<td>11.3</td>
<td>29.8</td>
<td>5.30</td>
<td>&lt;.001</td>
<td>.46</td>
</tr>
<tr>
<td>Hold test</td>
<td>-3.9</td>
<td>2.1</td>
<td>5.6</td>
<td>10.2</td>
<td>4.94</td>
<td>&lt;.01</td>
<td>.13</td>
</tr>
<tr>
<td>Best test</td>
<td>19.5</td>
<td>21.1</td>
<td>23.1</td>
<td>29.1</td>
<td>3.14</td>
<td>&lt;.05</td>
<td>.09</td>
</tr>
<tr>
<td>Demographics</td>
<td>0.4</td>
<td>3.8</td>
<td>15.6</td>
<td>32.7</td>
<td>24.00</td>
<td>&lt;.001</td>
<td>.42</td>
</tr>
</tbody>
</table>

Note. C = control; SCI = subjective cognitive impairment; MCI = mild cognitive impairment; AD = Alzheimer’s disease; SLDT = Swedish Lexical Decision Test; ISW = Irregularly Spelled Words test.

### Table 5

<table>
<thead>
<tr>
<th>Variables used to assess cognitive decline (premorbid – current FSIQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td>MMSE (raw score)</td>
</tr>
<tr>
<td>IQCODE</td>
</tr>
<tr>
<td>Cornell</td>
</tr>
<tr>
<td>APOE, e4 dose</td>
</tr>
<tr>
<td>Aβ42, ng/L</td>
</tr>
<tr>
<td>t-tau, ng/L</td>
</tr>
<tr>
<td>p-tau, ng/L</td>
</tr>
</tbody>
</table>

Note. FSIQ = Full Scale IQ test of the Wechsler Adult Intelligence Scale—Revised; SLDT = Swedish Lexical Decision Test; ISW = Irregularly Spelled Words test; MMSE = Mini-Mental Status Examination; ns = nonsignificant; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; Cornell = Cornell Depression Index; APOE = apolipoprotein E.

* p < .05. ** p < .01. *** p < .001.
Discussion

A heterogeneous sample of patients at a memory clinic was studied with regard to the relation between premorbid function and various indices of disease, specifically the clinical, genetic, and biological markers of the disease process in AD. There are several main findings in the present study.

To begin with, patient groups demonstrated a typical pattern of results with regard to global cognitive function (MMSE) as well as APOE gene dose and biomarker values (Aβ42, t-tau, and p-tau). They also followed a pattern that was in accordance with the typical advancement of degenerative disease, starting with the C group followed by the SCI and MCI groups and finally ending in mild AD. However, symptom load (IQCODE) was found to be comparable in the three patient groups, whereas depressive symptoms, as assessed by the Cornell test, were more frequent in the SCI group than in the other two patient groups. This pattern of symptoms indicates a simple dissociation between type of symptoms and patient group, demonstrating that SCI patients tend to be concerned with emotions and cognitive status despite the lack of objective signs of cognitive dysfunction, whereas objectively impaired patients show this pattern of reactions to a lesser degree. Similar observations have been reported in previous research (Kliegel et al., 2005), and this finding has clinical implications for how decisions are made regarding the various diagnostic entities.

The estimated premorbid function, based on the SLDT, the ISW, and demographics, did not differ between groups. This result lends support to the use of both the SLDT and the ISW in clinical examinations of patients with degenerative disease, at least in cases involving mild dementia. This type of finding has been reported in previous research in which the NART and equivalent tests were used (Maddrey, Cullum, Weiner, & Filley, 1996; O’Carroll, Balke, & Whittick, 1987; Paque & Warrington, 1995), although the opposite results have also been reported (Cockburn, Keene, Hope, & Smith, 2000). It is worth noting that the Hold method, as measured by Information in the WAIS–R, and the method of the Best test result did not work as expected or as suggested by the textbooks (Lezak et al., 2004).

It was also clearly demonstrated that the outcomes of the majority of the cognitive tests consistently varied in accordance with what would be expected over the course of the degenerative disease. It is interesting that this was true for the verbal tests that put demands on explicit semantic knowledge, such as the Information and Similarities section of the WAIS–R, and not the case with the SLDT and ISW, which are based on stable implicit verbal knowledge. This point concerns the various types of knowledge, which can be seen as spanning across a spectrum from explicit comprehension to implicit recognition and performance of speech. The specific nature of patients’ verbal ability appears to be of crucial importance when stability or change occurs during the development of dementia (cf. Paque & Warrington, 1995).

Fourth and most important, the SLDT and ISW were shown to have an advantage over the other methods of assessing premorbid
function (i.e., the Hold test, the Best current test, and demographics) with respect to the various markers of disease, as was particularly evident in the associations with the MMSE and Aβ42 and verified by the pattern of shared variance. The same pattern of SLDT-based advantage was observed regarding bivariate correlation coefficients ($\eta^2$) and the determination coefficient ($r^2$) in multiple regression analyses. The other methods, on the other hand, seemed to have a comparable predictive power with regard to the various markers of disease. Despite the fact that the SLDT and ISW were significantly related to various criteria, it has to be recognized that the degree of common variance is far from optimal. At most, the ISW and MMSE share 48% of the variance, and the SLDT and Aβ42 MMSE share only 35% of the total variance. This fact should be kept in mind. Nevertheless, these proportions of common variance for tests of premorbid function are in good agreement with other findings (cf. Berry et al., 1994; Crawford et al., 2001; Nelson & O’Connell, 1978; Watt & O’Carroll, 1999).

The most frequently used methods (e.g., the Hold test) have a long history (e.g., see Lehrl, Triebig, & Fischer, 1995; Yates, 1956). The current Best performance test has relatively recently been suggested as an alternative method for premorbid assessment that is not based on verbal tests only. In future research, other cognitive domains should be investigated to facilitate the development of other potential nonverbal tests of premorbid function. Finally, it has to be pointed out that the Best test method appeared to result in false estimates of cognitive decline in the control group, as well as an underestimated decline in clinical groups, which may disqualify this method for future applications.

It is also noteworthy that the degree of depressive symptoms could not be predicted with any of the methods investigated in the present study. The absence of this significant relationship may be due to these symptoms having a cause other than the cognitive symptoms.

Finally, it should also be stressed that decline of cognitive function has been compared here with the present status of cognitive function in terms of a biological marker of the disease process. This aspect is important to take into account when evaluating the results of this study. It is interesting to note that the association was most marked for Aβ42, which is supposed to relate to senile plaques, a neuropathological hallmark of AD. However, according to previous research, the number of senile plaques is less strongly associated with cognitive function than is the number of neurofibrillary tangles, the second neuropathological hallmark of AD (Arriagada, Growdon, Hedley-White, & Hyman, 1992), which is indicated in CSF by t-tau and p-tau. The reason for this paradoxical finding is not known.

It is interesting to speculate how lexical decisions and correct pronunciations are apparently possible even when patients are affected by the disease, considering that, in AD, the medial temporal cortices and posterior association areas are affected. Our interpretation is that there may be various routes involved in executing lexical decisions, as has been postulated in previous research (Ellis & Young, 1988; Gerhand, 2001), and that such routes rely on various processes and components of brain networks. This implies that no single brain area is necessary for lexical decisions. However, the specific coupling between the brain networks involved in reading/pronunciation (as assessed by the ISW) and lexical decision (as assessed by the SLDT) has to be further investigated.

A limitation of the present study pertains to the selection procedure, which lacks statistical strictness because it relied on a hospital-based sample of patients. However, validity has at least two faces (Kausler, 1991); the present study may still have clinical relevance (internal validity), despite having uncertain population relevance (external validity). Nonetheless, a cross-validation of these findings would be desirable for reaching a final conclusion regarding prediction.

Another critical point relates to the fact that the assessment of current cognitive function was assessed with five subtests of the WAIS–R. The relation between this shortened assessment of the FSIQ and the full assessment based on all 11 subtests of the WAIS–R has to be considered. However, short forms have been shown to have good psychometric properties in terms of their reliability and validity, compared with the complete forms, particularly when a reasonable number of subtests are used (Crawford, Allan, & Jack, 1992; Kulas & Axelrod, 2002; Ward & Ryan, 1996). Commonly, the set of subtests include Information, Similarities, Block Design, and Digit Symbol. In the present study, we have utilized these four WAIS–R subtests, as well as the Digit Span subtest, which lends support to the relevance of the method used in this study as a means to estimate FSIQ.

In conclusion, the present study has demonstrated that the SLDT and the ISW are able to predict premorbid cognitive function and decline in patients at various stages of AD development as assessed by clinical features and biomarkers of neurodegeneration.

References


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