Chapter 2

Cognitive Functioning and the Natural Course of Depressive Symptoms in Late Life


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ABSTRACT

Objectives
To investigate whether specific domains of cognitive functioning predict the natural course of depressive symptoms in older people.

Design and Participants
Using the nationally representative, population-based cohort of the Longitudinal Aging Study Amsterdam (LASA), 281 participants with clinically relevant depressive symptoms (Center for Epidemiologic Studies Depression Scale (CES-D) ≥16) age 55 and older were followed longitudinally during a period of six years.

Measurements
Using a maximum of 14 successive CES-D observations, three clinical course types of depressive symptoms were defined. At baseline general cognitive functioning was assessed using the Mini Mental State Exam (MMSE), memory performance (immediate recall and retention) by means of the Auditory Verbal Learning Test (AVLT) and processing speed by means of a timed coding task.

Results
Remission, fluctuating course and chronic course were seen in 22%, 50% and 28% respectively. In univariate analyses, a slowed processing speed was associated with a chronic course of depressive symptoms, as compared with remission (mean 21.5 (SD 6.6), versus mean 24.6 (SD 6.8), t=2.78, df 139, p<0.001). Using multivariate regression techniques, this association remained significant after correcting for potential confounders and a number of risk factors for vascular brain damage (OR 1.08, 95% C.I. 1.01 – 1.14). Global cognitive functioning nor memory performance were associated with any course type of depressive symptoms.

Conclusion
We found an independent association of a slowed processing speed with a poor natural course of depressive symptoms in older people. In clinical practice, when dealing with an older depressed person with comorbid cognitive decline, processing speed might be a more useful tool than the MMSE in predicting the prognosis.
INTRODUCTION

Depression is common in late life with prevalence rates for major depression and subthreshold depression of 1 to 4% and 8 to 16% in community samples respectively.\(^1\) The association of late life depression with functional decline, diminished well being, morbidity and mortality makes it a most relevant disease when caring for older people. Moreover, prognosis of depression is worse in older people when compared with adults, with a chronic course in more than 50%\(^2,3\) as opposed to 10 to 30% in adults.\(^4\) A worse prognosis might be explained by a higher prevalence of known risk factors for chronicity in older people, such as bereavement,\(^5\) social isolation\(^6\) and functional limitations.\(^7\) Additionally, specific age-related pathology, such as cognitive decline might account for the poorer prognosis. Prevalence rates of co-morbid depressions are high in patients with Mild Cognitive Impairment (MCI),\(^8\) Alzheimer disease\(^9\) and stroke.\(^10\) Moreover, late life depression has been shown to be associated with vascular brain damage.\(^11\) Therefore, cognitive decline may be an important candidate factor contributing to a specific course type of late life depression. When interpreting the association between cognitive impairment and depression, it might be important to distinguish different domains of cognition, since impairments in any of these could have a differential impact on the course of late life depression.

Recently a number of studies was published addressing the association of cognitive functioning and treatment response of depression in old age and these treatment studies show conflicting results.\(^12-15\) However, knowledge about the role of cognitive functioning in relation to the natural course of depression in old age is essential. Studies addressing this association are rare and inconclusive.\(^16-19\)

Studies investigating the course of depression use a limited number of follow-up measurements, varying from one,\(^17,18\) two\(^19\) to a maximum of four.\(^16\) When investigating the course of depression, a detailed assessment with frequent follow-up measurements is essential, since otherwise remissions might be missed and chronicity might be overestimated.\(^2,4\) To our knowledge, there are no prospective population based studies with frequent follow-up measurements investigating the association of the natural course of depressive symptoms in late life with cognitive functioning.

In the present community-based study, the natural history of depressive symptoms was prospectively assessed during a long interval (6 years), using 14 observations, as described previously.\(^3\) It was hypothesized that worse cognitive functioning is associated with chronicity of depressive symptoms in late life. More specifically, the following questions were addressed: (1) are specific domains of cognitive functioning associated
with a chronic course of depressive symptoms and if this appears to be so, (2) is this association independent from potential confounding factors and (3) is this association mediated by risk factors for vascular brain damage or CVA, since these might play an etiological role in late life depression.

**METHODS**

**Sampling and study design**

Data for this study were collected in the Longitudinal Aging Study Amsterdam (LASA), an ongoing study on predictors and consequences of changes in autonomy and well-being in the aging population in the Netherlands. A large representative sample of community living older persons (aged 55-85 years) was interviewed at baseline in 1992-1993. The sample was stratified for age and sex. A total of 3107 respondents (response 82%) took part in the LASA study and were interviewed face to face every three years. Non-response was associated with higher age (mean 72.4, SD 8.5 versus mean 70.1, SD 8.8, Students’ t-test, t=6.31, df 3803, p<0.001) but not with sex. For the present study, informed consent was obtained before the study, in accordance with legal requirements in the Netherlands; the study was approved by the Medical Ethical committee of the VU University Medical Centre.

To define a study sample, respondents had to have clinically relevant depressive symptoms (a score of ≥16 points on the Center for Epidemiological Studies Depression Scale (CES-D)) at baseline with complete depressive symptom data on at least two follow-up measurements and there had to be information about cognitive function at baseline. Four hundred forty eight respondents scored above the cut-off score of ≥16 points on the CES-D at baseline. This cohort was followed up with postal questionnaires every 5 months during a period of 6 years. This procedure resulted in a maximum of 14 observations covering 6 years. The minimum criterion of at least two follow-up observations after baseline reduced the sample from 448 to 309 respondents. The criterion of complete assessment of extensive cognitive function at baseline further reduced the sample to 281 respondents (63% of the original 448 depressed respondents). Compared with the 448 depressed respondents at baseline, the 281 respondents eligible for this study were younger (mean 71.5, SD 8.0 versus mean 74.9, SD 8.8, t=4.052, df 466, p<0.001) and had a slightly better Mini Mental State Exam (MMSE) score at baseline (median 27, interquartile range (IQR) 24-28 versus median 27, IQR 25-29, Mann-Whitney z=-5.105, p<0.001). Gender, number of chronic diseases and CES-D score at baseline did not differ ($\chi^2=1.605, df=1, p=0.205, t=1.611, df=443, p=0.108$ and Mann-Whitney z=-1.154, p=0.244, respectively).
Measurements

**Depressive symptoms**

Depressive symptoms were measured using a self-report rating scale (CES-D). The CES-D is a 20-item scale, developed to measure depressive symptoms in the community. It has been widely used in older community samples and has good psychometric properties in this age group, with similar psychometric properties for the Dutch translation. The total score on the CES-D ranges between 0 and 60. To identify those with clinically relevant levels of symptoms, the generally used cut-off score of 16 or more was used. Using this cut-off score, the criterion validity of the CES-D for major depressive disorder (MDD) was excellent (sensitivity, 100%; and specificity, 88%) and the reliability was high (Cronbach’s $\alpha=0.87$). Data were gathered in face-to-face interviews every three years while the additional five monthly follow-up assessments were collected using postal questionnaires. A mode effect was transformed as described previously.

**Course of depressive symptoms**

Using successive CES-D observations, three clinical course types of depressive symptoms were defined. The course types distinguished were remission, fluctuating course and chronic course. A remission was defined as a combination of a relevant (described below) decline of symptoms and the respondent remaining symptom free (CES-D score of <16) throughout the rest of the study. A fluctuating course was defined as a remission in which the respondent had a relevant increase of symptoms (CES-D $\geq$ 16) later on in the study. A chronic course was defined as 80% or more depressed observations (CES-D $\geq$ 16). Relevant change was defined as a change of 5 points or more between measurements on the CES-D, which is derived from the standard deviation of the CES-D and thereby crossing the cut-off score of 16. Characteristics for the three course type groups are shown in Table 1. The number of valid observations was similar for those who experienced a remission (mean 8.4, SD 4.4) and a chronic course (mean 8.2, SD 4.0; $t$=0.222, df=139, $p=0.825$). Those with a fluctuating course had more valid observations (mean 11.1, SD 3.5, $t$=-4.397, df=97.9, $p<0.001$, compared to remission group, Table 1).

**Cognitive Measures**

General cognitive functioning was measured using the MMSE, a screening instrument for global cognitive function. Memory function was measured by means of an adapted version of the Dutch Auditory Verbal Learning Test (AVLT). This test consists of 15 words, which have to be learned during three trials. After every trial the respondent is directly asked to recall as many words as possible. After a distraction
period of 20 min, respondents are asked to name any words they can remember. The total number of words reproduced during the three trials served as the immediate recall score, range 0 to 45. The number of words reproduced after 20 minutes served as the delayed recall score, range 0 to 15. The ratio of the maximum number of words at one of the trials at immediate recall and delayed recall is defined as the retention score. This reflects the percentage of words which respondents still remember compared to the learning phase. A higher score on immediate recall and retention indicates a better memory performance. Information processing speed was measured by means of an adjusted version of the coding task. This is a timed task, in which the respondent has to combine as many characters as possible, according to a given example. The example shows 15 combinations of two characters in a row of double boxes (the substitution key). The test itself shows rows of double boxes in which only the upper boxes contain characters and the lower boxes are empty. The respondent has to name the missing characters corresponding to the characters in the upper boxes (using the substitution key) as quickly as possible. The task consists of three identical one-minute trials. The score on each trial consists of the number of completed characters. The result of the best (fastest) trial was used in the present study.

Covariates

Potential confounders

Potential confounding variables included age, gender, educational level (primary versus more than 6 years), household composition (living alone versus not alone), smoking (never, former, current), number of chronic diseases (COPD, heart disease, arterial disease, DM, stroke, incontinence, arthrosis or rheumatoid arthritis, cancer, other, by self-report), use of benzodiazepines, antidepressants, β-blockers, calcium-antagonists and CES-D score at baseline.

Potential explanatory factors

Cardiac disease (ischemic heart disease, arrhythmia, congestive heart failure), cerebrovascular incidents (CVA) and diabetes mellitus (type I and II) were assessed combining self-report data and the ascertainment by medical records or medication use in an algorithm described previously. Hypertension was considered present when one of two criteria were met: (1) treatment for hypertension (self-report) or (2) a diastolic tension > 90 mm Hg or a systolic tension > 140 mm Hg (mean of three measurements in sitting position).
Statistical analyses

Differences in percentages and means of cognitive tests and covariates between the three clinical course types of depression were tested using Chi-square statistics for dichotomous and categorical variables, Students’ t-test for normally distributed continuous variables and Mann Whitney U test for not normally distributed continuous variables, with “remission” as reference category. Using ANOVA with Bonferroni post hoc comparisons, differences in means of cognitive tests between all three clinical course types of depressive symptoms were tested. Because MMSE scores had a skewed distribution, we computed the MMSE score into a reverse score and applied natural log transformation: ln(31-MMSE score), to obtain a normal distribution. Using multinominal regression models with “remission” or “chronic” as reference category, the association of the cognitive tests with depressive symptom course types was studied after successive adjustment for potential confounders (sociodemographics, smoking, number of chronic diseases, medication, CES-D score at baseline) and potential explanatory variables (risk factors for cerebrovascular disease and CVA); these associations were considered statistically significant at p<0.05. To rule out possible interaction between cognitive measures and sex, age or the presence of risk factors of cerebrovascular disease (heart disease, diabetes, hypertension) and CVA in predicting depressive symptom course type, product terms between relevant cognitive measures and covariates were tested; possible interactions were considered statistically significant at p<0.1. In all other analyses, conventional levels of statistical significance (p<0.05) were used. All analyses were performed using SPSS for Windows (version 15.0).

RESULTS

The sample included 281 respondents (96 men and 185 women) with a mean age of 71.5 years (SD 8.8 years). For the whole sample, the median MMSE score at baseline was 27 (IQR 25-29). Means of immediate recall score, retention score and the coding task at baseline were 17.8 (SD 6.3), 62.2 (SD 25.5) and 24.4 (SD 7.1), respectively. The median CES-D score at baseline was 21 (IQR 17-25).
Table 1. Characteristics of Three Depression Course Type Subgroups.

<table>
<thead>
<tr>
<th></th>
<th>Remission N = 63</th>
<th>Fluctuating N = 140</th>
<th>t or z</th>
<th>df (Fluctuating vs Remission)</th>
<th>p</th>
<th>Chronic N = 78</th>
<th>t or z</th>
<th>df (Chronic vs Remission)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of valid observations</td>
<td>8.4 (4.4)</td>
<td>11.1 (3.5)</td>
<td>-4.397</td>
<td>97.9</td>
<td>&lt;0.001</td>
<td>8.2 (4.0)</td>
<td>0.222</td>
<td>139</td>
<td>0.83</td>
</tr>
<tr>
<td>CES-D* at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of observations with CES-D≥ 16 of index episode</td>
<td>1 [1-1]*</td>
<td>1 [1-2]*</td>
<td>-2.027</td>
<td>0.04</td>
<td></td>
<td>6 [3-8]*</td>
<td>-9.180</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>% observations with CES-D ≥ 16 during 6 years follow-up</td>
<td>25.6 (19.1)</td>
<td>46.3 (18.5)</td>
<td>-7.289</td>
<td>201</td>
<td>&lt;0.001</td>
<td>94.8 (6.9)</td>
<td>-27.43</td>
<td>75</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean (SD) or median [IQR] * is given, p-values derived from Student’s T test and Mann-Whitney U test, with “Remission” as reference category.

* CES-D: Center for Epidemiological Studies Depression Scale
Respondents had a mean of 9.7 (SD 4.1) CES-D measurements during the course of the study. Using the successive CES-D observations, remission, fluctuating- and chronic course of depressive symptoms was seen in 22%, 50% and 28% respectively. The depressive symptom characteristics for these three course type groups differed; during the six year follow-up the percentage of observations with a CES-D score of ≥ 16 was 25.6% (SD 19.1%), 46.3% (SD 18.5%) and 94.8% (SD 6.9%) for the remission, fluctuating- and chronic course group respectively (t=-7.289, df=201, p< 0.001 for fluctuating- and chronic course compared to remission, see Table 1). Also, compared to the remission group, respondents with a chronic course had a higher CES-D score at baseline, indicative of more severe depressive symptoms. Finally, the chronic course group showed the longest index depressive episode with the greatest number of successive CES-D observations above the cut-off score (median 6 (IQR 3-8 CES-D ≥ 16 observations compared to 1 (IQR 1-1) in the remission group, Mann-Whitney z=-9.180, p<0.001, see also Table 1).

Clinical and demographic differences across the three depressive symptom course types are presented in Table 2, with remission as reference category. Respondents with a fluctuating course were more often female ($\chi^2=4.454$, df=1, p=0.04). The number of chronic diseases was not associated with any of the three depressive symptom course types. Antidepressant use was low in the whole sample and this was not different for the three course types (Table 2).

In table 3 differences in cognitive tasks for the three course types are shown, with remission as reference category. Respondents with a chronic course had a lower score on the coding task (t=2.781, df=139, p<0.01). A higher score on the MMSE was borderline significantly associated with a fluctuating course (z=-1.74, p=0.052). After correcting for potential confounders (age, gender, educational level), this borderline significance disappeared (OR 1.09, 95% C.I. 0.96 – 1.24).

Table 4 shows the univariate and multivariate regression analyses of the coding task; a lower score on the coding task (indicative of worse performance) was significantly associated with a chronic course of depressive symptoms, as compared with remission (OR 1.06, 95% C.I. 1.02 – 1.12); a one point decrease on the coding task gives a 6% higher odds of developing a chronic course as compared to remission. When correcting for potential confounders (age, gender, educational level, CES-D score at baseline) the OR for an association between the coding task and a chronic course of depressive symptoms remained significant (OR 1.08, 95% C.I. 1.01 – 1.14, Table 4).
<table>
<thead>
<tr>
<th></th>
<th>Remission (ref. group) N = 63</th>
<th>Fluctuating N = 140</th>
<th>t or $\chi^2$ df</th>
<th>p-value (Fluctuating vs Remission)</th>
<th>Chronic N = 78</th>
<th>t or $\chi^2$ df</th>
<th>p-value (Chronic vs Remission)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ‘years’</td>
<td>71.1 (8.6)</td>
<td>70.6 (9.1)</td>
<td>0.43</td>
<td>201</td>
<td>73.4 (8.0)</td>
<td>-1.64</td>
<td>139</td>
</tr>
<tr>
<td>Female</td>
<td>54 (34/63)</td>
<td>69 (97/140)</td>
<td>4.45</td>
<td>1</td>
<td>69 (54/78)</td>
<td>3.46</td>
<td>1</td>
</tr>
<tr>
<td>Low Education</td>
<td>52 (33/63)</td>
<td>47 (66/140)</td>
<td>0.48</td>
<td>1</td>
<td>59 (46/78)</td>
<td>0.62</td>
<td>1</td>
</tr>
<tr>
<td>Living Together</td>
<td>43 (27/63)</td>
<td>46 (65/140)</td>
<td>0.22</td>
<td>1</td>
<td>37 (29/78)</td>
<td>0.47</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Illnesses</td>
<td>1.6 (1.3)</td>
<td>1.3 (1.0)</td>
<td>1.35</td>
<td>95</td>
<td>1.8 (1.3)</td>
<td>-0.77</td>
<td>138</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>33 (21/63)</td>
<td>25 (35/140)</td>
<td>1.51</td>
<td>1</td>
<td>36 (28/78)</td>
<td>0.10</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (7/63)</td>
<td>7 (10/140)</td>
<td>1.71</td>
<td>1</td>
<td>4 (3/78)</td>
<td>1.73</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (22/63)</td>
<td>27 (37/136)</td>
<td>1.23</td>
<td>1</td>
<td>31 (23/75)</td>
<td>0.28</td>
<td>1</td>
</tr>
<tr>
<td>CVA</td>
<td>8 (5/62)</td>
<td>12 (16/139)</td>
<td>0.54</td>
<td>1</td>
<td>9 (7/78)</td>
<td>0.04</td>
<td>1</td>
</tr>
<tr>
<td>Smoking, never/former/current</td>
<td>43 (27/63)</td>
<td>48 (67/140)</td>
<td>1.03</td>
<td>2</td>
<td>45 (35/78)</td>
<td>0.76</td>
<td>2</td>
</tr>
<tr>
<td>Benzodiazepine Use</td>
<td>29 (18/63)</td>
<td>20 (28/140)</td>
<td>1.82</td>
<td>1</td>
<td>41 (32/78)</td>
<td>2.36</td>
<td>1</td>
</tr>
<tr>
<td>Antidepressant Use</td>
<td>3 (2/63)</td>
<td>6 (9/140)</td>
<td>0.90</td>
<td>1</td>
<td>5 (4/78)</td>
<td>0.33</td>
<td>1</td>
</tr>
<tr>
<td>β-blockade use</td>
<td>19 (12/63)</td>
<td>18 (25/140)</td>
<td>0.04</td>
<td>1</td>
<td>22 (17/78)</td>
<td>0.16</td>
<td>1</td>
</tr>
<tr>
<td>Ca-antagonist use</td>
<td>11 (7/63)</td>
<td>9 (13/140)</td>
<td>0.16</td>
<td>1</td>
<td>14 (11/78)</td>
<td>0.28</td>
<td>1</td>
</tr>
</tbody>
</table>

Mean (SD) or column percentages (raw ratio’s) are given; differences between the three clinical course types of depressive symptoms were tested using Students’ t-test for continuous variables and Chi-square statistics for dichotomous and categorical variables, with "Remission" as reference category.
Table 3. Results of Cognitive Tests for Each Depressive Symptom Course Type of the Study Sample (N = 281).

<table>
<thead>
<tr>
<th></th>
<th>Remission (ref. group)</th>
<th>Fluctuating</th>
<th>t or z</th>
<th>df</th>
<th>p-value (Fluctuating vs Remission)</th>
<th>Chronic</th>
<th>t or z</th>
<th>df</th>
<th>p-value (Chronic vs Remission)</th>
<th>Age- and education-equated normative group (CES-D&lt;16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>27 [25-29] *</td>
<td>28 [26-29] *</td>
<td>-1.94</td>
<td>28</td>
<td>0.05</td>
<td>27 [24-28] *</td>
<td>-0.69</td>
<td>139</td>
<td>0.49</td>
<td>28 [26-29] *</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>16.9 (6.1)</td>
<td>18.6 (6.4)</td>
<td>-1.77</td>
<td>201</td>
<td>0.08</td>
<td>16.8 (5.9)</td>
<td>0.12</td>
<td>139</td>
<td>0.91</td>
<td>18.1 (6.2)</td>
</tr>
<tr>
<td>Retention score</td>
<td>61.2 (24.4)</td>
<td>64.0 (26.6)</td>
<td>-0.72</td>
<td>201</td>
<td>0.47</td>
<td>59.6 (24.3)</td>
<td>0.38</td>
<td>139</td>
<td>0.71</td>
<td>60.6 (26.3)</td>
</tr>
<tr>
<td>Coding task</td>
<td>24.6 (6.8)</td>
<td>25.9 (7.1)</td>
<td>-1.19</td>
<td>201</td>
<td>0.24</td>
<td>21.5 (6.6)</td>
<td>2.78</td>
<td>139</td>
<td>&lt;0.001</td>
<td>25.4 (7.6)</td>
</tr>
</tbody>
</table>

Means (SD) or median [IQR] * are shown; differences between the three clinical course types of depressive symptoms were tested using Mann Whitney U test for MMSE and Students’ t-test for the other cognitive tests, with “Remission” as reference category. Last column shows scores of the cognitive measures of an age- and education-equated normative group of LASA respondents at baseline without depressive symptoms. * MMSE: Mini mental State Exam
When excluding those respondents from the studied population with a MMSE score below the cut-off point for significant cognitive decline, (MMSE<24, thereby reducing the sample from 281 to 243 respondents), the association between a slowed processing speed and chronicity of depressive symptoms remains significant in the full multinomial model (OR 1.07, 95% C.I. 1.00 – 1.15).

In order to test whether the association between the coding task and a chronic course is explained by risk factors for vascular brain damage or CVA, these potential explanatory variables were entered into the model. The OR did not change and remained significant (OR 1.08, 95% C.I. 1.01 – 1.14; Table 4). To rule out possible interaction by gender, age and risk factors for vascular brain disease and CVA, product terms between coding task scores and these covariates were entered in the regression models. No interactions were found (data not shown).

**Table 4.** Odds Ratios (with 95% confidence interval) of Coding Task on Course Type of Depression, Given One Point Increase in Coding Task.

<table>
<thead>
<tr>
<th></th>
<th>Fluctuating course vs. Remission §</th>
<th>Chronic course vs. Remission §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coding Task</td>
<td>0.97 (0.94–1.02)</td>
<td>1.06 (1.02–1.12)‡</td>
</tr>
<tr>
<td>+ Age</td>
<td>0.97 (0.93–1.02)</td>
<td>1.06 (1.01–1.12)‡</td>
</tr>
<tr>
<td>+ Gender</td>
<td>0.97 (0.93–1.02)</td>
<td>1.06 (1.01–1.12)‡</td>
</tr>
<tr>
<td>+ Educational Level</td>
<td>0.98 (0.94–1.03)</td>
<td>1.07 (1.01–1.14)‡</td>
</tr>
<tr>
<td>+ CES-D at Baseline</td>
<td>0.98 (0.94–1.04)</td>
<td>1.07 (1.01–1.14)‡</td>
</tr>
<tr>
<td>+ Cardiac Disease</td>
<td>0.98 (0.94–1.04)</td>
<td>1.07 (1.01–1.14)‡</td>
</tr>
<tr>
<td>+ DM</td>
<td>0.98 (0.94–1.04)</td>
<td>1.08 (1.01–1.15)‡</td>
</tr>
<tr>
<td>+ Hypertension</td>
<td>0.99 (0.94–1.05)</td>
<td>1.08 (1.01–1.15)‡</td>
</tr>
<tr>
<td>+ CVA</td>
<td>0.99 (0.93–1.04)</td>
<td>1.08 (1.01–1.15)‡</td>
</tr>
</tbody>
</table>

§Odds ratio’s derived from multinomial regression analyses, using a Wald chi-square test with 1 df with “Remission” as reference category.  
‡: p<0.05. € CES-D: Center for Epidemiological Studies Depression Scale.

To compare group differences without a reference category, additional analyses using One-Way ANOVA with Bonferroni post hoc comparisons were performed. These showed a significantly better performance for the MMSE (p=0.005) and coding task (p<0.001) in the fluctuating versus the chronic course type group. For the MMSE, using multinomial regression analysis, this association disappeared after correction for potential confounders age, education and sexe (OR 1.10, 95% C.I. 0.98 – 1.20). After correcting for potential confounders and potential explanatory variables, the OR for the association between the coding task and a fluctuating course compared to a chronic course remained significant (OR 1.10, 95% C.I. 1.04 – 1.17).
DISCUSSION

The present study investigates whether specific domains of cognitive functioning predict the natural course of depressive symptoms in older people. It is shown that there is an independent association of a slowed processing speed with a poor natural course of depressive symptoms in late life and this association is not explained by risk factors for vascular brain damage or CVA. On the other hand, global cognitive functioning and memory tasks are not associated with a worse prognosis of depressive symptoms. To be able to optimize treatment strategies for older depressed people, it is important to understand the role of concurrent cognitive impairment, a frequently co-occurring phenomenon of late life depression.

While it has been shown that decline of cognitive domains in depression might be mediated by a centrally slowed processing speed, one might wonder why the other cognitive domains tested in this study are not associated with chronicity. An explanation could be that the studied group is a relatively cognitive healthy one compared to the studies cited. Means of cognitive tasks in the present study differed less than one SD from age- and education matched controls without depressive symptoms (CES-D<16); indeed the difference was greatest for the coding task in the chronic group compared to the controls (21.5 (SD 6.6) versus 25.4 (SD 7.6)). Possibly, processing speed is the most sensitive cognitive domain that is first affected.

The present study extends findings from a study by Comijs et al., who showed that depressive symptoms predicted a slowed processing speed over a three year period, while this was not true for other cognitive domains. In combination with the present study, a reciprocal relationship between depressive symptoms and processing speed is thus shown. This could be explained by a common underlying pathology. Slowed processing speed may operate through fronto-striatal disconnection due to vascular lesions. Increased white matter intensities are described in late life depression and one study showed an association between cerebral lesions on MRI and persistence of depressive symptoms. The present study however does not support a vascular pathogenesis as a common underlying pathology and these findings are in line with other community based or primary care based studies dealing with this subject. Notably, recent findings suggest that cardiovascular risk factors are associated with depression only in those aged 85+, suggesting that vascular disease may be an explanatory mechanism for higher rates of depressive symptoms in the oldest-old only. The younger mean age in the present study might explain the absence of such an association for cardiovascular risk factors.
Alternatively, fronto-striatal dysfunction rather than fronto-striatal disruption might represent a non-vascular explanation of the link between slowed processing speed and chronicity of depressive symptomatology. Also in younger depressed subjects it is shown that executive functioning, which is closely related to processing speed, is associated with a worse clinical outcome of depressive disorders. In combination with the results of the present study, these findings are of importance in two ways; first, it makes clear that depressive symptoms with slowed processing speed represent a subgroup of depressive disorders with a worse outcome, irrespective of age. Second, from an etiological point of view, the link between slowed processing speed and chronicity of depressive symptomatology might be caused by fronto-striatal dysfunction resulting from inhibitory neurochemical processes, which could be independent from age. Finally, slowed processing speed and depressive symptoms might both represent frailty, a chronic syndrome frequently seen in older people.

Strengths of the current study include the size of the sample and the fact that it is a community based cohort, which avoids referral bias, thereby preventing overrepresentation of chronic cases. Moreover, the repeated measurements of depressive symptoms reduce the chance of over reporting chronic cases. Furthermore, an extensive number of covariates has been tested, including medication use and chronic diseases, allowing adjustment for possible confounding. Limitations also need to be addressed. In this study no formal depression diagnoses were applied, since the CES-D score measures depressive symptoms only. Depressive symptoms however appear to be as important as formal depression diagnoses with regard to morbidity, disability, wellbeing and mortality. A limitation might be the lack of data on cholesterol and MRI. The absence of MRI tempers our ability to draw firm etiological conclusions about the explanatory role of vascular brain pathology in the relation between processing speed and course of depressive symptoms. However, we think the data gathered in this observational study are especially valuable in identifying prognostic factors that are useful in clinical practice when determining the prognosis of an older patient with depressive symptoms, for instance in the field of the general practitioner, when MRI data are not available. Another limitation might be due to selective loss of respondents; those excluded at baseline were older and had lower MMSE score, indicative for a lower general cognitive performance. It is likely that those with compromised cognition have poorer prognosis of depressive symptoms. Therefore the true association between cognitive impairment and course of depressive symptoms is likely to be underestimated. The issue of selective loss of observations also has to be addressed; those with a fluctuating course had more valid follow-up observations as compared with the remission group. However, the number of follow-up observations between the chronic and the remission group was similar and since
the present study shows an association of a slowed processing speed in those with a chronic course as compared to the remission group as reference, the incongruency of follow-up observations in the fluctuating group does not influence this association. A minor limitation is that the cognitive domain of executive functioning is not separately tested in this study. It has been shown however that processing speed and executive function are highly correlated in late life depression. Therefore, we expect that also the domain of executive function would have shown an association with chronicity of depressive symptomatology.

In conclusion, we found an independent association of a slowed processing speed, but not of global cognitive functioning or memory performance with a poor natural course of depressive symptoms in older people. When dealing with clinically relevant depressive symptoms in an older person with comorbid cognitive impairment, processing speed might be a more useful tool than the MMSE in predicting the prognosis. Results of the present study may have implications for therapy. Our study suggests that global cognitive decline and memory impairment are no reason for withholding treatment of a depression in older people, since the natural course of depressive symptoms is not associated with performances on these cognitive domains. Moreover, preliminary studies show that patients with cognitive impairments benefit from specialized depression care. Future research is needed to further optimise treatment strategies for depressions in late life with different kinds and severities of cognitive impairments.
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