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Chapter 5

The effect of anxiety and depression on decline of memory function in Alzheimer's disease

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Abstract

Background: *Patients with Alzheimer's Disease (AD) and concomitant atrophy of the hippocampus may be extra vulnerable to the consequences of psychological distress, leading to more decline of memory function. The present study investigated whether symptoms of anxiety and depression predict decline of memory function in elderly people diagnosed with early stage AD.* **Method:** *A sample of 44 elderly people diagnosed with early stage AD was tested on their memory function, anxiety and depression and confounding variables with one year follow-up. Episodic memory was measured with a modified Dutch version of the Auditory Verbal Learning Test (AVLT) measuring learning and recall abilities. Linear regression analyses were used to investigate the association between anxiety and depressive symptoms and decline of memory function.* **Results:** *Anxiety symptoms predicted less decline in learning on the AVLT. Anxiety symptoms did not predict decline on the recall of the AVLT. No association was found between the depressive symptoms and decline in either learning or recall of the AVLT.* **Conclusions:** *In early AD, symptoms of anxiety and depression generally seem to be mild, and do not accelerate decline of memory function over time. On the contrary, anxiety symptoms were found to predict less decline of memory function.*

Introduction

Anxiety and depression are common in elderly people diagnosed with Alzheimer's disease (AD) occurring in about 25% to 70% of patients (1-8). Anxiety and depression are known to have an influence on cognition in non demented elderly people (9). Generally, studies on depression show a negative effect on cognitive decline (10-13). Some studies on the association between anxiety symptoms and cognition also found this negative effect (13). However, previous research in a population based cohort of elderly people, showed that mild anxiety symptoms enhanced cognitive abilities while severe anxiety symptoms were associated with a decline in cognitive abilities (9). A possible theoretical framework for the association between anxiety and depression on one side and cognitive decline on the other is based on the glucocorticoid cascade hypothesis (14)(15). This hypothesis indicates that psychological distress may lead to excessive levels of glucocorticoids (16). Especially the hippocampus is highly sensitive to these stress hormones, and plays a critical role in learning and memory. Therefore, exposure to long term high levels of the stress hormones might cause impairment of memory function (17-19). In patients with AD the hippocampus is already atrophied, psychological stress such as anxiety and depression might cause further hippocampal damage (16). This might lead to an accelerated decline of memory function in AD patients. Because variation and decline of memory function can be measured in patients with early stage AD, an influence of anxiety and depression on memory function is most likely to be detected in patients in this stage of AD. Therefore the present study will investigate whether symptoms of anxiety and depression influence decline of memory function in elderly people diagnosed with early stage AD.

Method

Sample

A study sample of 66 patients with early stage AD was collected in several general hospitals and mental health care institutes in the Netherlands. Patients were included when AD was recently diagnosed by a clinician, and when they had a score of 1 on the Clinical Dementia Rating (CDR (20)). A first-degree relative or caregiver in close contact with the patient had to be available to provide information about the patient.

The patients were examined with an interval of 12 months, in 2003 (baseline) and in 2004 (follow-up). This resulted in a study sample of 44 elderly people diagnosed with AD, with information on decline of memory function and anxiety and depression at two measurements. Drop out was not related to depression, any of the confounding variables or

the cognitive performance tests. However, patients who dropped out of the study did report less anxiety symptoms than patients who participated in both measurements.

All interviews were conducted in the patient's home by specifically trained and intensively supervised interviewers. Written informed consent was obtained from each patient, according to prevailing legal requirements. The Medical Ethics Committee of the VU Medical Center approved the study.

Measures

General cognitive functioning was measured by means of the Mini-Mental State Examination (MMSE ((21)) a frequently used screening instrument for global cognitive functioning. Scores range from 0 to 30 with higher scores indicating better cognitive functioning.

Episodic memory was measured with a modified Dutch version of the Auditory Verbal Learning Test (AVLT (22;23)). This test originally consists of 15 words, but because of limited cognitive abilities of the patients, the number of words is limited to 8, which have to be learned during five trials. The total number of words the patient has learned during the trials is the *learning score*, which ranges from 0-40. The number of words reproduced after 20 minutes is the *recall score*, ranging from 0-8. Higher scores on both variables indicate better memory functioning.

Anxiety symptoms were measured with the Hospital Anxiety and Depression Scale-Anxiety sub-scale (HADS-A (24)). This sub-scale consists of 7 items, which are self-rated on a 4-point scale by the patients. Scores of 7 and higher indicated clinically relevant anxiety symptoms (24); (9;25).

Anxiety disorders, according to the DSM-IV criteria (26), were diagnosed by means of the Composite International Diagnostic Interview (CIDI (27)). The 6-months prevalence rates for specific phobia, social phobia, agoraphobia without panic, panic disorder without agoraphobia, panic disorder with agoraphobia, and generalized anxiety disorder (GAD) were included in the present study.

Depressive symptoms were measured by means of the Center for Epidemiologic Studies Depression Scale (CES-D (28;29)). The CES-D is a self-report scale, consisting of 20 items. Each answer is rated on a 4-point scale. Higher scores indicate more depressive symptoms with scores of 16 and higher being indicative of clinically relevant depressive symptoms.

Depressive disorders according to DSM-IV criteria (26), were diagnosed by using the National Institute of Mental Health Diagnostic Interview Schedule (DIS (30)). For this study 6-month prevalence rate of major depression were included.

Confounders

Possible confounding variables that may be associated with both cognitive decline and anxiety and depression include socio-demographics, alcohol consumption, cardiovascular disease, diabetes mellitus and the use of medication. All information was cross-checked with information provided by the relative or care-giver of the patient.

The following *socio-demographic variables* were included: age and level of education. *Level of education* was classified into three categories: low level of education ((uncompleted) elementary education, lower vocational education), medium level of education (general intermediate education, intermediate vocational education, general secondary education), and high level of education (higher vocational education, college education and university education).

Alcohol consumption was assessed with a questionnaire developed by the Dutch Central Office of Statistics (31) and classified, according to Garretsen's Indication of Present Alcohol Use (32), into five categories (non-drinker and light, moderate, severe and excessive drinker) of present alcohol use. Because very few patients were severe or excessive drinkers, these categories were collapsed into one category in analyses.

Cardiovascular disease and diabetes mellitus were assessed by asking the patients if they had any of the following: cardiac disease, stroke, high blood pressure or diabetes mellitus.

Finally, the *use of medication* was assessed by asking the patients to name any medications they had taken in the two weeks prior to the examination. This information was compared with the information on the drug containers, provided by the patients. Drug use was classified into categories according to the Anatomic Therapeutic Chemical (ATC) classification. On behalf of the present study separate variables were computed for a) benzodiazepine use, anti-depressive medication use and anti-psychotic use and b) dementia medication use (both coded as 'yes' or 'no').

Statistical Analyses

First, the characteristics of the study population were established at baseline and the follow-up measurement. Next, scores of difference indicating decline in memory function over the period of a year were calculated for the memory test. Hereafter linear regression analyses were performed to determine any significant association between decline of memory function and anxiety and depression. Corrections were made for memory function at baseline and for the confounding variables measured at baseline. In analyses *p*- values lower than 0.05 were regarded as statistically significant. Statistical analyses were performed with SPSS, version

12.0.1.

Results

The characteristics of the participants are presented in table 1. Respondents scored an average of 22 points on the MMSE at the first measurement and an average score of almost 21 points at the second measurement.

Patients report few anxiety symptoms (2.45 at baseline and 1.79 at follow up) and depressive symptoms (9.23 at baseline and 10.95 at follow-up). The reported decline in anxiety symptoms reached the level of significance ($p = 0.02$). Depressive symptoms, however, did not change significantly ($p = 0.24$). Anxiety disorders are reported in 6% of patients at baseline, whereas none of the patients report an anxiety disorder at follow-up. Depression disorders are reported by 16.7% at baseline and by 6.8% of patients at follow-up. With respect to memory function; the mean learning score declined between the two measurements ($p = 0.04$), but no significant decline was found on the recall score ($p = 0.15$).

Table 1. Characteristics of the study sample

Measurement	T0	T1
N	66	44
Age (mean (SD))	78.74 (5.8)	79.52 (6.1)
Gender (N (%))		
- male	35 (53.0)	24 (54.5)
- female	31 (47.0)	20 (45.5)
Level of education (N (%))		
- low	22 (33.3)	12 (27.3)
- medium	28 (42.4)	20 (45.5)
- high	16 (24.2)	12 (27.3)
Alcohol consumption (N (%))		
- none	13 (19.7)	10 (22.7)
- light	38 (57.6)	24 (54.5)
- moderate	12 (18.2)	9 (20.5)
- severe/excessive	2 (3.0)	1 (2.3)
Cardio vascular diseases and Diabetes Mellitus (mean SD))	38 (57.6)	27 (62.8)
Medication use (N, %)		
- Benzodiazepine, anti-depressive and anti psychotic medication use	12 (19.7)	10 (25.0)
- Dementia medication use	11 (17.7)	22 (55.0)
Anxiety symptoms (mean (SD))	2.45 (2.9)	1.83 (2.4)
DSM IV diagnose anxiety, past year (N, %)		
- no	61 (93.8)	44 (100.0)
- specific phobia	1 (1.5)	0 (0)
- social phobia	0 (0)	0 (0)
- agoraphobia without panic	1 (1.5)	0 (0)
- panic disorder without agoraphobia	0 (0)	0 (0)
- panic disorder with agoraphobia	1 (1.5)	0 (0)

- Generalized Anxiety Disorder	1 (1.5)	0 (0)
Depressive symptoms (mean (SD))	9.23 (7.5)	11.17 (10.2)
DSM IV diagnose depression, past year (N, %)	11 (16.7)	3 (7.0)
General cognitive functioning (MMSE) (mean (SD))	22.15 (3.0)	20.88 (4.0)
Episodic memory (AVLT) (mean (SD))		
- Learning	19.85 (6.7)	19.02 (7.7)
- Recall	0.59 (1.1)	0.28 (0.8)

Note: MMSE = Mini Mental State Examination, AVLT = Auditory Verbal Learning Test

Regression analyses were performed to investigate the effect of anxiety and depression symptoms on decline in memory function (table 2). Analyses showed the level of anxiety symptoms was associated with less rapid decline on learning of the AVLT. After correcting for confounding variables the association was still significant ($B = -0.657$, $p = 0.02$). Anxiety symptoms did not seem to influence the decline on the recall of the AVLT. Furthermore, no association was found between the depressive symptoms and decline in memory function on both the learning and the recall of the AVLT.

Tabel 2 The association between cognitive decline and anxiety and depressive symptoms measured at T0

	Anxiety symptoms		Depressive symptoms	
	B	P	B	P
Episodic memory (AVLT)				
- Learning	-0.625	0.03	-0.231	0.06
- Recall	0.024	0.53	-0.004	0.78

Note: AVLT = Auditory Verbal Learning Test

We found no association between depressive disorders and decline in memory function (results not shown), and were not able to establish a possible association between anxiety disorders and decline in memory function due to the low prevalence of anxiety disorders.

Discussion

The present study investigated whether psychological distress such as anxiety and depressive symptoms would result in an accelerated decline of memory function in AD patients. Against our expectations, it was found that higher levels of anxiety symptoms were associated with less decline of memory function, specifically the learning phase, over a one-year period, whereas depressive symptoms were not related to decline of memory function. In our sample of early stage AD patients, levels of anxiety and depressive symptoms were low. These mild

levels of anxiety and depressive symptoms might not have caused the distress we assumed and therefore the hypothesized damaging effect of hypersecretion of stress hormones could not be established. Nevertheless, our findings are interesting and fit previous cross-sectional research in a population-based sample of elderly persons ((9), which also showed that sub-clinical levels of anxiety symptoms enhance cognitive performance, while severe anxiety symptoms were associated with lesser cognitive abilities. The enhanced memory function as a consequence of mild anxiety symptoms is probably caused by an arousing function that services performance (33). According to our results, this mechanism is also applicable to elderly diagnosed with AD, which is remarkable in the light of previous research by Berger et al. (2005). Berger et al. indicated that the influence of individual difference variables, such as depressive symptoms, on cognitive performance, is overshadowed by the dementing process itself. The enhanced memory function as a consequence of mild anxiety symptoms is probably caused by an arousing function that services performance (33).

The measurements of anxiety (HADS-A) and depressive symptoms (CES-D) are both developed for measuring anxiety and depression in the general, cognitively healthy, population. The present study population is cognitively impaired and questions might rise on their abilities to correctly report on anxiety and depression over a previous time period. Research by Harper et al. (34) and Lichtenberg et al. (35) however, showed that only the most severely impaired dementia patients are incapable of accurately reporting their mood. Our study sample contains elderly in an early phase of dementia who are therefore considered capable of correct reportage.

The findings have to be placed in the context of the strengths and limitations of this study. Strengths of the current study are that elderly people diagnosed with early stage AD are followed over a period of one year providing data on decline of memory function and anxiety and depressive symptoms and confounding variables. However there are also limitations. Firstly, studying enough AD patients with serious distress will acquire a much larger study population. The second limitation is that the performance on the recall of the AVLT might have suffered from a floor effect causing the lack of association between anxiety or depression and decline of memory performance on this component. The patients scored on average 0.59 at baseline and 0.28 at the follow up measurement even though the scale ranges from 0 to 8.

Concluding, symptoms of anxiety and depression generally seem to be mild in early AD patients, and do not seem to effect decline of memory function in patients diagnosed with

AD. On the contrary we found anxiety symptoms were associated with less decline of memory function.

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