Cognitive performance in depression: patterns and determinants

Neuropsych Publishers, Maastricht

ISBN: 90-9016302-6

Digitale opmaak: grafische afdeling Altrecht
Drukwerk: Bergdrukkerij Amersfoort

Neuropsych Publishers is a nonprofit organization, which aims at promoting the science of 'Brain and Behavior' and improving the application of the products of this science in health care and education. Neuropsych Publishers accomplishes these aims by publishing books, dissertations and other products of scientific activity, by disseminating educational materials and publication of tests, assessment scales and other psychometric instruments in the field of Neuropsychology, Neuropsychiatry and other areas within the domain of Brain and Behavior.

Postal address:
Neuropsych Publishers
Department of Psychiatry and Neuropsychology
Maastricht University
P.O. Box 616
NL-6200 MD Maastricht
The Netherlands

Cognitive performance in depression: patterns and determinants

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. A.C. Nieuwenhuijzen Kruseman,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen op
vrijdag 22 november 2002 om 12.00 uur

door

Mariska den Hartog

geboren op 10 april 1973 te Utrecht

Promotor

Prof. dr. J. Jolles

Beoordelingscommissie

Prof. dr. F.R.J. Verhey (voorzitter)
Dr. A.T.F. Beekman (Vrije Universiteit Amsterdam)
Prof. dr. E.H.F. de Haan (Universiteit Utrecht)
Prof. dr. H.L.G.J. Merckelbach
Prof. dr. J.J. van Os

The studies described in this thesis were carried out at the Maastricht Brain & Behavior Institute (division of Cognitive disorders), and the department of Psychiatry and Neuropsychology of Maastricht University and the Psychomedical Centre Vijverdal Maastricht

Publication of this thesis was financially supported by AstraZeneca Nederland, Roche Nederland, SmithKline Beecham Nederland and Pfizer Nederland.

Contents

CHAPTER 1

Cognitive problems in depression: an overview

Introduction

Major depressive disorder is a psychiatric syndrome that is present when certain criteria, defined by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [1] are met. At least five of the following symptoms, which indicate a change compared to earlier functioning, must have developed within 2 weeks of each other: depressed mood, a decrease in interest or pleasure, change in weight which is not due to a diet, sleeping disorders, psychomotor agitation or restraint, tiredness or loss of energy, feelings of worthlessness with disproportional feelings of guilt, decrease in the ability to think, to concentrate, or to decide, recurrent thoughts of death. Symptoms of depressed mood or a decrease in interest or pleasure are required for the diagnosis. Symptoms must cause significant suffering or lead to restrictions in social or professional functioning. The diagnosis cannot be made in the presence of manic symptoms or symptoms caused by the direct physiological effects of substances, by a somatic disorder, or by mourning. Although these criteria define major depressive disorder, they do not give an impression of the depressive state. The following description, quoted from Widlöcher [2], gives a good impression of clinical aspects of (severe) major depressive disorder:

" There is a general slowing down of motor activity. It may be observed in limbs or trunk. The patient rarely moves his limbs, gestures are awkward, and amplitude of movements is below normal. Proximal portions of arms are often fixed; only the hands move. Trunk appears immobile, either plastered against the back of the chair or with the shoulders drooping. Gait and stride are impaired. Patient often drags his feet and there is a paucity of suppleness to the stride or to the swing of arms. There is a paucity of movements of head and neck. The patient does not explore the room and stares toward the floor. The expression is unchanging, with immobile and blank faces. Psychic activity is also slowed down. Patient is unable to respond quickly and spontaneously to the interviewer. There is an impoverishment of new themes spontaneously brought up by the patient and, when examiner suggests some new topic, responses are brief and laconic; there is difficulty moving to a new idea. There is also difficulty in concentrating, which interferes with ordinary pursuits such as reading a newspaper or watching television. There is often an apparent memory disorder due to an impaired recall. Generally, the patients are aware of the trouble and can accurately describe it. Motor and mental slowing are generally felt as fatigue, distressing them in their everyday life and not improved by rest. On the contrary, inactivity increases it. Another expression of subjective experience of psychic retardation is the perception of ruminative thinking. Patients have the impression that their thoughts dwell on two or three themes that recur over and over, adversely affecting their current life and invading their internal world. The clinical stereotype is that cessation of usual activities is due to a general lack of interest, and rumination is often

interpreted as a consequence of mental pain. However, by carefully scrutinizing what is really felt, the clinician will observe that love, attachment, and interest are not lost but that there is a defect in the capacity to act in accordance with these emotions. Speech is affected by retardation in both motor and cognitive aspects. Voice is weak and monotonous and verbal flow is slowed. Brevity of responses appears as a consequence of mental slowing. Finally retardation appears as an alternation of the subjective experience of the flow of time; present time passes slowly and in most severe cases passage of present time is suspended and there is a painful perception of an infinite present."

Depression and cognitive performance: the problem.

Depressive disorder has a major impact on wellbeing and the quality of life of depressed patients and their relatives. It is sometimes considered the common cold among psychiatric disorders [3] because of its high prevalence (the number of cases at risk per 1000 persons at a certain moment; see table 1). Although many possibilities for pharmacological treatment of depression have been developed in the past 50 years, there has only been a modest increase in our knowledge of the etiological factors and pathogenesis of the disorder. Obviously, mood problems are the best-known feature. But, as also accurately shown by Widlöcher's description, cognitive problems are also important. To date, cognitive deficits are generally believed to be a direct consequence of depressive disorder. However, although this idea may have some face validity, the causal relationship between depressive disorder and cognitive dysfunction is not clear. For example, recent publications have shown that cognitive dysfunction does not always clarify with remission of depression [4-8], which is hardly in line with the idea that these deficits are secondary to depressive disorder. Furthermore, Roberts et al. [9 10] demonstrated that subjective cognitive problems predicted the development of depressive disorder 1 year later. Finally, Van Os et al. [11 12] demonstrated that childhood general cognitive ability was an independent risk factor for the development of depressive illness in adulthood. These results suggest that cognitive dysfunction may also precede depressive disorder, instead of merely being a secondary phenomenon.

This thesis specifically concerns the relationship between depressive disorder and cognitive functioning. The remainder of this introduction will give an impression of the topics addressed. First, the epidemiology of depressive disorder is described briefly, followed by a paragraph about cognitive symptoms in depression, and a paragraph about possible mechanisms that may be involved in cognitive deficits in depression.

Table 1. *Annual prevalence of depressive disorder per 1000 persons*

	Prevalence
Population	67
General practitioner, total	54
General practitioner, recognized	26
Mental health outpatient	4.4
Mental health inpatient	1.5

Epidemiology of depressive disorder

As shown in table 1, which gives the 1-year prevalence of depressive disorder in adults [3], depressive disorder is fairly common (67 per 1000 persons). Not all patients consult a general practitioner (54 per 1000 persons), and of those who do, less than half (26 per 1000) are recognized as being depressed. Thus, there seems to be a major problem in primary care in recognising depressive disorder. It appears especially difficult to recognize depressive symptoms in the elderly [13], because elderly individuals typically tend to display more vegetative signs and cognitive disturbances and tend to complain less of dysphoria than do their younger counterparts. Depression may consequently be misattributed to physical illness, dementia, or the aging process itself. The general practitioner treats the majority of patients in whom depression is recognized, referring the minority to secondary (4.4 per 1000) or tertiary (1.5 per 1000) care. The American Epidemiologic Catchment Area Program, which is one of the largest epidemiological studies of psychiatric disorders, estimated the lifetime prevalence of major depressive disorder to be about 43 per 1000 [14], which is roughly in accordance with the data given in table 1. When not only major depressive disorder is considered, but all clinically relevant depressive disorders, the prevalence rises to 120-170 per 1000 adults (12-17%) [15-17]. These figures are a good reflection of the situation in the Netherlands [15 16]. The incidence (which reflects the annual number of new cases) of depressive disorder in the Netherlands is estimated to be between 2 and 7 per 1000 adults.

Depressive disorder characteristically starts in the late 20s, but the disorder may begin at any age [18]. It is about twice as common in women than in men [15 17 19]. A lower education [10 15] and a poorer socio-economic situation [3 16] are associated with a higher prevalence. As yet, it is not completely clear whether older age poses a risk. Although the prevalence of depression in older populations seems to be at the upper end of the range (for example [16]), this effect is probably mediated by a higher incidence of physical illness and bereavement in the elderly, which are known risk factors for depressive symptoms. Depressive disorder is best characterised as a chronic disease. The most important predictor of depressive illness is prior depression [9 20-23]. Over 50% of people who have had an episode will eventually have another episode [18], and it is estimated that 20% will have a true chronic course [24].

Cognitive functioning in depression

Depressive symptoms are related to subjective complaints about memory function. In fact, memory complaints seem to be more strongly associated with depressive symptoms than with objective cognitive functioning [25 26]. Nonetheless, cognitive deficits are very common in major depressive disorder. Most research has compared older patients with older healthy controls, and has shown that the patients generally perform worse on tests of psychomotor speed [7 27], memory [28 29]], attention [4 30], and executive function [29 31]. Results are not uniform, partly because older age, psychotropic medication, and severity of symptoms may influence cognitive functioning. Very few studies of cognitive functioning have been performed with younger adult depressive patients, and again, results are not uniform. Deficits in executive functioning are reported in younger individuals using medication (for example [32 33]), whereas two studies of younger unmedicated outpatients found a poorer performance on only one of several tests involving short-term memory and attention [34] or executive functioning [35]. It is not clear whether cognitive dysfunction in depressive disorder can be characterised by a certain pattern of deficits. Some authors have suggested that cognitive deficits in depressive disorder are associated with a decrease in speed of information

processing [2 36]. In contrast, other authors have suggested that problems are related to effortful processing [37 38], as determined in studies of memory processing in older depressed subjects.

Cognitive dysfunction in depression: possible mechanisms

The mechanisms that may be involved in cognitive dysfunction in depressive disorder are not clear. There is increasingly more attention for the role of cortisol and the hypothalamus-pituitary-adrenal axis (HPA-axis) in relation to memory deficits. A stress situation induces a cascade response in which the paraventricular nucleus of the hypothalamus secretes corticotrophin-releasing hormone (CRH), which releases adrenocorticotrophin hormone (ACTH) from the pituitary. When ACTH enters the bloodstream, the stress hormone cortisol is secreted from the adrenal gland. The circulation of cortisol in the blood, together with other substances that are secreted during stress, leads to the alarmed feeling experienced during stress. When the acute stress situation is over, cortisol decreases the production of ACTH and CRH through a negative feedback mechanism, with as end-result a decreased secretion of cortisol. It has become increasingly clear that depressive disorder is associated with elevated levels of cortisol [39], probably due to a defective negative feedback mechanism. Hypothetically, elevated levels of cortisol released from the HPA-axis negatively affect the hippocampus, which is crucially involved in memory functioning [40 41]. Supportive results have come from studies of older depressive subjects, but there are few studies involving younger subjects. Furthermore, there is a lack of studies that relate cortisol to cognitive functions other than memory.

A second mechanism that may be involved in cognitive dysfunction in depressive disorder involves aspecific effects of being ill. It is conceivable that secondary effects of not feeling well cause cognitive dysfunction. Most studies have compared depressive patients with healthy controls. However, healthy controls differ from depressive patients not only in the absence of psychiatric illness, but also in the absence of secondary disease-related aspects. On the basis of such comparisons, it is not clear whether the altered cognitive function is specific for depressive illness or merely represents a non-specific effect of illness. Inclusion of a physically ill control group can be crucial for understanding the mechanisms underlying altered cortisol levels and cognitive dysfunction.

A third mechanism may be related to age. In line with the brain reserve capacity theory of Satz [42], it is possible that older depressive people are less able to compensate for minor cognitive deficits than younger people are. However, since aging itself is characterised by a decrease in cognitive functioning and especially slower speed of information processing [43], older age is also a confounder of cognitive functioning in depression. It is therefore crucial to investigate cognitive functioning in younger depressive patients.

Outline and aims of the studies

This thesis focuses on one of the defining criteria of major depressive disorder, namely “a decrease in the ability to think”, or cognitive dysfunction. The scope of this thesis covers the spectrum between dysphoria in otherwise healthy people and the psychiatric diagnosis of major depressive disorder. Depressive disorder is associated with a wide range of cognitive deficits. The challenge of the research described in this thesis was not to identify more deficits, but to search for some unifying or integrative factors or mechanisms that are central to the cognitive impairment.

It is known that depressive disorder is associated to a variety of cognitive deficits, but it is not clear whether there is a pattern to these deficits. In *chapter 2* we investigated the current functioning of outpatients with major depression in terms of cognitive speed, attention, executive functioning, working memory, verbal memory, and search in semantic memory. Two theories concerning patterns in cognitive dysfunction were tested: the effort theory, which states that performance on effortful tasks is disproportionately impaired compared with performance on automatic tasks, and the cognitive speed theory, which states that depression is characterised by cognitive slowness.

It is known that depression is related to subjective complaints of memory, but we do not know whether it is related to subjective complaints of other cognitive functions. Therefore, in *chapter 3* we investigated the relation between subjective complaints of cognitive speed, attention, and memory and depressive symptoms. The prevalence and pattern were investigated in younger and older subjects from the general population, i.e. subjects who can be considered healthy.

When considering mechanisms that may relate to both depressive disorder and cognitive deficits, it is important to determine the specificity of cognitive deficits for major depressive disorder. To study whether cognitive deficits are merely a reflection of aspecific effects of disease, we compared depressive patients with healthy controls and with control patients with severe symptomatic allergic rhinitis. Allergic rhinitis is a chronic disease of non-neurological origin, and possible effects on cognition are not expected to be caused by allergic rhinitis itself. The disease has a considerable negative effect on quality of life, and patients need to consult a specialist of the outpatient clinic regularly. In these aspects patients with allergic rhinitis are comparable to patients with depression. In *chapter 4* we compared the allergic rhinitis group with the healthy control group with regard to several parameters of cognitive functioning and psychological well-being. We investigated the effect of these secondary disease-related factors on cognitive functioning in *chapter 2* and their effect on cortisol in *chapter 5*.

We tested another possible mechanism of cognitive deficits in major depression in *chapter 5*. In this study, we investigated whether altered levels of cortisol are related to performance of memory and cognitive speed in unmedicated outpatients with major depression.

It has been suggested that cognitive deficits are not merely secondary to depressive disorder but may be determinants of depression. In the investigation of impaired cognitive function as a possible determinant of depression, it is necessary to avoid the possible long-lasting influence of a depressive syndrome on cognitive function. Therefore, in *chapter 6* we followed-up middle-aged and older subjects who had never been clinically depressed, in a longitudinal study. The aim of this study was to investigate whether cognitive functioning is a determinant of later development of depressive symptoms. We extended the study to include subjects with major depressive disorder (*chapter 7*). Here, the study question was whether cognitive performance is a determinant of depressive disorder in middle-aged and older patients.

We studied the effects of increasing age on cognitive deficits in depression in *chapters 2, 3, and 4* of this thesis. The studies in these chapters help to answer the question whether older age is crucially implicated in cognitive dysfunction in depressive disorder.

In *chapter 8* we provide a summary of the findings and a discussion of implications for further research and for clinical practice.

CHAPTER 2

Cognitive functioning in young to middle-aged unmedicated outpatients with major depression: testing the effort and cognitive speed hypotheses*

ABSTRACT

Cognitive deficits are common in major depressive disorder, but their nature is unclear. The effort hypothesis states that performance on effortful tasks is disproportionately impaired compared with the performance on automatic tasks. The cognitive speed hypothesis states that depression is characterised by cognitive slowness, which is a source of cognitive dysfunctioning. The present study investigated both theories in unmedicated adult depressive patients. It was also investigated whether the cognitive deficits can be attributed to more general physical illness-related factors or specifically to depressive disorder. Thirty non-psychotic depressive outpatients were compared with 38 healthy control subjects and 25 patients with severe allergic rhinitis. The effects of group on more automatic and more effortful aspects of cognitive tasks measuring cognitive speed (Concept Shifting Task, Stroop Colour Word Test, Memory Scanning Test) and memory retrieval (Visual Verbal Learning Task, Verbal Fluency) were evaluated by regression analysis and ANOVA for repeated measures. Age, sex, education, and premorbid intelligence were treated as covariates. The depressive group had cognitive deficits in speed of processing (B=-2.69, p=0.012), interference (B=-4.30, p=0.042), memory scanning (B=-2.29, p=0.019), and working memory (B=0.49, p=0.010). Performance on more effortful tasks was not disproportionately impaired compared with that on more automatic tasks. The effort hypothesis does not apply to young to middle-aged unmedicated outpatients with depressive disorder. The results are more consistent with the cognitive speed hypothesis. Cognitive functioning in depressive disorder seems characterised by a reduced speed of information processing.

* H.M. den Hartog, M.M.A. Derix, A.L. van Bemmel, B. Kremer & J. Jolles: submitted.

Introduction

Cognitive deficits are common in major depressive disorder. Most research has focused on older subjects with depressive disorder and these individuals generally perform worse than healthy controls on tests of information processing, such as psychomotor speed [7 27], memory [28 29]], attention [4 30], and executive function [29 31]. In younger depressive patients using psychotropic medication, deficits in set-shifting and other aspects of executive functioning [32 33] have been found, whereas in unmedicated younger depressive patients deficits in speed and memory recall were found in an inpatient group with mixed depressive illnesses [44]. Two studies of younger unmedicated outpatients found a poorer performance on only one of several tests involving short-term memory and attention [34] or executive functioning [35].
It is still not clear whether a more general cognitive mechanism is responsible for the cognitive dysfunction in major depression. One hypothesis states that cognitive functioning is characterised by slowed information processing [2 7]. Speed of information processing could be considered a resource for cognitive functioning [36 45] and therefore reduced cognitive speed may negatively affect higher cognitive functioning. In older depressive patients, several studies have provided support for this speed hypothesis of cognitive deficits [7 27 46]. However, since aging itself is characterised by a slower speed of information processing [43], old age is a confounder of cognitive functioning in depression. It is therefore crucial to test this hypothesis in younger depressive patients. If problems in higher cognitive processing are not accompanied by speed problems then this hypothesis would appear not to be valid.

The hypothesis concerning effortful, or controlled, processing [37 38] also provides an explanation for the cognitive deficits seen in depression. According to this hypothesis, depressive disorder is characterised by problems in allocating effort to cognitive tasks. Some tasks require more effortful processing, for example when they rely on elaborate processing activities such as rehearsal, imagery, organization, clustering, or systematic searching. This is in contrast with automatic processing (see [37 38 47] for detailed information). According to the effort hypothesis, the performance of tasks that involve more mental effort is disproportionately impaired compared with the performance of tasks that depend on more automatic processing. Most support for this hypothesis has come from research on memory performance in older individuals (see for reviews [27 29 47]).
Few studies have explicitly investigated the effort hypothesis for cognitive domains other than memory. In a meta-analysis of cognitive function in older individuals with major depression, Zakzanis et al. [27] found that the performance of effort-demanding tasks could almost completely discriminate between major depressive patients and controls (especially tasks of encoding of information), while the performance of automatic tasks was not a reliable discriminator. Several studies have shown younger depressive patients to have a defect on effortful tasks of executive function and attention (for example [48-50]). However, very little information is available about automatic processing in cognitive domains other than memory in younger patients. To test the effort hypothesis in younger depressive patients, tasks that involve effortful processing should be compared with tasks that involve automatic processing. If problems in automatic information processing are present without accompanying disproportionately greater problems in effortful information processing, then this hypothesis would appear not to be valid.

It is important to determine the specificity of cognitive deficits for major depressive disorder, when studying mechanisms of cognitive functioning in this disorder. Most studies have compared the cognitive functioning of depressive patients with that of healthy control subjects. However, healthy controls differ from depressive patients not only in the absence of psychiatric illness, but also in the absence of secondary disease-related aspects, for example the stress that accompanies not feeling well. This makes it difficult to determine whether cognitive deficits are caused by the depressive illness itself or by these more general disease-related aspects. Although a few studies have compared the cognitive performance of depressive patients with that of psychiatric control subjects [33 51], few studies have been performed with a physically ill control group, which is necessary to investigate the role of more general disease-related aspects.

In the present study we tested the cognitive speed hypothesis and the effort hypothesis as applied to several cognitive domains. A group of non-psychotic patients with major depression was compared with a healthy control group and a physically ill control group. The physically ill group consisted of patients with severe allergic rhinitis. Allergic rhinitis is a chronic disease of non-neurological origin, and possible effects on cognition are not expected to be caused by symptomatic allergic rhinitis itself, but merely by the secondary aspects of not feeling well. Allergic rhinitis has a considerable negative effect on quality of life [52-54], and patients –especially those with severe complaints– need to consult a specialist regularly. For subjects in all groups, special care was taken to include young to middle-aged adult subjects without any psychotropic medication to avoid the effects of these drugs on cognition. With this design, cognitive performance cannot be explained in terms of old age or medication.

With respect to cognitive functioning, we contrasted automatic information processing with controlled information processing by comparing the subjects' performance on subtasks involving these aspects. We used tasks that measure speed of information processing as well as tasks that measure non-speed related memory processes. With regard to speed of information processing, we compared more automatic versus more controlled aspects of set-shifting (speed of naming alphabet and numbers versus set shifting [29]), response inhibition (speed of reading and colour naming versus interference [55]), and searching of working memory (automatic detection versus controlled search [56]). With regard to memory, we compared tasks that rely on more automatic emptying of information stored in working memory with tasks that require more controlled search and retrieval strategies [47 57]. These aspects are measured in verbal memory and search in semantic memory.
We wanted to answer three questions. 1. Are younger unmedicated depressive outpatients characterised by cognitive deficits? 2. Are cognitive deficits specific for depressive disorder, or are they associated with more general disease-related aspects? 3. Is the pattern of cognitive functioning more consistent with the cognitive speed hypothesis or with the effort hypothesis?

Methods and materials

Study design

In a cross-sectional design, a group of outpatients with major depression was compared with two control groups: an outpatient group with severe symptomatic allergic rhinitis and a healthy control group. The test protocol included several neuropsychological measures of intelligence, speed, and memory, and self-report inventories, and lasted approximately 1.5-2 hours, including a short break. The protocol was reviewed and approved by the Medical Ethics Review Committee and the subjects gave informed consent. All subjects were paid 11.4 euro for participation and received a written report of their neuropsychological results.

Subjects

Depressive patients were recruited from the ambulatory service of the psychiatric hospital Vijverdal, Maastricht, the Netherlands. The depressive group included 30 unmedicated outpatients with major depression, diagnosed by a psychiatrist following DSM-IV criteria [1]. This was the first episode for twenty-three patients; 4 patients had experienced one earlier episode, and 3 patients had experienced two or three earlier episodes. Symptom severity was measured using the Beck Depression Inventory (BDI [58]). Medication-free subjects that entered the hospital were assessed before medication was prescribed. Patients in whom medication treatment was altered because of insufficient efficacy entered the study after a wash-out period of 2 weeks, or 3 weeks in the case of previous fluoxetine treatment. Subjects were aged 18-65 years. Exclusion criteria were use of any psychotropic medication, other psychiatric disorders, neurological disorders, somatic disorders that affect cognitive function (e.g. diabetes, thyroid dysfunction), drug or alcohol abuse, and dyslexia. No subject had received electroconvulsive therapy in the past. Depressive subjects were assessed in the psychiatric hospital.

The group with allergic rhinitis consisted of 25 outpatients from the Department of Otorhinolaryngology, Head, and Neck Surgery of the university hospital of Maastricht, the Netherlands. Patients with seasonal allergic rhinitis, allergic to grass- and/or tree-pollen, and patients with perennial allergic rhinitis, allergic to house dust mite, were included. Subjects were examined during a symptomatic period. Possible symptoms were nasal secretion, nasal blockage, itching, and sneezing. Symptoms were rated on a 4-point scale (absent, mild, moderate, and severe). All patients had a symptom score which was at least moderate for at least two symptoms, which is generally regarded to indicate severe symptoms of allergic rhinitis, and/or had a Rhinitis Quality of Life Questionnaire (RQLQ)-score [52] higher than 1. Other inclusion criteria were age between 18 and 65 years, a positive medical history of seasonal or perennial allergic rhinitis, anti-allergy treatment in a previous season, and a positive radio-allergosorbent-test (RAST) for serum-specific immunoglobulin E or a positive skin prick test for tree- and/or grass- pollen or for house dust mite allergens. Exclusion criteria were use of psychotropic medication, a history of treatment for neurological or psychiatric disorder, drug or alcohol abuse, and dyslexia. Any anti-allergy treatment (e.g. nasal decongestants, anti-histaminics, anticholinergics, sympathomimetics, theophylline preparations) was ended before the assessment took place. Allergic subjects were assessed in the Department of Otorhinolaryngology, Head, and Neck Surgery.

Thirty-eight healthy control subjects were selected from a large pool of healthy controls, collected for use in the Maastricht Aging Study [59 60]. Inclusion and exclusion criteria were

the same as for the allergic patients, with the exception of the allergy requirement, which was an additional exclusion criterion in this group. Healthy subjects were assessed in the same environment as the depressive group.

Measurements

As a measure of visuomotor tracking and set shifting, the *Concept Shifting Task* (CST) was used [61]. In part A, 25 consecutively numbered circles arranged in a larger circle have to be crossed out as fast as possible. Part B is the same for letters. In part C the subject has to alternate between circles with numbers and letters (1-A-2-B-etc). Part 0, in which the subject has to cross out empty circles, reflects the motor speed component. By subtracting part 0 from the other parts, a reliable estimate of the cognitive processes can be made. Parts A and B minus part 0 both reflect cognitive speed for relatively automatic information processing, and these parts were combined into a mean value of cognitive speed ('CST-speed'). Part C minus part 0 reflects speed of set shifting, which involves more effortful processing.

The *Stroop Colour Word Test* (SCWT) [62] is a measure of response inhibition. The Stroop test consists of a reading condition in which the subject is required to read out loud as fast as possible the names of colour words; a similarly administered colour naming condition; and an interference condition, in which colour naming is required of colour words printed in non-matching ink. Parts 1 and 2 both reflect the cognitive speed of relatively automatic information processing, and were combined into a mean value of cognitive speed (SCWT-speed). Part 3 involves suppression of the dominant response, which involves more effortful processing.

To study the search of working memory, the *Paper & Pencil Memory Scanning Test* (MST) [56] was given to the subjects, which is based upon the Sternberg-paradigm [63]. In this measure a set of one to four letters has to be memorised and crossed out as fast as possible on sheets containing matrices of letters. The extra time needed to complete a subtask with increasing working memory is a measure of the ease with which information is processed in working memory. In this study the subtask with one letter (more automatic detection) and the subtask with two specific letters in between other letters (more controlled search) were used.

To assess memory storage and memory retrieval, the *Visual Verbal Learning Test* (VVLT) was used [64]. In this test, fifteen words are sequentially shown on a computer screen and the subject is asked to recall as many words as possible. This procedure is repeated five times. After a distraction period of 20 minutes, delayed recall is measured. The first trial is used to assess working memory [65] and involves the more automatic process of retrieving words stored in working memory. Retrieval after 20 minutes involves more effortful search and retrieval strategies, required for intentional learning.

To study *Verbal Fluency* a semantic Verbal Fluency subtest (animals) was used. Subjects were asked to name as many animals as possible in 1 minute and response is recorded. The number of animals named in the first 15 second involves the more automatic process of retrieving words stored in working memory, whereas the number of animals named in seconds 15-60 involves more effortful search and retrieval strategies [57 66].

Covariates

Age, sex, level of education, and estimated premorbid intelligence are known to influence cognitive performance [67] and were controlled for in the analyses. Educational level was indexed on an 8-point scale, ranging from unfinished primary school (1) to university degree

(8) [68]. Current IQ was measured using the Groninger Intelligence Test (GIT). This test yields results that are comparable to those of the Wechsler Adult Intelligence Scale [69]. Premorbid intelligence was estimated using the subtest "vocabulary" of the GIT.

Data reduction and statistical analysis
Prior to analysis, all variables were examined for missing values and outliers, using various SPSS programs. In the healthy control group, two scores for memory recognition were missing due to technical computer problems, and both values were replaced by the mean of the healthy control group. In each group, outliers were identified using z-scores ($z>3.29$ or $z<-3.29$, $p< 0.001$) [70]. There were no outliers in the depressive group and the allergic control group. In the healthy control group two outliers were replaced by the most extreme value within the normal distribution [70].
Differences in age, education, and current and premorbid intelligence were measured using an analysis of variance (ANOVA), and difference in sex was measured using Chi-square tests. Separate linear regression analyses were computed to determine whether the independent variable (group) was related to the dependent variables (cognitive performance), controlled for age, sex, education, and premorbid intelligence (vocabulary score). All post-hoc tests for group comparisons were adjusted with Scheffé's test. To measure whether performance on effortful tasks was disproportionately impaired compared to performance on automatic tasks, the slopes of the groups were compared with repeated measures ANOVA. Two-tailed probabilities of 5% or less were considered significant. Statistical tests were performed with SPSS for Windows version 9.0 (SPSS, Inc. Chicago).

Results

Table 1 gives descriptive data for age, sex, education, current intelligence, vocabulary scores, and BDI scores for the depressive group, and the allergic and healthy control groups. The groups differed in education ($F_{(2, 92)}=4.09$, $p=0.02$) and BDI scores ($F_{(2, 92)}=125.50$, $p=0.00$) Post-hoc tests with Scheffé's correction for multiple comparisons revealed that the depressive group was significantly less-well educated than the allergic control group. Further analyses were controlled for education. Not surprisingly, the depressive group had higher BDI scores than both control groups, which did not differ in depressive symptoms from each other. The depressive group (24.6±9.0) had BDI scores indicative of moderate to severe depression, whereas both control groups had depression scores that were in the normal range [58 65].

Figure 1a shows the performance of each group on subtasks of the CST, SCWT, and MST, which all measure speed of information processing. The performance of each group on subtasks of retrieval of stored information in working memory and the performance on subtasks involving intentional search and retrieval strategies are given in Figure 1b. Separate multiple linear regression analyses of group on cognitive performance, controlled for age, sex, education, and premorbid intelligence, were performed. Table 2 shows the scores (mean ± SD) for all groups on subtasks for CST, SCWT, MST, VVLT, and Verbal Fluency. The unstandardised B-values and significance of intergroup differences, adjusted for age, sex, education, and premorbid intelligence are also given. The last column indicates which groups

differed from each other, after adjustment for Scheffé's test for multiple comparisons. The results are presented in more detail for each cognitive task.

Table 1. *Descriptive data for age, sex, education, current IQ, vocabulary, and depressive symptoms for all groups*

	Depressive group (n=30)	Allergic group (n=25)	Healthy group (n=38)	test-value	p-value
Age (mean ± sd)	41.6 ± 12.4	39.9 ± 12.3	44.1 ± 11.2	$F_{(2, 90)}$=1.01	0.37
Sex (% female)	46.7 %	44.0 %	52.6 %	χ^2=0.50	0.78
Education (mean ± sd)	3.3 ± 1.3	4.4 ± 1.2	4.0 ± 1.7	$F_{(2, 90)}$=4.09	0.02
IQ	112.0 ± 10.5	114.2 ± 9.4	113.2 ± 9.9	$F_{(2, 90)}$=0.35	0.71
Vocabulary	12.5 ± 3.3	13.9 ± 2.7	13.4 ± 2.8	$F_{(2, 90)}$=1.66	0.20
BDI	24.6 ± 9.0	4.7 ± 2.8	4.2 ± 3.4	$F_{(2, 90)}$=125.50	0.00

Set-shifting (CST):
An effect of group on simple speed of processing (speed of crossing out numbers and letters: B=-1.16, p=0.03) and set shifting (B=-1.81, p=0.04) emerged. However, when post-hoc analysis of variance was corrected for multiple comparisons with Scheffé's correction, significant differences between the three groups were no longer present. ANOVA with a repeated measures design showed that the slopes between speed of processing and set-shifting were not different between the groups (Wilks Lambda=0.99, $F_{(2, 86)}$=0.51, p=0.60), which indicates that no group had a disproportionately worse performance on the speed or set-shifting subtask.
Response inhibition (SCWT):
Effects of group on both simple speed of processing (reading and colour naming: B=-2.69, p=0.01) and interference (B=-4.30, p=0.04) were revealed. Post-hoc analyses corrected for multiple comparisons (Scheffé) revealed that the depressive group took significantly longer than the two control groups to complete simple speed of processing task. The two control groups did not differ from each other. Regarding interference, the depressive group had a poorer performance than the allergic control group only; the two control groups did not differ from each other. ANOVA with a repeated measures design showed that the slopes between speed of processing and interference were not different between the groups (Wilks Lambda=0.98, $F_{(2, 86)}$=0.81, p=0.45), which indicates that the depressive group did not have a disproportionately worse performance on the speed or interference subtask.
Search in working memory (MST):
An effect of group on set size 1 (B=-2.29, p=0.02) emerged, but not on set size 2 (B=-2.48, p=0.11). The depressive group took significantly longer than the allergic control group to complete the subtask with set size 1; the two control groups did not differ from each other. The slopes between set size 1 and set size 2 were not different between the groups (Wilks Lambda=0.99, $F_{(2, 86)}$=0.15, p=0.87), which indicates that the depressive group did not have a disproportionately worse performance on the subtask with set size 1.

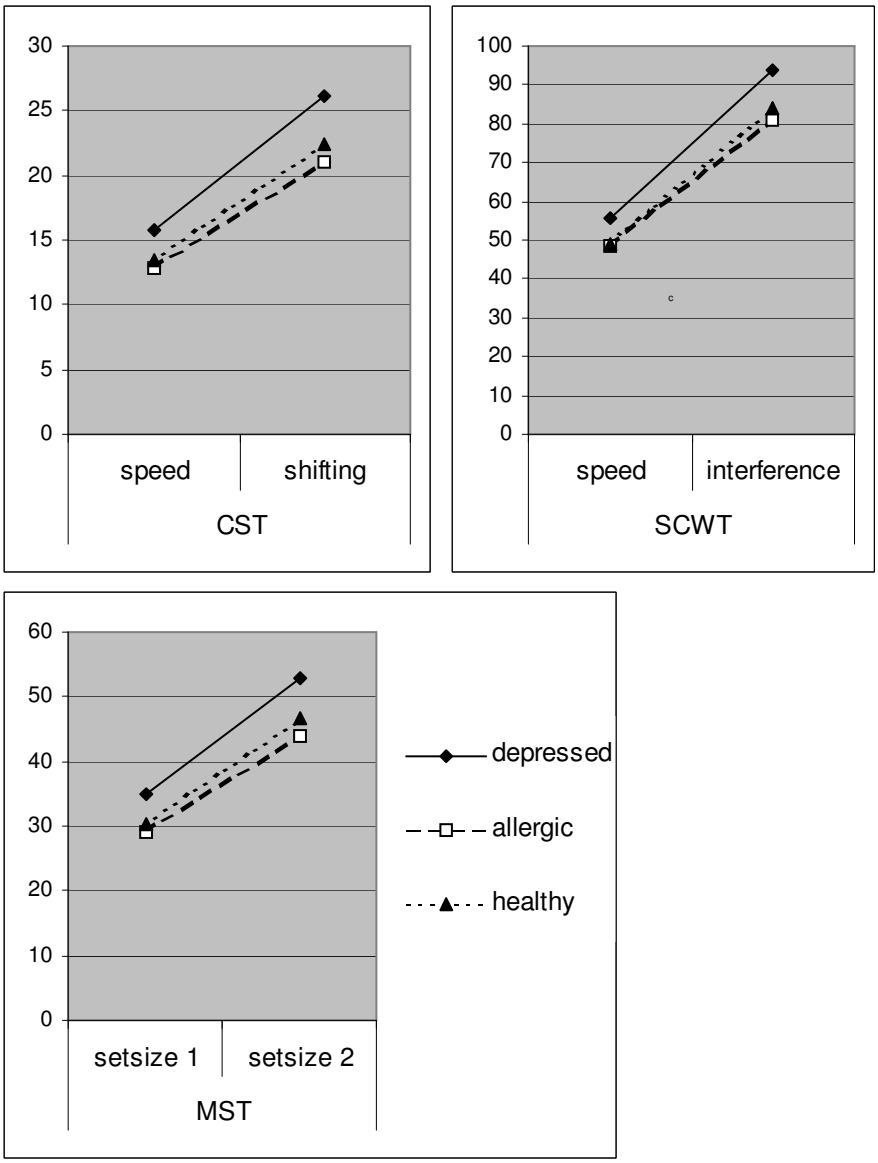

Figure 1a. *Performance of each group on subtasks of Concept Shifting Task (CST), Stroop Colour Word Test (SCWT), and Memory Scanning Test (MST)*

Verbal memory (VVLT):

Group had an effect on working memory (B=0.49, p=0.01), but not on memory retrieval (B=0.42, p=0.18). Corrected post-hoc analysis showed that the depressive group retrieved significantly fewer words from working memory, than did the healthy control group; the two control groups did not differ from each other. The slopes between working memory and memory retrieval were not different between the groups (Wilks Lambda=0.99, $F_{(2, 86)}$=0.05, p=0.95), which indicates that the depressive group did not have a disproportionately worse working memory performance.

Search in semantic memory (Verbal Fluency):

The groups did not differ in number of retrieved words in the first 15 seconds (B=0.22, p=0.46) or in number of retrieved words in seconds 16-60 (B=0.87, p=0.11). The slopes did not differ between the groups (Wilks Lambda=0.98, $F_{(2, 86)}$=0.74, p=0.48).

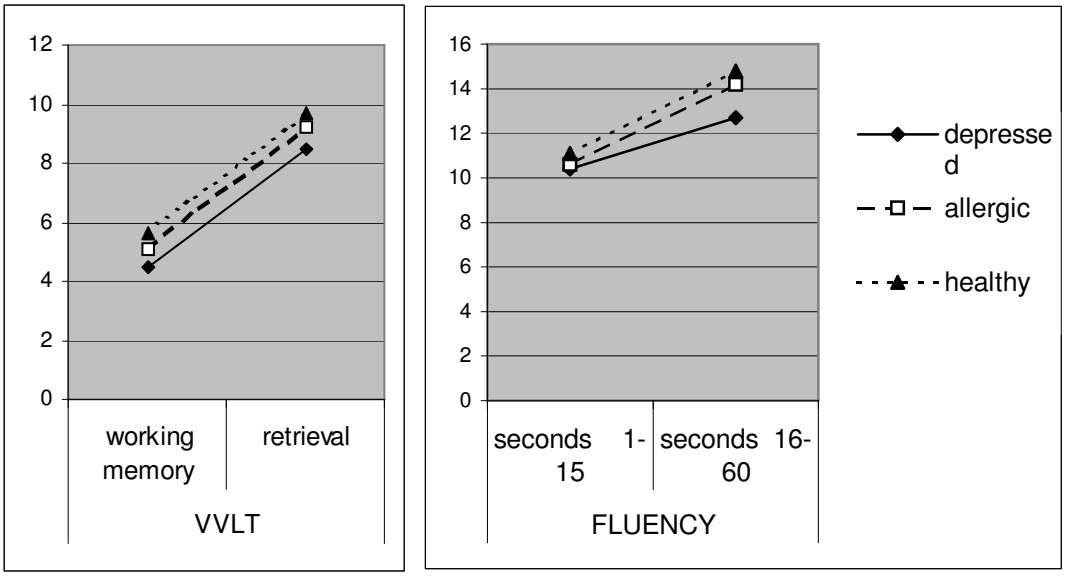

Figure 1b. *Performance of each group on subtasks of the Visual Verbal Learning Test (VVLT) and Verbal Fluency (fluency)*

Discussion

In this study, we attempted to answer three questions: are younger to middle-aged unmedicated depressive outpatients characterised by cognitive deficits; are cognitive deficits specific for depressive disorder; and is the pattern of cognitive functioning more consistent with the cognitive speed hypothesis, or with the effort hypothesis? To this end, the performance of a group of non-psychotic outpatients with major depressive disorder was compared with that of a physically ill control group and a healthy control group on more automatic and more effortful information processing tasks (set shifting, response inhibition, search in working memory, verbal memory, and searching of semantic memory). All groups consisted of adults not using psychotropic medication. Analyses were controlled for age, sex, education, and premorbid intelligence (vocabulary).

Concerning cognitive functioning, the depressive patients in this study had an impaired performance on tasks of response inhibition, searching of working memory, and verbal memory compared with both control groups. Indeed, these deficits seemed specific for the depressive group, because neither control group showed any cognitive deficits. The results suggest that cognitive deficits may be specifically attributed to depressive disorder and cannot be fully ascribed to more general physical disease-related factors (for example, stress, not feeling well) that are also present in patients with severe chronic allergic rhinitis.

Regarding the pattern of cognitive dysfunction, we distinguished between automatic and more effortful information processing and between speeded and non-speeded measures. The construct of automatic processing was operationalised using subtasks that are, according to the literature, considered to involve automatic information processing in adults [29 38 47 55-57]: reading, colour naming, simple ordering of numbers, alphabet naming, detecting one specific

Table 2. *Cognitive performance for groups (separate models): mean scores ± SD, unstandardised B-values and significance level adjusted for age, sex, education, and premorbid intelligence, and differences between groups, adjusted with Scheffé's test*

Task	Performan-ce measure	Depressed group (1)	Allergic group (2)	Healthy group (3)	B	p-value	Group difference
Concept Shifting Test	Speed	15.7±6.4	12.9±4.0	13.5±4.1	-1.16	0.03	-
	Shifting	26.2±11.3	21.0±7.4	22.4±7.0	-1.81	0.04	-
Stroop Colour Word Test	Speed	55.6±11.0	48.4±8.0	49.1±7.9	-2.69	0.01	1 – 2/3*
	Interference	93.8±22.3	81.0±17.9	83.8±13.8	-4.30	0.04	1-2
Memory Scanning Test	Set size 1	35.1±11.0	29.0±7.0	30.3±6.6	-2.29	0.02	1-2
	Set size 2	53.0±16.5	43.9±13.6	46.8±10.4	-2.48	0.11	-
Visual Verbal Learning Test	Working memory	4.5±1.6	5.1±1.8	5.6±1.8	0.49	0.01	1-3
	Retrieval	8.5±2.7	9.2±2.9	9.7±2.6	0.42	0.18	-
Verbal Fluency	Seconds 1-15	10.4±2.5	10.6±2.5	11.1±2.9	0.22	0.46	-
	Seconds 16-60	12.7±4.6	14.2±4.5	14.8±4.5	0.87	0.11	-

* the depressive group differed from both control groups, which did not differ from each other

letter between other letters, and retrieving information stored in working memory. For the operationalisation of the construct of effortful processing, we used subtasks requiring elaborate processing activities: set shifting, interference, and strategic searching of memory. On tasks measuring speed of information processing, depressive patients had a poorer performance on subtasks involving more automatic as well as more effortful processes of set shifting (CST) and response inhibition (SCWT), but only the latter was present after correction for multiple testing. However, the impairment in effortful processing was not disproportionate compared with that in automatic processing, which is inconsistent with the effort hypothesis. Furthermore, regarding speed of search in working memory (MST), the depressive group only performed poorer on the automatic detection task, but not on the effortful search task, compared with the two control groups. Also, the results for tasks measuring memory processes did not support the effort hypothesis. In verbal memory (VVLT), the depressive group performed worse only on retrieval of stored words in working memory, which reflects the more automatic processing of mnemonic material. Finally, in the semantic memory searching task (Verbal Fluency), the groups did not differ in their performance of automatic or effortful subtasks. Thus, the results of this study do not support the effort hypothesis. We suggest that additional factors that were carefully excluded in this study (such as older age, medication, and psychotic symptoms) might explain the results of studies that favour the effort hypothesis.

In order to investigate whether older age causes disproportionately greater deficits in effortful processing in depressive individuals, the interaction effects of age and group on the slopes of the tasks were tested post-hoc in a repeated measure ANOVA. Two age groups were created, arbitrarily based on the median split of the whole sample (42 years). Because the control groups did not differ from each other in terms of cognitive performance, the two control groups were combined and compared with the depressive group. Effects on cognition were tested within a repeated measure ANOVA, adjusted for sex, education, and premorbid intelligence. Results showed that although older age had a negative effect on the slopes of set-shifting (CST $F_{(1, 86)}$=12.48, p=0.00), response inhibition (SCWT $F_{(1, 86)}$=6.55, p=0.01), and search in working memory (MST $F_{(1, 86)}$=5.35, p=0.02), no interaction effects between age group and patient group were significant (results not shown), and no interaction effects between age group, patient group and the slopes were detected for any measure (CST $F_{(1, 86)}$=1.63, p=0.21; SCWT $F_{(1, 86)}$=3.00, p=0.09; MST $F_{(1, 86)}$=1.89, p=0.17; VVLT $F_{(1, 86)}$=2.37, p=0.13; Verbal Fluency $F_{(1, 86)}$=0.04, p=0.85). These results indicate that older age may have an additional negative effect on cognitive functioning, whereas it does not have a disproportionately negative effect on effortful processing. However, since all subjects were of pre-senior age, it still is possible that the individuals in the older group were too young to show effects of age on effortful processing. The role of medication or psychotic symptoms in the effort hypothesis could not be tested in this study.

The results provide support for the cognitive speed hypothesis, but not for the effort hypothesis. The depressive group had fairly consistent deficits in the performance of speed tasks (CST, SCWT, MST), but less consistent deficits in the performance of memory tasks that do not reflect speed of information processing (VVLT and Verbal Fluency). This suggests that in young to middle-aged unmedicated depressive outpatients, cognitive deficits are probably best characterised by cognitive slowness. Interestingly, in the field of cognitive aging research, Salthouse and others [36 45] argued that the speed of information processing should be considered a resource for cognitive functioning. According to these authors, a slower speed of information processing may affect higher information processing, for example because the end products of basic processing are sometimes no longer accessible when they are needed for higher cognitive processing. This might explain why our depressive group had a deficit in the retrieval of words stored in working memory. Nebes et al. [7] suggested that both cognitive speed and working memory should be considered resources for cognitive functioning. Our results are in line with there being a cognitive resource problem in major depressive disorder, irrespective of whether cognitive resources are defined by cognitive speed or by cognitive speed and working memory. It is possible that younger outpatients are more able to compensate for slower cognitive speed than older patients, or more severely depressed inpatients. This would explain why deficits of higher cognitive functioning over and above decreased cognitive speed are found in older or in more severely depressive individuals [28-31 48].

In summary, this study showed that deficits in several cognitive domains are present in unmedicated adult depressive outpatients. In this study, the deficits were attributable to major depressive disorder and were not likely to be caused by more general physical disease-related factors that would also be present in individuals with severe allergic rhinitis. The results are not in line with the effort hypothesis in major depression: although depressed patients showed

impairment of automatic and effortful subtasks, their performance on effortful tasks was not disproportionately poorer than that on automatic tasks. In contrast, results are consistent with the cognitive speed hypothesis, by which depressive disorder is characterised by a reduction in cognitive resources. Reduced speed of information processing seems the central cognitive deficit in major depressive disorder, and slowness in cognitive speed is likely to be a general limiting factor for higher cognitive functioning, like memory retrieval, or executive functioning.

CHAPTER 3

Complaints of mental slowness, forgetfulness, lack of concentration, and depressive symptoms in young versus old subjects: results from the Maastricht Aging Study[*]

ABSTRACT

There is a lack of information on the relation between depressive symptoms and specific cognitive complaints in the general population, and on the influence of physical illness and demographic variables. We examined this relationship, focusing on complaints of memory, cognitive speed, and concentration in a younger (N=642) and an older (N=675) age group. Cognitive complaints were related to depressive symptoms in both groups, independently of confounding variables. Of all complaints, decreased cognitive speed was most prevalent. Overall, decreased cognitive speed was most strongly related to depressive symptoms. Cognitive complaints are independently associated with depressive symptoms and could be helpful in recognising depressive symptoms in the general population.

[*] H.M. den Hartog, H. Bosma, M. van Boxtel & J. Jolles: submitted.

Introduction

Depressive symptoms are highly prevalent in the general population and especially in the elderly, with percentages ranging from between 13% and 35% [15 17 71]. This high prevalence among elderly subjects is sometimes ascribed to the higher incidence of physical illness in the elderly [9]. Depressive symptoms, especially in the elderly, can be disguised as somatic complaints, stress, tiredness, or sleeping problems [72]. They have also been related to changes in objective and subjective cognitive functioning. Especially forgetfulness appears to be important in this respect [25 26 65 73]. Indeed, a moderate-to-strong positive association has been found between the severity of depressive symptoms and memory complaints [25 26]. More precise information with regard to the relation between depressive symptoms and cognitive functioning is sparse, at least in the general population. There is a lack of information with regard to complaints of mental slowness, whereas evidence exists that performance decrements in speeded tasks appear earlier than those on memory tasks (for example [45]). Likewise, a lack of information exists with respect to the possible influence of co-morbid diseases and physical condition, which could especially be of importance in older subjects.

Thus, three issues are important when evaluating the possible relation between depressive symptoms and cognition in the general population. First, there is a lack of studies that explicitly address the relation between depressive symptoms and various aspects of cognitive functioning in the general population, especially among young and middle-aged subjects. The only studies of younger subjects involved individuals with psychiatric conditions or neurological impairments [74 75]. Second, it is not known whether cognitive complaints in domains other than memory functioning could be of relevance in the etiology of depressive symptoms. Subjective cognitive slowing could be important in this respect in view of recent studies showing that decreased speed of information processing may be of greater importance than a reduction in memory functioning, at least in older people [45 76]. Third, most studies of depressive symptoms and cognitive complaints did not control for physical health as possible confounding variable. Because the prevalence of both memory complaints and physical disease increase with age [77], the relationship between depressive symptoms and cognitive complaints could be mediated by physical illness.

It is important to evaluate the relation between depressive symptoms and subjective cognitive functioning in a normal aging population because of the high prevalence of cognitive complaints among older individuals, which may approach 50% in subjects older than 50 years of age [78-80]. A substantial proportion of older people with memory complaints may actually suffer from unrecognized depressive symptoms. Indeed, Lépine et al. [17] found in a multi-centre European study that 43% of the people who were found to be depressed had failed to seek any help, and that the subjects' depression was unrecognized before the study. Half of these individuals complained of memory or concentration problems [81].

The aim of the present study is therefore to evaluate the relation between depressive symptoms and cognitive complaints of memory, cognitive speed, and concentration in a large population sample involving more than 1300 healthy subjects aged 24-88 years. We controlled for potential risk factors for depressive symptoms, such as demographic variables (sex, education, and marital status) and physical health (somatic disorders and instrumental activities of daily life), and evaluated a possible effect of the factor 'age' by comparing younger and older groups of subjects.

Methods and materials

Participants

The present study was based on cross-sectional questionnaire data derived from the Maastricht Aging Study [59 60], an ongoing longitudinal study of determinants of cognitive aging. Participants were recruited from the Registration Network Family Practices (RNH [82]). The RNH was established primarily as a sampling frame for research purposes. In the period 1993-1995, 1,869 people were examined. In the present study, for 1,317 (70.5%) healthy individuals complete data sets were available (see 'measurements' section below) and these individuals were included. The mean age was 51.3 years (± 16.3) and 642 (47.7%) participants were women. Participants were clustered into two age groups (24-50 years and 50-88 years), based on the median age of the total group.

Measurements

Depressive symptoms

Depressive symptoms were measured with the Depression subscale of the revised Symptom Checklist (SCL-90 [83]; Dutch version [84]). The SCL-90 is a widely used multidimensional self-report inventory of current psychopathology. Items are rated on a 5-point scale. The subscale depression contains 16 items, which reflect symptoms of depression (score range 16-80). This subscale was used as an index of the severity of depressive symptoms. The study of Steer et al. [85] showed a concurrent validity of 0.89 of the Depression subscale of the SCL-90 with the Beck Depression Inventory [58] in a sample of psychiatric outpatients.

Cognitive function

Subjective cognitive complaints were assessed by asking the respondents whether they considered themselves forgetful (memory complaints; yes/no), whether they had difficulties in concentrating (concentration complaints; yes/no), and whether they had difficulties in activities and work because of slower thinking (cognitive speed complaints; yes/no).

Possible confounding variables

Sex, level of education, marital status, and physical health were entered in the analysis as confounders, because of their possible effect on depressive symptoms. Educational level was indexed on an 8-point scale, ranging from unfinished primary school (1) to university degree (8) [68]. Marital status (unmarried, married or living together, divorced, widowed) was transformed into a dichotomous variable with the categories 'married or living together' and 'other'. Physical health was measured by the presence of several chronic somatic disorders, as well as by problems with instrumental activities of daily life (IADL). Chronic somatic disorders that were included were chronic obstructive pulmonary disease or chronic bronchitis, hepatitis, liver cirrhosis, inflammation of the gut, kidney disease, cardiac angina, history of heart attack, cardiac insufficiency, hypertension, diabetes mellitus, thyroid dysfunction, rheumatism or arthritis, or cancer. A dichotomous somatic disease variable was constructed with the categories 'no somatic disorders' and 'one or more somatic disorders'. Problems with IADL were measured by asking the respondents whether they needed help with shopping, housekeeping, personal hygiene, dressing, and preparing meals. A composite score of 0-5 was used as covariate, in which a higher score reflected worse IADL.

Statistical methods

Between the younger and the older age groups, differences in age were measured using a Student t-test, differences in education and IADL were measured using Mann-Whitney U-tests, and differences in sex, marital status, and somatic diseases were measured using Chi-square tests. Within each age group, separate linear regression analyses were computed to determine whether the independent variables (cognitive complaints) were related to the dependent variable (depression). A linear regression analysis in which all variables were entered together (sex, marital status, somatic disorders, IADL, memory, cognitive speed, and concentration) was performed for each age group. In this way, each cognitive variable was controlled for all possible confounding variables and for the other cognitive complaints. All tests were two-sided with a significance level of 0.05. Statistical tests were performed with the SPSS for Windows software, version 9.0 (SPSS, Inc., Chicago).

Results

Table 1 shows the descriptive characteristics of the total group, and of the young and old groups. The young and old groups did not differ in depressive symptoms (overall mean 20.6 ± 6.2; score range 16-62), sex, or marital status. However, the young group was higher educated, had fewer somatic disorders, and had better IADL function, which is in line with common knowledge of age-related effects. In the total groups, complaints of memory (31.0%) and especially speed (50.3%) were highly prevalent, in contrast to complaints of concentration (8.0%). Complaints were not evenly distributed over the two age groups. The young group had significantly fewer complaints of memory, cognitive speed, and concentration, compared with the old group. Especially higher prevalence of complaints of speed in the old group compared to the young group was considerable, as twice as many older individuals than younger individuals complained of diminished cognitive speed (66.7% versus 33.2%). Older individuals also complained more of memory problems (35.9% versus 25.9), and concentration problems (9.8% versus 6.1%).

Within the young group, unadjusted linear regression analyses with separate models for cognitive complaints of memory, speed, and attention showed significant associations between depressive symptoms and all cognitive complaints (Table 2). Cognitive speed showed the strongest association with depressive symptoms (B=4.33). To test which variables were independently related to depressive symptoms after controlling for confounding variables, a linear regression analysis was performed in which all studied variables (sex, marital status, somatic disorders, IADL, memory, cognitive speed, and concentration) were entered in the analysis. In this way, each cognitive variable was controlled for all confounding variables, including the other cognitive complaints. In the young group depressive symptoms were significantly related to complaints of memory (B=1.47), complaints of cognitive speed (B=3.71), complaints of concentration (B=2.44), and marital status (B=1.60) (see Table 3). Having cognitive complaints, and not being married, or not living together were independent risk factors for depressive symptoms in the young age group.

Table 1. *Baseline descriptive statistics for young and old age groups*

	Total group (N=1317)	Young age group (N=642)	Old age group (N=675)	test	df	p-value
Age (mean±sd)	51.3±16.3	36.8±8.0	65.0±8.5	t=-61.81	1315	0.00
Sex (% female)	48.7%	50.2%	47.4%	χ^2=1.00	1	0.32
Level of education (mean±sd)	3.7±1.9	4.3±1.8	3.1±1.8	z=-12.20	7	0.00
Marital status (% married or living together)	78.3%	78.3%	78.8%	χ^2=0.04	1	0.84
Somatic disorders (% disorders)	45.2%	28.7%	60.9%	χ^2=138.00	1	0.00
IADL (mean±sd)	0.2±0.6	0.0±0.3	0.3±0.7	z=-7.67	4	0.00
Depressive symptoms (mean±sd)	20.6±6.2	20.6±6.7	20.6±5.7	t=0.05	1315	0.96
Memory complaints (% yes)	31.0%	25.9%	35.9%	χ^2=15.37	1	0.00
Cognitive speed complaints (% yes)	50.3%	33.2%	66.7%	χ^2=147.62	1	0.00
Concentration complaints (% yes)	8.0%	6.1%	9.8%	χ^2=6.15	1	0.01

Table 2. *Effects of cognitive complaints on depressive symptoms for younger and older age groups unadjusted for covariates. Reported are unstandardised B-weights and confidence intervals*

	Young age group		Old age group	
	B	95% CI	B	95% CI
Memory	2.47 **	1.31 - 3.63	2.80 **	1.92 - 3.68
Cognitive speed	4.33 **	3.29 - 5.37	2.90 **	2.00 - 3.79
Concentration	3.02 **	0.87 - 5.16	-0.12	-1.58 - 1.34

**p<0.01

Within the old group, unadjusted linear regression analyses with separate models for cognitive complaints of memory, speed, and attention showed significant associations between depressive symptoms and complaints of memory and cognitive speed (Table 2). There was no significant association between depressive symptoms and complaints of concentration. Again, complaints of cognitive speed showed the strongest association with depressive symptoms (B=2.90). To test which variables were independently related to depressive symptoms after controlling for possible confounding variables, a linear regression analysis was performed in which all variables (sex, marital status, somatic disorders, IADL, memory, cognitive speed, and concentration) were entered in the analysis (Table 3). In the old age group, after controlling for confounding variables, depressive symptoms were positively associated with complaints of memory (B=2.13), complaints of cognitive speed (B=2.49), female sex (B=1.12), and lower IADL function (B=1.14).

Table 3. *Effects of demographic, physical, and cognitive variables on depressive symptoms in young and old age groups. Reported are unstandardised B-weights and confidence intervals*

		Young age group		Old age group	
Domain	variable	B	95% CI	B	95% CI
Demography	Sex	0.94	-0.04 – 1.91	1.12 *	0.20 – 2.04
	Education	-0.09	-0.38 – 0.19	-0.23	-0.47 – 0.05
	Marital status	1.60 **	0.42 – 2.78	-0.26	-1.36 – 0.84
Physical health	Somatic disorders	1.01	-0.07 – 2.09	0.84	-0.04 – 1.71
	IADL	1.51	0.00– 3.02	1.14 **	0.51 – 1.78
Cognitive complaints	Memory	1.47 *	0.34 – 2.59	2.13**	1.21 – 3.04
	Cognitive speed	3.71 **	2.62 – 4.79	2.49 **	1.61 – 3.38
	Concentration	2.44*	0.41 – 4.47	0.07	-1.34 – 1.48

* p< 0.05

**p< 0.01

Discussion

We studied the relationship between cognitive complaints and depressive symptoms in a large population-based sample of individuals who did not suffer from major depression. The possible effect of age on depression-related factors was taken into account by studying a young (24-50 years) and an old (50-88 years) group. The possible effects of some depression-related demographic and physical factors were taken into account by statistically adjusting for these variables.

In the total group, complaints of memory (31.0%) and speed (50.3%) were highly prevalent, in contrast to complaints of concentration (8.0%). Compared to the young group, the old group had more complaints of cognitive function. Interestingly, the prevalence of complaints of cognitive speed was disproportionately higher: older subjects had twice as many complaints of speed, and this was considerably higher than the increase in complaints of memory and concentration. As expected, in the young group depressive symptoms were positively related to complaints of cognitive speed, memory, and attention, even after adjustment for possible demographic and physical confounders. Indeed, complaints of cognitive speed were more strongly related to depressive symptoms than were complaints of memory. In the older age group complaints of speed and memory were related to depressive symptoms, even after controlling for possible confounding variables.

The finding that complaints of cognitive speed were at least as strongly related to depressive symptoms as complaints of memory were, is a new and interesting finding. Until now, research has tended to focus on subjective memory problems, but recent research of cognitive

aging shows that cognitive slowing may account for many age-related dysfunctions in cognitive performance, including deficits of memory [36]. Cognitive slowing is related to several normal and pathological phenomena. For example, cognitive slowing is related to normal cognitive aging [45], to severe white matter lesions in otherwise healthy elderly individuals [76], and to major depression [7 86]. Our finding that complaints of cognitive slowness are related to depressive symptoms in a normal aging population is consistent with these findings.
Some of the demographic and physical variables were related to depressive symptoms. In the young group depressive symptoms were related to not being married, or not living together, and in the old group depressive symptoms were related to female sex, and poorer IADL. After controlling for these variables the relation between cognitive complaints and depressive symptoms still remained. Thus, cognitive complaints are related to depressive symptoms and are not merely secondary to physical illness. Therefore, the detection of cognitive complaints might be of value in primary care in order to improve the recognition of depressive symptoms. This might be especially relevant in older individuals, a group in which it seems especially difficult to detect depressive symptoms. Our results suggest that in older individuals complaints of diminished cognitive speed and memory might be indicators of current depressive symptoms.

Some limitations of the current study must be kept in mind when interpreting the data. First of all, the cross-sectional design of the study means that conclusions cannot be drawn about causality. Second, the findings are limited to cognitive complaints, and cannot be generalised to objective cognitive functioning because there is only a weak association between cognitive complaints and current objective cognitive functioning [25 26]. Third, it is possible that the subjective complaints of cognitive speed, memory, and attention reflect negative affect. However, since we found a very large discrepancy in the incidence of complaints of concentration compared to complaints of memory and cognitive speed, this possibility seems unlikely. This is further strengthened by low Pearson's correlation coefficients between the cognitive complaints, with the highest coefficient of r=0.17 between complaints of cognitive speed and complaints of memory.
In summary, this study showed that specific cognitive complaints are related to depressive symptoms. Although until now studies have concentrated on complaints of memory, this study showed that complaints of cognitive speed are at least as important in relation to depressive symptoms.

CHAPTER 4

Relationship between allergic rhinitis, disturbed cognitive functions and psychological well-being*

ABSTRACT

Symptomatic allergic rhinitis reduces quality of life as a result of the symptoms experienced and possibly as a result of impaired psychological well-being and cognitive functioning. In allergic rhinitis, few investigations have measured cognitive functions objectively and it remains uncertain whether allergic rhinitis is related to an objective reduction in cognitive functions. The objective was to evaluate the relationship between symptomatic allergic rhinitis, cognitive functions, and psychological well-being. Differences between subjective and objective cognitive impairments were evaluated. The cognitive functions (working memory, memory retrieval, speed of information processing, and flexibility of information processing) and psychological well-being of 26 patients with symptomatic allergic rhinitis and 36 healthy controls matched for intelligence, education, age, and sex were compared. The influence of education, intelligence, sex, and age was considered. Overall, psychological well-being was significantly impaired in the patient group, as shown by higher scores in feelings of insufficiency, complaints of somatisation, sleep disturbances, and depressive feelings, whereas cognitive function was not. Allergic rhinitis was related to significantly impaired psychological well-being and to perceived impaired cognitive functioning. However, no significant objective impairment of cognitive functioning was found. Possibly, allergic patients may temporarily put more effort in sustaining performance, resulting in earlier exhaustion, which is not noticed during assessment but which impairs psychological well-being.

* B. Kremer, H.M. den Hartog & J. Jolles. Clinical and Experimental Allergy: in press.

Introduction

Allergic rhinitis (AR) is one of the most common chronic diseases. Its prevalence is 15-20% in industrial nations, with an even higher prevalence of 42% among children [87]. The effects of AR are often underestimated and the disease is often unjustly considered trivial. Besides the immediate symptoms, illnesses such as polyposis nasi, allergic asthma, or sensitization to other allergens subsequently occur in patients with AR. Not only physical symptoms of the affected organ, but also psychological disorders, disruption of social activity, and the inability to function in every-day life contribute to a reduced quality of life (QOL) [52-54]. Symptoms appear which may either be caused by, or lead to, a reduction in cognitive functioning, e.g. the reduced ability to concentrate or remember. Other symptoms may be reduced productivity, fatigue, a worn-out feeling, frustration, unrest, irritability, and stress.

So far, there is little direct evidence for there being a relationship between AR and disturbed cognitive functions [88-90]. Marshall et al. [88] found that allergic patients were significantly slower in information processing than controls in one out of five cognitive speed measures. Thus, on four measures no differences were found. The question is whether this is really indicative of cognitive dysfunction in symptomatic allergic rhinitis. This question is very relevant because cognitive dysfunction frequently has a direct negative impact on most aspects of daily life. Complex aspects of cognitive functioning, such as remembering things and making decisions [59], as well as basic cognitive functions such as speed [45 76], directly influence most aspects of daily activities. Consequently, a slowing down of thinking and motor action for example may lead to an increased effort of the part of the patient in an attempt to maintain a certain level of productivity. The result may be increased fatigue or reduced productivity and increased susceptibility to distraction. When cognitive functions are affected, one might find that it is more difficult to remember the shopping list or drive safely through rush hour traffic. As a result, compromised cognitive functions indirectly affect well-being. The question arises whether cognition is compromised, to what extents in patients with AR, and whether cognitive dysfunctions affect well-being in patients with AR. Evidence of a correlation between AR and impaired cognitive functions could provide new arguments for the healthcare discussion, of the treatment costs and the costs of AR to society, since not only the patient's subjective physical and emotional condition and quality of life, but also his/her productivity at work may be affected. This might open the door to a new dimension in the determination of possible health effects from AR.

The following study was performed to clarify whether the subjective decrease in cognitive functions of patients with symptomatic AR (quality of life measurements) can be objectified with standardised, neuropsychological measures and whether psychological well-being is affected. We examined cognitive functions that are sensitive to mild impairments [91], namely working memory, memory retrieval, speed of information processing and flexibility of information processing.

In contrast to the existing research we evaluated the education and intelligence of our subjects because both are known to have a major influence on a person's cognitive functions. Moreover, because age and sex influence cognitive functions as well [45 59 76], a multivariate analysis including age, sex, education, and intelligence as covariates was performed. Psychological well-being is known to be influenced by age and sex, and therefore these two factors were used as covariates in a separate analysis.

Methods and materials

Study design

Patients with symptomatic seasonal allergic rhinitis (sSAR) or symptomatic perennial allergic rhinitis (sPAR) and healthy controls, groupwise matched for age, sex, education, and intelligence, were included in a cross-sectional study performed between September 1999 and June 2001. Allergic rhinitis patients were outpatients fromt the Department of of Otorhinolaryngology, Head, and Neck Surgery of the university hospital of Maastricht, the Netherlands. Control patients were healthy people from the general population, who had declared in the past to be willing to participate in scientific research.

SSAR patients were examined during pollen allergen exposure in the spring and summer and sPAR patients were examined during increased symptom burden in the fall and winter. Inclusion criteria were age between 18 and 65 years; a positive medical history of sSAR of sPAR; anti-allergic pre-treatment during a previous season; positive radio-allergo-sorbent tests for serum-specific immunoglobulin E or positive skin prick test for tree- and/or grass- and/or weed pollen in the sSAR group and for house dust mite and/or animal allergens in the sPAR group; the presence of at least two symptoms of AR being at least of moderate strength in the patient groups and/or a RQLQ [52] score of >1; and in all cases a written consent. Exclusion criteria were the presence of any form of rhinitis in the control group; the presence of forms of rhinitis other than sSAR and sPAR in the patient groups; the presence or history of psychiatric disorder in both groups; the use of interfering medications (any nasal decongestants, nasal corticosteroids, anticholinergics, sympathomimetics, theophylline preparations, sedatives, antidepressants, and all other types of psychotropic drugs), anti-allergy treatment before the start of the study depending on the pharmacokinetics of the drugs used; the presence of contraindicated illnesses, e.g. asthma, diseases or traumas of the central nervous system, severe common diseases, pregnancy, nursing or insufficient contraception; drug or alcohol addiction; impaired visual or auditory functions which could disturb communication and/or examination; and insufficient knowledge of the Dutch language. The assessment was carried out in one session of two hours.

Evaluation of education and intelligence

Educational level was indexed on an 8-point scale, ranging from unfinished primary school (1) to university degree (8) [68]. To get a reliable estimation of the intelligence quotient (IQ) of the patients, the shortened form of a widely used Dutch intelligence test, the Groninger Intelligence Test [92], was used. This shortened form consisted of arithmetic, vocabulary, mental rotation, and analogies/reasoning capacity.

Evaluation of cognitive functions

To minimilise the risk of false positive (statistical type I) errors, we reduced the number of measures to four by selecting highly sensitive measures [59 76 91]. To assess verbal memory, the computerised *Visual Verbal Learning Test* (VVLT) [64] was used. Fifteen words were visually presented on a computer screen and the subject was asked to recall as many words as possible. This procedure was repeated five times. Performance on the first trial reflects capacity of working memory. Working memory is the form of memory that is used to store information with a limited capacity for a brief period of time. The total number of words actively remembered after 20 minutes is a measure of the retrieval of the learned words from

long-term memory ('memory retrieval'). To test the speed and flexibility of information processing, the *Stroop Colour Word Test* (SCWT) [62] was used. The test involves three cards displaying colour names (SCWT-1), coloured patches (SCWT-2), and colour names printed in incongruously coloured ink (SCWT-3). On the first and second cards, the coloured names and patches have to be read aloud as quickly as possible, which both reflect speed of information processing. The performance on these reading tasks was averaged to give one measure of speed of information processing. On the third card, the amount of time needed to discard irrelevant but very salient information (reading of colour name) in favour of a less obvious aspect (naming colour of ink) is recorded. The percentage difference between SCWT-3 and the mean of SCWT-1 and SCWT-2 reflects 'colour word interference', which is regarded here as a measure of cognitive flexibility.

Evaluation of allergic symptoms and QOL

All patients with AR rated the severity of nasal symptoms (itching, secretion, sneezing and congestion) on an ordinal scale ranging from 0 to 3 (0=no, 1=slight, 2=moderate, 3=severe symptoms). The individual symptom scores were summed to give an overall symptom score. Furthermore, in all patients with AR the Rhinitis Quality of Life Questionnaire (RQLQ) was used as a disease-specific questionnaire [52]. The RQLQ assessed the extent of subjective disturbances by scoring the presence of various rhinitis symptoms and their emotional and practical effects. Twenty-eight symptoms, divided into seven subgroups (nasal symptoms, ocular symptoms, general symptoms, sleeping disorders, practical problems, limitations of activity, and emotional disorders) were evaluated. Scores ranged from 0 (non existent) to 6 (maximum). The overall QOL was calculated from the mean values of the 28 symptoms.

Evaluation of psychological well-being

The Symptom Checklist (SCL-90) [84] is a 90-item multidimensional questionnaire designed to screen for a broad range of psychological problems. Each of the 90 items is rated on a 5-point Likert scale, ranging from 0 (not at all) to 4 (extremely). The total score is a measure of overall psychological well-being, and the higher the score the worse the psychological well-being. The questions are divided over eight primary symptom dimensions: hostility (anger), insufficiency (in thinking and acting), somatisation (somatic complaints), agoraphobia (fear of being in places in which it is difficult to get help), anxiety, depression, sensitivity (distrust in other people), and sleep. Symptoms of depression were measured with the Beck Depression Inventory (BDI) [58], a widely used self-report questionnaire for this purpose.

Ethical-legal aspects

The study was performed in compliance with the declaration of the 18th Conference of the World Physicians´ Association in Helsinki and its revised versions. The ethics review board of the local Medical Faculty approved the study protocol before the study was initiated. Each patient gave his/her written consent for participation.

Statistical analysis

Statistical tests were performed with SPSS for Windows version 9.0 (SPSS, Inc. Chicago). All tests were two-sided and the significance level was set at 0.05. The normal distribution of all variables was tested with Kolmogorov-Smirnov Goodness of Fit Tests. Depending on the normality of the distribution, parametric (MANOVA, Student T-test) or nonparametric

(Mann-Whitney, Chi-square) tests were used to determine group differences and the relationship between the independent variable (group) and the dependent variable (cognitive function and psychological well-being). Group differences in age and IQ were measured using Student T-tests, differences in education were measured using Mann-Whitney tests, and differences in sex were measured using Chi-square tests. The cognitive variables existed of working memory (first trial of VVLT), memory retrieval (VVLT-delayed recall), speed of information processing (average of SCWT-1 and SCWT-2), and flexibility of information processing (SCWT-interference). For the operationalisation of well-being, our variables of primary interest were the overall psychological well-being score of SCL-90 and BDI.
Although groups were matched on age, sex, education, and intelligence, some variance may still be present this way. Therefore, these variables were used as covariates in a MANCOVA to test the effect of group on working memory, memory retrieval, speed of information processing, and flexibility of information processing. The criterion of Wilks's Lambda was taken as an indicator of a significant omnibus effect. Since only age and sex had an effect on mental well-being, only these variables were used as covariates in a separate MANCOVA to test the effect of group on overall psychological well-being (SCL-90 and BDI). When the results for the overall measure of psychological well-being of SCL-90 were significant, the eight subscales of the SCL-90 were analysed, using post-hoc ANOVA. Correction for post-hoc multiple testing was achieved by dividing the overall significance level of 0.05 by the number of post-hoc tests.

Results

Homogeneity of the groups
Thirty-nine allergic patients were included in the study. Of these, 4 patients were excluded due to the presence of contraindicated illnesses (asthma, COPD). Of the remaining 35 patients, 8 patients had insufficient symptom and RQLQ scores, which left 27 patients. One patient was excluded because of probable depressive disorder, leaving 26 patients who remained in the study. Thirty-six healthy controls were included, group wise matched for age, sex, education and intelligence. There were no significant differences between the groups with respect to age, sex, education, and intelligence (table 1).

Table 1. *Demographic data for groups*

	Patient group (n=26)	Control group (n=36)	Test value	p-value
Age mean (sd)	38.5 (11.8)	42.1 (11.6)	T= -1.21	0.23
range	20.7-61.5	22.1-62.8		
Sex (m/f)	13/13	15/21	χ^2= 0.01	0.99
Education mean (sd)	5.0 (1.5)	4.6 (1.6)	Z= -0.82	0.41
range	2-8	2-8		
IQ mean (sd)	116.1 (11.6)	116.1 (9.4)	T= 0.32	0.75
range	79-132	95-132		

Symptomatology and QOL Scores

Symptom scores as well as RQLQ scores were only assessed in the patient group. We assumed that the healthy controls would show normal scores, as has been confirmed in numerous previous studies [52 54 93]. Twenty patients in the patient group had a symptom score ≥4 (at least two moderate symptoms) and an RQLQ score >1 (RQLQ mean value 2.48 ± 0.76, range 1.32-3.79). Three patients did not meet the required symptom score, bur their RQLQ-score was >1 (1.14, 1.79 and 4.29). One patient had an RQLQ score <1, but fulfilled the symptom score and two patients with RQLQ scores of 3.18 and 1.14 had missing symptom score information.

Cognitive functions

Table 2 shows the mean cognitive performance of the patient and control groups. A between-subjects multivariate analysis of covariance (MANCOVA) with group (patient and control) as independent variable was performed on 4 dependent variables: working memory, memory retrieval, speed of information processing and flexibility of information processing. Age, sex, intelligence, and education were treated as covariates. There was no significant omnibus effect of group on the dependent variables ($F_{(4, 53)}$=0.52, p=0.73), indicating that the patient and control groups did not differ significantly in cognitive performance. In this model, significant omnibus effects emerged for the covariates age ($F_{(4, 53)}$=4.89, p=0.00) and intelligence ($F_{(4, 53)}$=4.27, p=0.01), indicating that age and intelligence had a significant effect on one or more of the cognitive variables. Between-subjects effects showed a significant effect of age on flexibility of information processing ($F_{(1, 56)}$=7.42, p=0.01) and on memory retrieval ($F_{(1, 56)}$=4.42, p=0.04) and a significant effect of intelligence on flexibility of information processing ($F_{(1, 56)}$=15.36, p=0.00). Since these covariates have a significant effect on flexibility of information processing and memory retrieval, it is possible that an interaction effect existed between group and age, and there may also be an interaction between group and intelligence on flexibility of information processing. To test for these interaction effects on cognition, post-hoc analyses were performed which were corrected for sex, education and intelligence (for the interaction between group and age), or for sex, education and age (for the interaction between group and intelligence). Since three post-hoc analyses were necessary, post-hoc multiple testing effects were corrected for by dividing the required significance level by three (p< 0.017).

In order to test the interaction-effect between group and age on flexibility of information processing and on memory retrieval, patients and controls were divided into a younger (21-41 years) and an older (42-63 years) age group, based on the median value as a cut-off point. Analyses were controlled for sex, education and intelligence. An interaction between patient group and age group on memory retrieval was revealed ($F_{(1, 55)}$=7.28, p=0.01) in which the older patient group had a significantly compromised performance on memory retrieval (mean words 8.1) compared with the older control group (mean words 10.2). No interaction between patient group and age group on flexibility of information processing ($F_{(1, 55)}$=0.46, p=0.50) was revealed. In order to test the interaction-effect between group and intelligence on flexibility of information processing, intelligence was divided in two classes (high and low), arbitrarily based upon the median value as a cut-off point (median=117). No interaction was revealed between patient group and intelligence-group on flexibility of information processing ($F_{(1, 55)}$ =0.17, p=0.68).

Thus, the overall patient group did not differ significantly from the overall control group on cognitive performance. When age groups were considered no significant differences were found for working memory, speed of information processing, and flexibility of information processing. There was an effect of age on memory retrieval, which was significantly worse in the older patient group than in the older control group. When intelligence was considered patient groups and control groups still did not differ on the cognitive measures.

Table 2. *Cognitive performance for groups*

	Patient group	Control group	t-value	p-value
Working memory: mean number of words (sd)	5.6 (2.1)	5.8 (1.7)	-0.28	0.78
Memory retrieval: mean number of words (sd)	9.9 (3.2)	10.1 (2.4)	-0.22	0.82
Speed of information processing: mean seconds (sd)	47.2 (7.5)	46.5 (6.4)	0.38	0.71
Flexibility of information processing: mean percentage (sd)	67.7 (34.8)	76.2 (22.3)	-1.18	0.24

Psychological well-being

Table 3 shows descriptive data for depressive symptoms of BDI, overall well-being of SCL-90 and of the subscales hostility, insufficiency, somatisation, agoraphobia, anxiety, depression, sensitivity, and sleep of the SCL-90 for the patient group and control groups. A between-subjects MANCOVA with group (patient and control) as independent variable was performed on overall psychological well-being (SCL-90 score) and depression (BDI score). Age and sex were treated as covariates. Results showed an omnibus effect of group ($F_{(2, 57)}$=3.32, p=0.04). Between-subjects effects showed that group had an effect on well-being ($F_{(1, 58)}$=6.69, p=0.01) and on depression ($F_{(1, 58)}$=5.41, p=0.02). Patients had significantly worse psychological well-being and higher depression scores than healthy controls. To find out which subscales of the SCL-90 were responsible for the overall effect, post-hoc analyses with group as independent variable and the eight subscales of SCL-90 as dependent variables were performed, controlled for age and sex. To control for post-hoc multiple-testing effects, a significance level not exceeding 0.006 (0.05 divided by 8) was required. The patient group had significantly higher scores on the SCL-90 subscales insufficiency (patient 16.9 versus control 13.1, $F_{(1, 58)}$=11.06, p=0.002), sleep (patient 5.9 versus control 4.6, $F_{(1, 58)}$=8.03, p=0.006), and somatisation (patient 21.5 versus control 17.2, $F_{(1, 58)}$=12.04, p=0.001), reflecting worse well-being in the patient group.

Table 3. *Psychological well-being for groups*

	Normal score range[#]	Patient group mean (sd)	Control group mean (sd)
BDI	0-9	7.0 (5.3)	4.8 (4.2)
SCL-90 overall well-being	108-129	133.4 (33.5)	118.0 (21.5)
SCL-90 hostility	6-7	7.7 (1.6)	6.9 (1.3)
SCL-90 insufficience	12-14	16.9 (7.0)	13.1 (2.8)
SCL-90 somatisation	15-18	21.5 (6.8)	17.2 (4.7)
SCL-90 agoraphobia	7-8	7.8 (1.3)	8.0 (2.5)
SCL-90 anxiety	11-13	13.8 (4.7)	12.9 (2.9)
SCL-90 depression	18-22	23.4 (7.4)	21.7 (6.4)
SCL-90 sensitivity	23-26	24.9 (9.1)	22.8 (4.0)
SCL-90 sleep	3-4	5.9 (2.7)	4.6 (1.6)

[#] Based on norm scores in manual [58]

Discussion

Since the introduction of the RQLQ by Juniper and Guyatt in 1991 [52], the evaluation of quality of life of patients with AR has played an increasingly central role in the determination of the severity of the disease and in monitoring the response to therapy. It became clear that patients not only complain of disease-related symptoms but also of more common symptoms such as fatigue, a feeling of being worn out, and a diminished productivity and a reduced ability to concentrate. They also had emotional problems, for example irritability, frustration and impatience as well as restlessness. Besides the actual costs of treatment and sickness leave, there are the additional costs of reduced productivity at home as well as in the work place [89]. Treatment costs are playing an increasingly important role in health economics. Our main interest was to determine whether symptomatic AR affected cognitive functioning, which could affect the patient's productivity.

A fundamental problem of using questionnaires to determine QOL is that questionnaires reflect subjective feelings. It is possible that patients considered their cognitive functions to be impaired, whereas objectively this is not the case. We therefore used standardised objective measures of cognitive functioning, assessing only those functions that are sensitive to mild impairments [59 91]. Contrary to previous studies [88], intelligence, education, sex, and age were taken into consideration in both groups, since these variables have a significant impact on cognitive performance. A multivariate analysis controlling for those variables was performed. The psychological well-being and the presence of depressive symptoms were determined by standardised questionnaires (SCL-90, BDI).

The cognitive functioning of healthy controls and patients with symptomatic AR was not significantly different. However, age and intelligence affected cognitive functions in both groups, but the influence of intelligence did not differ between the two groups. When the patient and control groups were divided into age groups, memory retrieval was significantly poorer in the older patient group than in the older control group. This is an indication that the influence of allergic rhinitis may become evident in subjects who are more vulnerable. No

other significant age-related intergroup differences were detected. The patient group had significantly more depressive symptoms and had a lower overall psychological well-being than the control group. The latter could be explained by higher scores on several subscales of the SCL-90 (insufficiency, somatisation and sleep) in the patient group. Age and sex did not have a significant effect on depressive symptoms or psychological well-being. The results of this study indicate that AR does not affect cognitive functions when measured by a multi-trial word learning test and a complex information processing test. Although allergic patients do have more complaints related to psychological well-being, they clearly do not have objective deficits in cognitive functioning.

To our knowledge only one comparable study of cognitive functions was performed earlier. Marshall et al. [88] found that allergic patients had a significantly slower speed of information processing, measured with the Hick paradigm choice reaction time test [94], than controls, but no significant differences in four other measures of speed of information processing were found. Marshall et al. did not statistically correct for possible effects of multiple testing, which makes it possible that the one significant finding was a false-positive result. Furthermore, intelligence and age were not taken into account.

In our study the psychological well-being of the controls was better than that of the patients, as was also found in earlier studies of quality of life [52-54 93]. In other patient groups evidence was found for a causal relationship between psychological ailments, and especially depressive symptoms, and the experience of subjective cognitive complaints [25 74 95 96]. However, these studies also failed to find a correlation between subjective cognitive complaints and an objective limitation of cognitive functions.

A possible explanation for the discrepancy between subjective and objective cognitive performance might involve the psychological construct ´effort` [37 38]. Patients who suffer from symptomatic AR may need to exert themselves more to achieve the same performance as controls, which cause them to tire more easily. Thus allergic patients may be able to sustain a normal performance for a short period of time, for example, during the 2-hour assessment of this study. This investment of more effort results in earlier exhaustion of resources, which patients notice, but not in reduced cognitive functions apparent during the assessment. To test the hypothesis concerning effort, we recommend using neuropsychological assessment protocols that take longer to complete. A second recommendation for future research is to apply a longitudinal study design. This could give interesting additional information on the effects of season and precise information about the intra-individual impact of symptoms on cognitive performance and psychological well-being. This would also overcome possible systematic differences other than the presence of symptomatic allergic rhinitis between patient and control groups, which is a point of discussion in case control studies generally.

CHAPTER 5

Salivary cortisol patterns and cognitive speed in major depression: a comparison with allergic rhinitis and healthy control subjects*

ABSTRACT

Few studies have investigated the relationship between cortisol and cognitive functions other than memory in depression. This study investigated daily salivary cortisol patterns (basal cortisol levels at 8 a.m., 4 p.m., and 9 p.m. and flatness of the diurnal curve) in relation to cognitive speed and memory. 27 unmedicated outpatients with major depressive disorder (MDD) were compared with 36 healthy controls and with 20 allergic rhinitis patients, to determine whether effects should be ascribed to MDD or to more general disease-related processes. MDD patients were characterized by a flatter diurnal cortisol curve and by reduced cognitive speed. Flatter cortisol curves were associated with cognitive slowness over all subjects. However, this relationship is unlikely to be causal; after control for depressive symptoms, flatness of the diurnal cortisol curve was no longer a significant predictor of cognitive slowness. Thus, MDD and related depressive symptoms appeared to be independently associated with altered cortisol secretory patterns and with decrements in cognitive speed.

* H.M. den Hartog, N.A. Nicolson, A.L. van Bemmel, M.M.A. Derix, B. Kremer & J. Jolles. Biological Psychology: accepted.

Introduction

Major depressive disorder (MDD) is characterized by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [39], with approximately 50% of MDD inpatients showing hypercortisolemia. Abnormally low cortisol levels have also been reported, for example in atypical depression [98], as well as flattening of the diurnal secretory curve [99]. In MDD, elevated cortisol levels are associated with memory dysfunction, at least in older people [41 100]. Chronically elevated levels of cortisol are thought to have a negative effect on the hippocampus, which is crucially implicated in memory functioning [40 101]. The vast majority of studies on the influence of glucocorticoids on cognition have focused on geriatric depression. Furthermore, few studies have related cortisol to cognitive functions other than memory; a negative association between global intellectual functioning and daily cortisol levels was found in patients with MDD [102], and an association between higher evening cortisol and faster choice reaction time in healthy older men has been reported [103]. In MDD, cognitive speed of information processing might be especially relevant, as slowing of the speed of information processing has been reported in both geriatric and younger patients with major depression [7 104 105]. To our knowledge, no studies have been undertaken to specifically address the relationship between cortisol and cognitive speed in MDD.

Since the HPA axis is activated by stress, it is conceivable that the stress that accompanies disease could lead to both altered cortisol levels and cognitive impairment. Altered HPA activity in depression might thus reflect an aspecific effect of disease. Many studies have compared depressive patients with healthy controls. However, healthy controls not only lack psychiatric illness, but they also lack secondary disease-related stress and malaise. It is therefore not yet clear whether alterations in cortisol level and in cognitive function are specific features of MDD or reflect non-specific effects of disease. For this reason, the present study compares a group of MDD outpatients to both a healthy control group and to a group of patients with severe symptomatic allergic rhinitis (AR). Like MDD, AR has considerable negative impact on quality of life [52-54], and individuals with severe complaints are likely to consult regularly with medical specialists. AR is a chronic disease of non-neurological origin, and any abnormalities in cognition or cortisol are not expected to be caused by symptomatic allergic rhinitis itself, but rather by the secondary aspects of not feeling well.

The current study investigates basal salivary cortisol levels over the day in relation to cognitive speed and memory in non-psychotic, young to middle-aged, unmedicated MDD outpatients. Since chronic sleep loss can result in higher evening cortisol levels [106 107], possible effects of subjective early waking problems on cortisol were investigated, as well as possible effects of depressive symptoms. We address three questions: (1) Do MDD outpatients show elevated cortisol levels over the day? (2) Are diurnal cortisol levels related to deficits in cognitive speed and memory? (3) Are cortisol patterns and cognitive impairment specific to MDD, or do they reflect more general, disease-related processes?

Methods and materials

Study design

An outpatient group with MDD was compared to two control groups: an outpatient group with severe symptomatic allergic rhinitis (AR) and a healthy group. The examination included neuropsychological measures of intelligence, cognitive speed, memory, and self-report measures of mood and other psychological changes, administered in a single session of approximately 1.5-2 hours, including a short break. At the end, subjects were instructed how to take samples of saliva at home or at work and were given written instructions concerning the timing and procedures for saliva sampling. Saliva samples were taken on two consecutive days directly following the examination. The protocol was reviewed and approved by the Medical Ethical Committee, and subjects gave informed consent. All subjects were paid 11.4 euro for participation and received a written report of their neuropsychological results.

Subjects

The MDD group included 27 outpatients diagnosed by a psychiatrist, following DSM-IV criteria, as having a current episode of major depression. This was the first episode for 22 patients; 2 patients had experienced one earlier depressive episode, and 3 patients had experienced two earlier episodes. MDD patients who were medication-free when they first visited the clinic were assessed before any pharmacological treatment. Patients in whom medication was to be changed because of inadequate clinical response entered the study after a wash-out period of 2 weeks, or 3 weeks in case of ending fluoxetine-treatment. For inclusion, subjects had to be 18-65 years. Exclusion criteria were current use of any psychotropic medication, other current Axis I psychiatric disorders, neurological disorders, somatic disorders that can affect cognitive function (e.g. diabetes, thyroid dysfunction), and drug or alcohol abuse. No subject had ever received ECT treatment.

The group with symptomatic allergic rhinitis included 20 consecutively assessed outpatients from the university department of Otorhinolaryngology, Head and Neck Surgery. Patients with seasonal AR, allergic to grass- and/or tree-pollen, and patients with perennial AR, allergic to house dust mite, were included. Subjects were examined during a symptomatic period. Possible symptoms were nasal secretion, nasal blockage, itching, and sneezing, all self-rated on 4-point severity scales (absent, mild, moderate, or severe). For inclusion, ratings of at least 2 symptoms as moderate or severe (an indication of severe allergic rhinitis) and/or a mean score $\geq$1 on the Rhinitis Quality of Life Questionnaire (RQLQ, see below) [52] were required. Other inclusion criteria were age 18 - 65 years, a positive Radio-Allergo-Sorbent-Test (RAST) for serum-specific immunoglobulin E, and a positive skin prick test for tree and/or grass pollen or for house dust mite allergens. Exclusion criteria were use of psychotropic medication, self-reported history of treatment for neurological or psychiatric disorder, depressive symptoms (a score ≥10 on the Beck Depression Inventory; Beck & Steer, 1993), and drug or alcohol abuse. Any allergy medications (e.g., nasal decongestants, antihistaminics, anticholinergics, sympathomimetics, theophylline preparations) were ended before the assessment took place, with the wash-out period depending on the respective pharmacokinetics.

Thirty-six healthy control subjects were selected from a large pool of healthy control subjects who were participants in the Maastricht Aging Study [59]. Inclusion and exclusion criteria

were the same as for the AR patients, except that the presence of any kind of current allergies or allergies in the past was an additional exclusion criterion for this group.

Measurements

Basal cortisol levels

On two consecutive days at prearranged times in the morning (8 a.m.), late afternoon (4 p.m.) and evening (9 p.m.), subjects collected saliva samples with a cotton dental roll, which was stored in a capped plastic vial ("Salivette", Sarstedt, Etten-Leur, the Netherlands). Subjects were instructed to write down the exact time of cortisol sampling. Uncentrifuged samples were frozen at –20 degrees Celsius until analysis. Salivary cortisol has been shown to be highly correlated with plasma or serum levels; it is largely unbound and represents the free, biologically active fraction of the hormone [108]. Salivary cortisol levels were determined in duplicate by direct radioimmunoassay, using ^{125}I-cortisol and antiserum made against the 3-CMO-BSA conjugate. The lower detection limit of the assay was 12 ng/dl, with a mean intra-assay coefficient of variation of 4.8%. Dividing by 36.2 converts cortisol values from ng/dl to nmol/l.

Allergic Rhinitis

The *Rhinitis Quality of Life Questionnaire* (RQLQ) [52] is a disease-specific questionnaire, which assesses the extent of subjective disturbances by scoring the presence of various rhinitis symptoms and their practical effects. Twenty-eight symptoms, divided into seven subgroups (nasal symptoms, ocular symptoms, general symptoms, sleeping disorders, practical problems, limitations of activity, and emotionality) were evaluated. Scores ranged from 0 (non existent) to 6 (maximum). The overall score was calculated from the mean values of the 28 symptoms.

Cognitive functioning

As a measure of cognitive speed, parts A, B, and 0 of the *Concept Shifting Task* [61], and parts 1 and 2 of the *Stroop-Colour-Word Test* (SCWT) [62] were used. In part A of the Concept Shifting Task, subjects are instructed to cross out as quickly as possible 25 consecutively numbered small circles arranged in a larger circle. Part B is the same for letters. Part 0, in which the subject has to cross out empty circles, assesses the motor speed component. By subtracting scores on part 0 from the other scores, a reliable estimate of the cognitive speed component can be made. Performances on parts A and B (minus part 0) both reflect speed of automatic information processing; scores on those parts were averaged as a measure of cognitive speed ('CST-speed'). Part 1 of the Stroop-Colour-Word Test (SCWT) involves a card displaying colour names (SCWT-1), and part 2 involves a card displaying coloured patches (SCWT-2), which both have to be read aloud as quickly as possible. SCWT-1 and SCWT-2 both reflect the speed of automatic information processing; scores were averaged as a second measure of cognitive speed ('SCWT-speed').

To assess memory storage and memory retrieval, the *Visual Verbal Learning Test* (VVLT) [64] was used. In this test, fifteen words were sequentially shown on a computer screen, and the subject was asked to recall as many words as possible. This procedure was repeated five times. Scores on the first trial (assessing working memory), the total number of recalled words after five trials, and delayed recall after 20 minutes (retrieval) were used in the analysis.

Possible confounding variables

We investigated whether an association between cognitive dysfunction and cortisol alterations might in part reflect independent associations of these variables with either depressive symptoms or sleep problems (early waking). Depressive symptoms were measured with the

Beck Depression Inventory (BDI) [58], a 21-item self-report scale. The sleep subscale assesses general problems with falling asleep and disturbed sleep during the night. The BDI item concerning sleep was used to indicate whether a subject had problems with early waking. This item has response categories 0 'I sleep as well as before', 1 'I don't sleep as well as before', 2 'In the morning I wake up 1-2 hours earlier', and 3 'In the morning I wake up hours earlier and can't fall asleep afterwards'. For data analysis, early waking was categorized as absent (scores 0 and 1), or present (scores 2 and 3). Educational level was indexed on an 8-point scale, ranging from unfinished primary school to university degree [68].

Data reduction

Cortisol values

Of all 492 cortisol values, 4 (0.8%) physiologically unlikely high values (>1600 ng/dl), all at 8 a.m., were removed. To avoid bias in cortisol values due to inadequate compliance with the time sampling, samples taken more than 60 minutes before or after the fixed sample time were deleted from analyses. Over the two days, 31 (6.3%) values at 8 a.m., 26 (5.3%) values at 4 p.m., and 27 (5.5%) values at 9 p.m. were either outside the acceptable time window or missing. Of these 84 missing values, 27 were from the MDD group, 21 from the AR control group and 36 from the healthy control group. The two cortisol values obtained at the time points on the two days were significantly correlated (8 a.m. r=0.40, p=0.00; 4 p.m. r=0.54, p=0.00; 9 p.m. r=0.35, p=0.00); mean cortisol values for each time point were therefore computed for each subject. When only one cortisol measure was available, this was used as the mean value. In six MDD, five AR, and four healthy individuals, both cortisol values at one of the three time points were sampled out of the time window. In order to include these subjects in the analysis, the missing cortisol values were replaced by the mean cortisol value for each group [70]. The distributions of all cortisol measures were positively skewed, and natural logarithmic transformations were therefore applied prior to analysis to normalize the distributions. The main effect of group on overall cortisol levels was more closely examined by first standardizing the cortisol values at each time point over all subjects, and then averaging the three values to obtain a measure of daily average cortisol *(DAC)* [109]. The flatness of the cortisol curve over the day was defined as the change in log-transformed cortisol values from 8 a.m. to 9 p.m. (*delta cortisol*); higher values reflect steeper curves.

Cognitive values

To reduce the number of cognitive measures and the chance of Type I errors due to multiple tests, two compound variables were created: *cognitive speed* (CST-speed and SCWT-speed) and *memory* (AVLT-trial 1, AVLT-immediate recall and AVLT-delayed recall). These compound scores were created by first transforming each cognitive value into a normalized z-score and then calculating the mean value. The z-score for cognitive speed was inverted, so that lower z-scores always reflect worse performance. Before analysis, the data were examined for missing values and outliers. Cognitive speed had one outlier, in the healthy control group, which was replaced by the most extreme value within the normal distribution (Tabachnick & Fidell, 2001). There were no missing values.

Statistical analysis

To test for group differences in cortisol secretory patterns, an analysis of variance (ANOVA) for repeated measures was performed, with age and sex as covariates. The effect of early

awakening on delta cortisol was tested using the dichotomized BDI sleep item as independent variable. Wilks' Lambda was taken as criterion for significance. Post-hoc univariate testing, adjusted for multiple tests with Scheffé's test, was used to assess group differences. Group differences in cognitive measures (memory and cognitive speed) were tested using MANOVA, with age, sex, and education as covariates, and post-hoc comparisons as above. Effects of cortisol (DAC and delta cortisol) on cognition were determined within the total group and within separate groups using linear regression. Possible confounding effects of depressive symptoms were investigated by first entering total BDI score as independent variable in the regression equation, followed by the two cortisol variables. Two-tailed probabilities of $p \leq 0.05$ were considered significant. Statistical tests were performed with SPSS for Windows version 9.0 (SPSS, Inc. Chicago).

Results

Descriptive data

A total of 27 MDD outpatients, 20 AR controls, and 35 healthy controls were included in the study. Descriptive data on age, sex, education, and depressive symptom scores (BDI) are shown in Table 1. There were no differences in age or sex distribution, but the three groups differed significantly in education, with the MDD group having a lower educational level than the AR group. As expected, the MDD group had significantly more depressive symptoms than either control group, whereas the two control groups did not significantly differ in this respect.

Table 1. *Descriptive data on age, sex, education, and depressive symptoms (BDI) by group*

	MDD (N=27)	AR (N=20)	Healthy (N=36)	Test value	p-value
Age (mean ± SD)	41.8±12.7	41.8±10.7	44.6±11.9	F(2, 80)=0.59	0.56
Sex (% women)	44.4%	35.0%	55.6%	χ^2=2.29	0.32
Education (mean ± SD)	3.3±1.3	4.6±1.3	4.0±1.7	F(2, 80)=4.71	0.01
BDI (mean ± SD)	25.6±9.2	5.2±3.1	3.8±2.8	F(2, 80)=126.02	0.00

MDD=major depressive disorder
AR=allergic rhinitis

Group differences in cortisol

Figure 1 shows untransformed cortisol values (ng/dl) for all groups. Analysis of variance (ANOVA) with repeated measures for cortisol at 8 a.m., 4 p.m., and 9 p.m., adjusted for age and sex, showed a significant main effect of time (F(2, 77)=9.09; p=0.00) and an interaction effect of group on time (F(4, 154)=3.20; p=0.02). Age (F(2, 77)=0.19; p=0.83) and sex (F(2, 77)=0.89; p=0.42) did not have an effect on time. Post-hoc analyses showed that the MDD group had significantly elevated evening cortisol values compared with the healthy control group (mean difference 0.47 s.d.; F(2, 80)=5.21, p=0.01). Values for the derived variables DAC (the mean of the three standardized cortisol values) and delta cortisol (the change in log-

transformed values from 8 a.m. to 9 p.m.) for the three groups are shown in Table 2. ANOVA adjusted for age and sex showed an effect of group on delta cortisol (F(2, 78)=6.63, p=0.00), but not on DAC (F(2, 78)=1.49, p=0.23). Univariate tests adjusted for multiple testing showed that the MDD group differed in delta cortisol from the healthy control group (mean difference –0.73 s.d., p=0.00), but not from the AR group (mean difference –0.47 s.d., p=0.12): the MDD group had lower delta cortisol (a flatter curve). The flatter cortisol curve of the MDD group was related to significantly elevated evening cortisol values and to non-significantly (mean difference 0.26 s.d.; F(2, 80)=1.54, p=0.22) lower morning cortisol values compared to the healthy control group. Since sleep loss can result in altered cortisol levels (especially in evening levels), the effect of habitual early waking on delta cortisol was tested by adding the dichotomised BDI sleep item (presence or absence of early waking problems) to the ANOVA model. Group differences in delta cortisol remained significant.

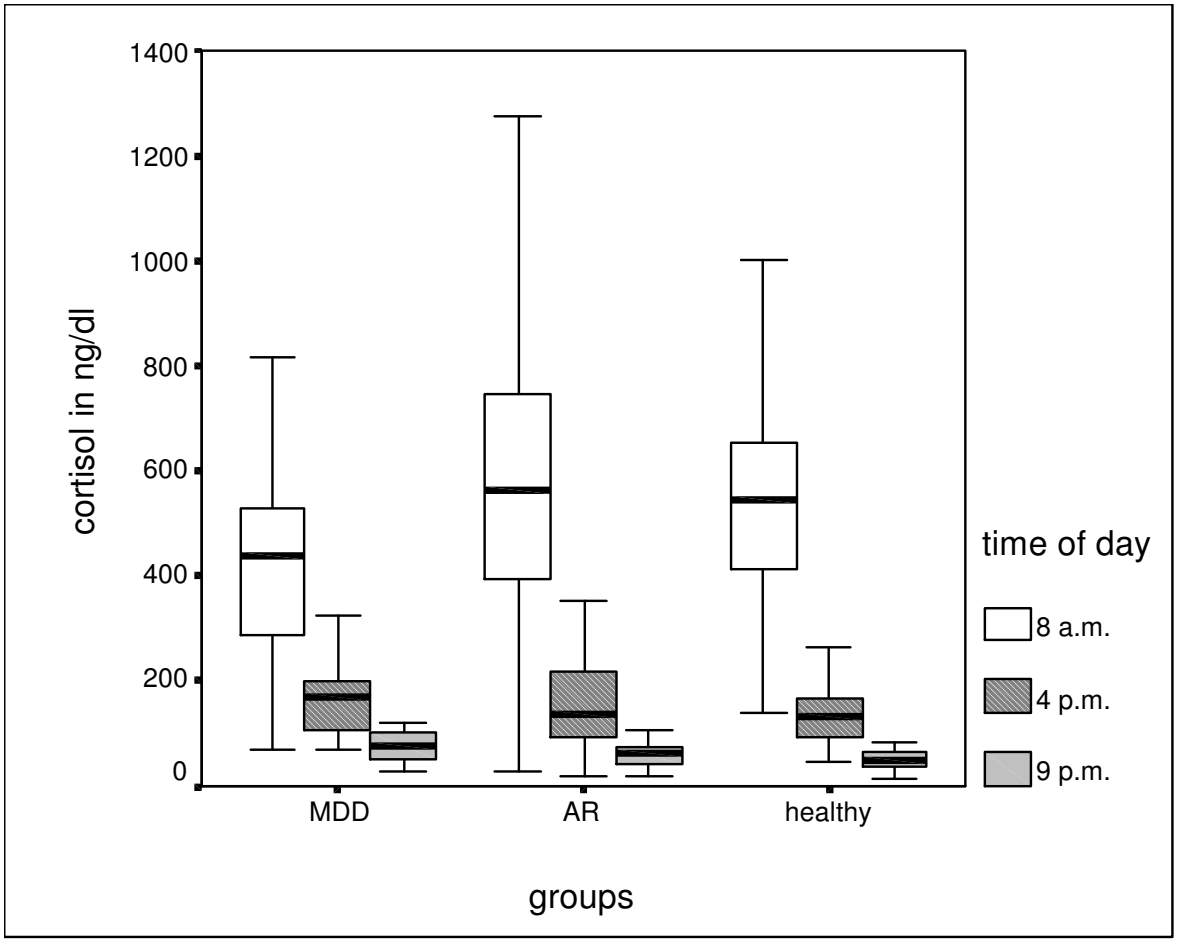

Figure 1. *Untransformed basal cortisol values (ng/dl) for morning, afternoon, and evening samples. Boxes show the median and interquartile range for each group (MDD=major depressive disorder; AR=allergic rhinitis), with whiskers extending from the 10th to the 90th percentile*

Table 2. *Daily average cortisol (DAC*) and (delta cortisol**) for groups*

	MDD (N=27)	AR (N=20)	Healthy (N=36)	Test value	p-value
DAC (mean ± SD)	0.174 ± 0.66	0.121 ± 0.64	0.070 ± 0.56	F(2, 78)=1.49	0.23
Delta cortisol (mean ± SD)	1.585 ± 0.93	2.056 ± 0.71	2.312 ± 0.64	F(2, 78)=6.63	0.00

MDD=major depressive disorder

AR=allergic rhinitis

* DAC is derived from the cortisol values at 8 a.m., 4 p.m., and 9 p.m.; the values for each time of day were first standardized over all subjects and then averaged

** delta cortisol is the change in log-transformed cortisol values from 8 a.m. to 9 p.m.

Group differences in cognition

MANOVA showed a significant omnibus-effect of group on the dependent cognitive variables (F(4,152)=2.93, p=0.02). Univariate analysis showed an effect of group on speed (F(2, 77)=4.7, p=0.01), but not on memory (F(2, 77)=1.80, p=0.12). Post-hoc analyses showed that the MDD group had significantly poorer performance on cognitive speed compared with both the AR group (mean difference z=-0.73, p=0.01) and the healthy group (mean difference: z=-0.56, p=0.03). AR and healthy groups did not differ from each other in cognitive speed (mean difference: z=0.18, p=0.74). Figure 2 shows z-scores of cognitive speed and memory performance for all groups.

Association between cortisol and cognition

Separate linear regression analyses were performed to investigate possible effects of cortisol measures (DAC and delta cortisol) on cognitive speed and memory performance, after controlling for age, sex, and education. Over all subjects, DAC was not related to performance on either speed or memory (Table 3). No associations between memory performance and delta cortisol were found, but reduced cognitive speed was associated with lower delta cortisol (flatter diurnal curve) (B=0.24, t=2.29, p=0.03) (Table 3). However, when the analysis was repeated separately for each of the three groups, the effect of delta cortisol on cognitive speed was significant only in the AR control group (AR: B=0.38 t=2.34, p=0.03; MDD: B=0.14, t=0.59, p=0.56; healthy: B=0.16, t=0.13, p=0.27). The association between delta cortisol and cognitive speed in this group might be explained by our finding that delta cortisol and cognitive speed both were strongly related to depression; the AR group had slightly higher depression scores compared to the healthy control group. After adjustment for depressive symptoms (BDI total score), the relation between delta cortisol and cognitive speed was no longer significant (B=0.14, t=1.26, p=0.21). The results indicate that a flatter diurnal cortisol curve and reduced cognitive speed are probably not causally related to each other, but that both vary as a function of the severity of depressive symptoms.

Table 3. *Results of linear regression analyses for effect of daily average cortisol (DAC*) and flatness of cortisol curve (delta cortisol**) on speed and memory performance*

	Overall group		
	B	Test value	p-value
DAC on speed	- 0.11	-0.18	0.44
DAC on memory	0.13	0.94	0.35
Delta on speed	0.24	2.29	0.03
Delta on memory	0.03	0.32	0.75

* DAC is derived from the cortisol values at 8 a.m., 4 p.m., and 9 p.m.; the values for each time of day were first standardized over all subjects and then averaged

** delta cortisol is the change in log-transformed cortisol values from 8 a.m. to 9 p.m.

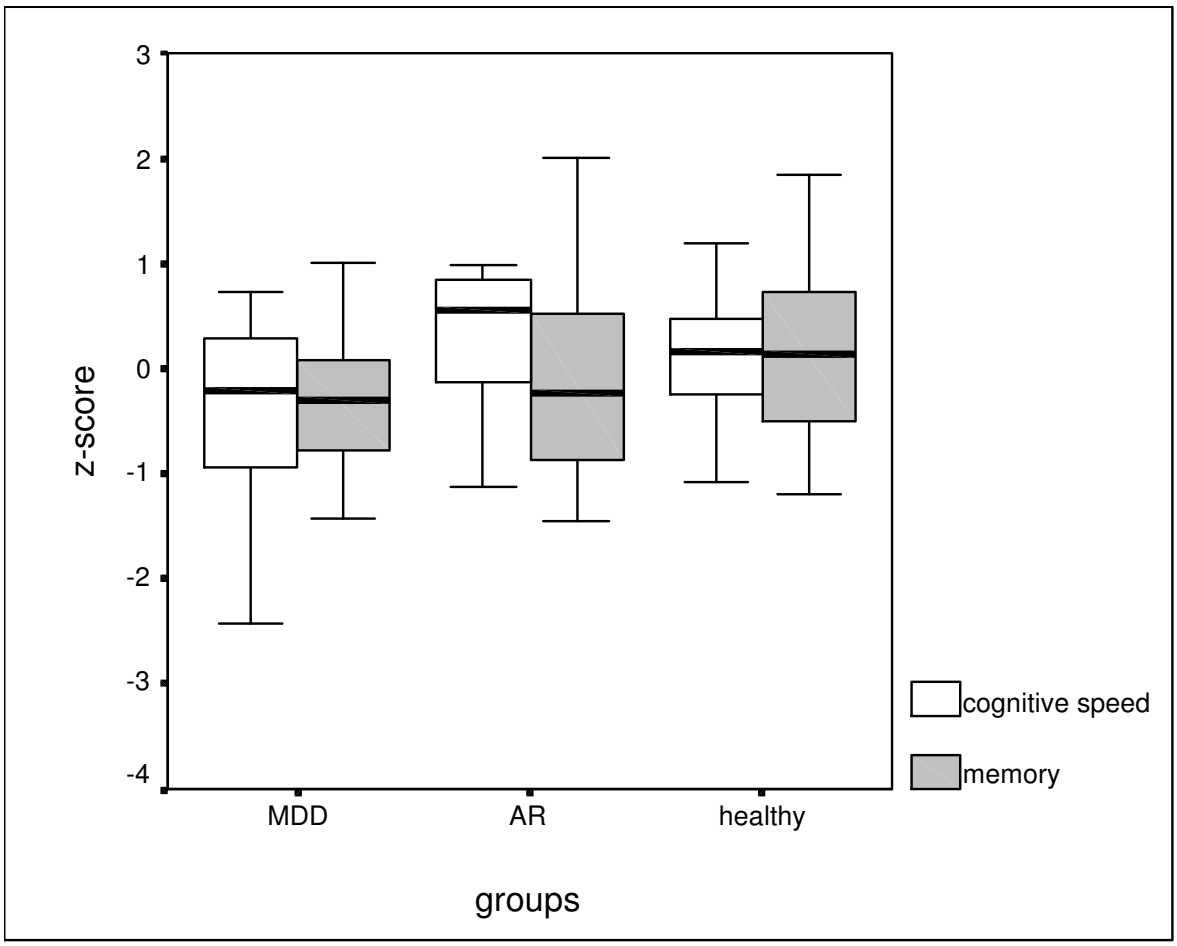

Figure 2. *Z-scores for cognitive speed and memory performances. Boxes show the median and interquartile range for each group (MDD=major depressive disorder; AR=allergic rhinitis), with whiskers extending from the 10th to the 90th percentile*

Discussion

We investigated basal cortisol levels over the day in relation to cognitive performance (cognitive speed and memory) in young to middle-aged MDD outpatients, with the following specific questions: (1) do these unmedicated MDD outpatients have elevated cortisol levels over the day? (2) is cortisol related to deficits in cognitive speed and memory? and (3) are changes in cortisol and cognitive functioning specific to MDD?

Results showed that the MDD group was not characterized by an overall increase or decrease in cortisol levels, but instead by a flattening of the cortisol curve over the day, compared with the healthy control group. This flattening appeared to be mainly due to significantly higher cortisol value in the evening, but non-significantly lower morning cortisol levels were present as well. Higher levels of evening cortisol are not only a feature of hypercortisolemia in older depressive patients [100 110], but have also been reported in adolescents with major depression [111] and may be a more general characteristic of MDD. Although the possibility of flatter basal cortisol curves over the day has received far less attention than have absolute values of cortisol at specific time points over the day, some recent studies have reported this phenomenon in depression [99 112]. One possible explanation for the flatter cortisol curve is early morning awakening, which is often reported by depressive patients. Cortisol secretion follows a diurnal pattern with high levels in the early morning, followed by a decrease over the day, with the trough of the curve in the late evening [113]. The peak of cortisol secretion occurs approximately 30 minutes after awakening [114]. In this study, cortisol was measured at a fixed time in the morning (8 a.m.), without reference to awakening time (which was not recorded). If MDD subjects woke substantially earlier, on average, than healthy and AR control subjects, their morning peak in cortisol secretion would have occurred well before the 8 a.m. sample. If they were mainly due to lower morning cortisol values, the flatter cortisol curves in the MDD group might therefore be an artefact. Two findings argue against this explanation: firstly, self-reported early habitual awakening was not significantly associated with cortisol levels in the MDD group (results not shown), and secondly, the flatter curves appeared to reflect high evening cortisol more strongly than low morning cortisol. Results should be replicated using morning cortisol samples with appropriate control for time since awakening.

With respect to cognitive functioning, results showed significant differences in cognitive performance among the groups, but only in cognitive speed: the depressive group showed significant decrements on this measure in comparison to both control groups. This finding is consistent with studies in geriatric depressive patients [7 8 115] and in younger depressive patients [105]. Surprisingly, memory performance did not differ among the three groups. However, although memory deficits have consistently been reported in older depressive patients [28 29] as well as in younger psychotic depressive patients [48], results for younger non-psychotic depressive patients have been mixed, with some negative findings [32 35]. Current theories of cognitive aging may help explain why memory deficits are less likely to be observed in younger MDD patients. Salthouse and colleagues [36 45] have argued that speed of information processing should be considered a resource for cognitive functioning. According to them, slower information processing may affect higher information processing, for example because end products of basic processing are sometimes no longer accessible when they are

needed for higher cognitive processing. This mechanism may apply to depressive disorder as well. Whether or not higher cognitive functioning such as memory is affected may depend on several factors, such as the degree of impairment in information processing speed and the degree to which individuals are able to compensate. It is possible that younger outpatients are better able to compensate for reduced cognitive speed than older or more severely depressed patients. Accordingly, deficits in higher cognitive functioning (like memory) may not manifest themselves in younger depressive outpatients.

With respect to the relationship between cortisol and cognitive functioning, it is noteworthy that over all subjects, increasing flatness of the cortisol curve was associated with reduced cognitive speed. However, when the separate groups were looked at, this association was not present in the MDD group. This suggests that a flatter diurnal cortisol curve is not causally related to reduced cognitive speed within the MDD group, but that it is likely that both a flatter diurnal cortisol curve and reduced cognitive speed are influenced by the same factors. Our results confirmed that after adjustment for depressive symptoms, flatness of cortisol curve and cognitive speed were no longer related to each other. This finding suggests that a flatter cortisol curve and reduced cognitive speed are probably not causally related to each other, but that both stem from depressive symptoms.

Finally, we investigated the specificity of changes in cortisol and cognitive functioning for MDD. The depressive group differed on flatness of cortisol curve from the healthy group, but not from the AR group. This suggests that a flatter diurnal cortisol curve is not specific for depressive disorder. This is in line with findings from Smyth et al. [116] and Stone et al. [117], who reported that 10% to 17% of healthy people do not show a diurnal cycle. With respect to cognitive function, the deficit in cognitive speed was specific for the MDD group, which makes it unlikely that this impairment in caused by more general secondary disease-related factors.

In summary, young to middle-aged unmedicated outpatients with MDD, compared to healthy individuals and AR outpatients, showed reduced cognitive speed and a flatter cortisol curve over the day, with significantly higher cortisol levels in the late evening. We found no clear evidence that the observed association between a flatter cortisol curve and reduced cognitive speed was causal; instead, both abnormalities appear to reflect the severity of depressive symptoms.

CHAPTER 6

Cognitive slowness predicts depressive symptoms three years later: findings from the Maastricht Aging Study (MAAS)*

ABSTRACT

Depressive symptoms and cognitive dysfunction are strongly related. There are indications that objective changes in cognitive functioning may precede development of a depressive syndrome. The present paper investigates whether dysfunctions of memory, cognitive speed, attention, and general cognitive functioning may be predictors for development of depressive symptomatology in normal and healthy people aged 50 years and over. A longitudinal design was used, in which 134 individuals who developed depressive symptoms after 3 years were compared to 254 individuals without later depressive symptoms. Groups were matched for age, sex, level of education and IQ. The effects of cognitive speed, attention, memory and overall cognitive functioning on later depressive symptoms were analysed using logistic regression analysis, with and without adjustment for marital status, physical health, and mental health. Reduced cognitive speed (odd's ratio 1.4) and reduced overall cognitive function (odd's ratio 1.5) were determinants of depressive symptoms at follow-up, even after adjustment for marital status, physical health, and mental health (odd's ratio cognitive speed 1.7; odd's ratio overall cognitive function 1.6). Outcome was best predicted by cognitive speed and baseline depressive symptoms. Reduced cognitive speed seems a determinant for later depressive symptoms in healthy subjects aged 50 and over.

* H.M. den Hartog, M. van Boxtel & J. Jolles: submitted.

Introduction

Depressive symptoms are highly prevalent in the general population, ranging from about 13% to even 35% [15 118]. The prevalence in older populations seems to be at the upper end of the range [9], although this effect could be mediated by a higher incidence of physical illness and bereavement in the elderly, which are risk factors for depressive symptoms (for example [9]). Depressive symptoms have been related to changes in cognitive functioning. Especially aspects of memory functioning appear to be important in this respect [7 26 28 71], but objective deficits in cognitive speed, attention, memory, and executive function have also frequently been reported [28-31 119]. It is generally believed that cognitive deficits are a direct consequence of depressive symptomatology, and that cognitive deficits will improve with improvement of the depressive symptoms. However, several studies have shown that cognitive dysfunctions are sometimes still present after remission of a depressive episode [4-6]. Furthermore, recent findings suggest that cognitive deficits are a determinant of relapse in patients with depressive disorder [22 49]. These findings raise the question whether cognitive dysfunction may precede the development of depressive symptomatology, and whether they may be a causal factor in this development.

The results of Van Os et al. [11] are consistent with this possibility. The authors demonstrated that a lower level of childhood general cognitive ability was an independent risk factor for the development of depressive illness in adulthood. Furthermore, Berger et al. [120] found that lower general cognitive ability (Mini-Mental State Examination) [121] was predictive of depression after 3 years in older individuals. However, both studies used rather crude measures of cognitive performance and both studied the incidence of depressive syndrome. In the investigation of cognition as a possible determinant of depressive symptomatology, it is important to avoid the possible long-lasting influence of a depressive syndrome on cognitive function. If not, it cannot be ruled out that cognitive dysfunctions are in fact epiphenomena of depressed mood. In order to evaluate the hypothesis that cognitive dysfunction can precede depressed mood, one has to perform a longitudinal study in subjects who are healthy and without depressive symptoms at the start. This was the aim of the present study.

Individuals were drawn from the Maastricht Aging Study (MAAS), a large-scale longitudinal study into the determinants of cognitive aging. Healthy middle-aged, and older individuals from the general population without a history of depressive disorder were included in the study. It was investigated whether cognitive dysfunction predicts later depressive symptoms independently of variables related to demography, physical health, and mental health. Cognitive speed, attention, verbal memory, and overall cognitive function were taken as indicators of cognitive ability. In our view, especially cognitive slowness is of potential importance because it has been related to several structural differences in the brain that are also related to depressive symptoms [76 122]. To our knowledge, this large prospective study that takes into account a number of established confounding variables is the first to investigate possible cognitive determinants of depressive symptoms in initially healthy subjects.

Methods and materials

Procedure

The present study was based on data from the Maastricht Aging Study (MAAS) [59 60], an ongoing longitudinal study of determinants of cognitive aging. Participants in MAAS were selected from a register of family practices in the Netherlands. 2,933 men and women, aged 24-81 years, without medical conditions known to interfere with normal cognitive dysfunction (for example dementia, mental retardation, and cerebrovascular pathology) were asked to participate in an in-depth neuropsychological and medical examination at the university. In the period 1993-1995, 1,869 people were actually examined (response=64%). Three years later (1996-1998), all individuals who were 50 years or older (n=1,069) were again invited to participate in a neuropsychological examination. Owing to refusal (n=138), death (n=50), and loss-to-follow-up (n=43), 838 people (response=78%) were actually tested in the 3-year follow-up.

In the present study, the outcome of depressive symptomatology at follow-up was studied. The outcome was dysphoria; individuals did not develop a psychiatric diagnosis of depressive syndrome. A group that later developed depressive symptoms ('depressed group') was compared with a group that did not develop depressive symptoms ('not depressed') (see section 'depressive symptoms' below). Individuals from both groups were matched for age (± 3 years), sex, level of education (± 1 level), and intelligence (± 10 points) because these demographic variables have a strong influence on cognitive performance. Educational level was indexed on an 8-point scale, ranging from unfinished primary school (1) to university degree (8) [68]. To obtain a measure of general intelligence (IQ), the Groninger Intelligence Test [92] was used, which is an instrument widely used for this purpose in the Netherlands. Each individual from the 'depressed' group was matched with one, and if possible two, individuals from the 'not depressed' group. After matching, the 'depressed' group included 134 individuals and the 'not depressed' group included 254 individuals.

Measurements

Independent variables: cognitive performance

To assess memory storage and memory retrieval, we used the *Visual Verbal Learning Test* (VVLT) [64]. In this test, fifteen words are sequentially shown on a computer monitor and the subject is asked to recall as many words as possible. This procedure is repeated five times. The first trial (a reflection of 'working memory' [65]), the total number of recalled words after five trials, and delayed recall after 20 minutes (retrieval) are recorded.

The *Concept Shifting Task* (CST) [61] was used as a measure of visual conceptual and visuomotor tracking. In part A, 25 consecutively numbered circles arranged in a larger circle have to be crossed out as fast as possible. Part B is the same for letters. In part C the subject has to alternate between circles with numbers and letters (1-A-2-B-etc). Part 0, in which the subject has to cross out empty circles, reflects the motor speed component. By subtracting part 0 from the other parts, the cognitive processes can reliably be estimated. Parts A and B (minus part 0) both reflect cognitive speed of automatic information processing, and these parts are combined to give a mean value of cognitive speed ('CST-speed'). The percentage difference between CST-C and CST-speed reflects slowing due to shifting between concepts (interference).

The *Stroop Colour Word Test* (SCWT) [62] is a measure of selective attention. This test consists of a reading condition in which the subject is required to read out aloud as fast as possible the names of colour words (SCWT-1); a similar administered colour naming condition (SCWT-2); and an interference condition, in which colour naming is required of colour words printed in non-matching ink (SCWT-3). SCWT-1 and SCWT-2 both reflect the cognitive speed of automatic information processing, and are combined into a mean value of cognitive speed (SCWT-speed). The percentage difference between SCWT-3 and SCWT-speed reflects slowing due to suppression of the dominant response (interference).

Dependent variable: depressive symptoms

Depressive symptoms at follow-up were measured with the Centre for Epidemiologic Studies Depression scale (CES-D) [123]. This self-report inventory consists of 20 items, which are rated on a 4-point scale, ranging from 0 'rarely or never' to 3 'mostly or always'. Higher scores indicate more depressive symptoms. The CES-D has good psychometric properties in elderly samples [124]. Based on the CES-D score, we compared a group with high scores for depressive symptoms (score 16 or higher) to a group with normal scores for depressive symptoms (score 10 or lower). The cut-off point of 16 has proven to be a valid score for detecting depressive symptoms, with a sensitivity of 100% and a specificity of 88% [124].

Covariates

Groups were matched on baseline variables of age, sex, level of education, and IQ since these variables affect the independent variables (cognition). Several variables were entered in the model as covariates, because of their known effect on the dependent variable (depressive symptoms). The first covariate was marital status (unmarried, married or living together, divorced, widowed). This variable was transformed into a dichotomous variable with the categories 'married or living together' and 'else'. The second covariate was physical health at baseline. Physical health was assessed in terms of the presence of several chronic somatic disorders and problems with instrumental activities of daily life (IADL). The chronic somatic disorders that were included were chronic obstructive pulmonary disease or chronic bronchitis, hepatitis-c, liver cirrhosis, colitis, kidney disease, angina pectoris, heart attack, cardiac insufficiency, hypertension, diabetes mellitus, disturbed thyroid function, rheumatism or arthritis, and cancer. This variable of somatic disorders was transformed into a dichotomous variable with the categories 'no somatic disorders' and 'somatic disorders'. Problems with IADL were measured by asking the respondents whether they needed help with shopping, housekeeping, personal hygiene, dressing, and preparing meals. A composite score of 0-5 was used as covariate. The third covariate was mental health at baseline. Mental health was measured with the continuous variable depressive symptoms at baseline as well as with the dichotomous variable death of a beloved one in the past year. Since the CES-D was only available at follow-up, depressive symptoms at baseline were measured with the subscale Depression of the Symptom Checklist (SCL-90) [83].

Data reduction and statistical analysis

To reduce the number of measures and therefore minimise the chance of multiple testing false-positive errors, four compound variables were created which measure the constructs of cognitive speed (CST-speed and SCWT-speed), attention (CST-interference and SCWT-interference), memory (AVLT-working memory, AVLT-immediate recall and AVLT-delayed

recall), and an overall measure Cognitive Index (cognitive speed, attention, and memory). The four cognitive compound scores were created by transforming each cognitive variable into a normalised z-score, whereafter a mean value was created. Z-scores for cognitive speed and attention were inverted for clarity, so that lower z-scores reflect poorer performance. Prior to analysis, all variables were examined for missing values and outliers. Outliers were replaced by the most extreme value within the normal distribution (as proposed by Tabachnick & Fidell) [70]. Data for 17 individuals (4.4%) with missing values were excluded from further analyses.

Between-group differences in age, IQ, and CES-D scores were measured using Student T-tests, differences in education were measured using Mann-Whitney tests, and differences in sex were assessed using Chi-square tests. Separate logistic regression analysis computed odds ratios with a confidence interval of 95%, to determine whether the independent variables (cognitive performance test outcome) were predictive of the dependent variable (depressive symptoms). The analyses were repeated after control for possible confounders, with stepwise entering of blocks of covariates (marital status, physical health at baseline, and mental health at baseline). To test which independent variables together predicted outcome best, a stepwise forward conditional logistic regression analysis was used, in which all independent variables and covariates were entered. The improvement of the model after addition of a predictor variable was tested using the change in -2 Log Likelihood (-2LL). All tests were two-sided with a significance level of 0.05. Statistical tests were performed with SPSS for Windows, version 9.0 (SPSS, Inc., Chicago).

Results

Table 1 shows the baseline characteristics of the two groups that were 'depressed' or 'not depressed' at three years follow-up. After matching, at baseline the 'depressed' (n=134) and the 'not depressed' (n=254) outcome groups were comparable in age, sex, level of education, and IQ. Groups did not differ in marital status, presence of somatic disorders, IADL, and recent experience of bereavement. However, at baseline the later 'depressed' group had significantly higher depressive symptom scores (26.1±9.3) than the group that was 'not depressed' at follow-up (19.0±3.3).

Figure 1 shows the baseline mean z-scores for the outcome groups. T-tests showed that both groups differed significantly in cognitive speed (t=-2.46, p=0.01) and the overall cognitive index (t=-2.18, p=0.030), but not in attention (t=-0.53, p=0.57) and memory (t=-1.67, p=0.10). The differences in the four cognitive measures between the two groups were subtle, as can be expected in a healthy population. There were no interactions between cognitive performance and age, sex, education, or IQ and depressive symptoms (results not shown).

Table 2 (left) shows the predictive value of cognitive performance for later depressive symptoms. In separate analyses, reduced cognitive speed (OR=1.40) and a lower value of the overall cognitive index (OR=1.52) significantly predicted later depressive symptoms. Performance on attention (OR=1.09) and memory (OR=1.22) tasks did not predict depressive symptoms. The analyses were repeated after entering the covariates marital status, physical health (a block of somatic disorders and IADL), and mental health (a block of baseline

depressive symptoms and death of a beloved one). Results remained the same after entering the covariates: cognitive speed (OR=1.65) and the cognitive index (OR=1.58) had a significant effect on outcome (see Table 2, right).

Table 1. *Baseline descriptive statistics for 'depressed' and 'not depressed' outcome groups*

	Outcome groups			
	Depressed	Not depressed	test-value	p-value
Age (mean±sd)	63.8±9.1	63.6±8.8	t= -0.23	0.82
Sex (% female)	65.7	63.4	χ^2=0.20	0.66
Level of education (mean±sd)	2.8±1.6	2.8±1.6	z=-0.35	0.73
IQ	113.1±11.9	113.9±11.5	t=0.63	0.59
Marital status (% married)	78.9%	78.2%	χ^2=0.03	0.88
Somatic disorders (% no disorders)	29.5%	28.4%	χ^2=0.06	0.81
IADL (mean±sd)	0.19±0.47	0.34±0.79	z=1.24	0.22
Recent bereavement	23.6%	24.6%	χ^2=0.05	0.83
Baseline depressive symptoms (mean±sd)	26.1±9.3	19.0±3.3	t=-10.71	0.00

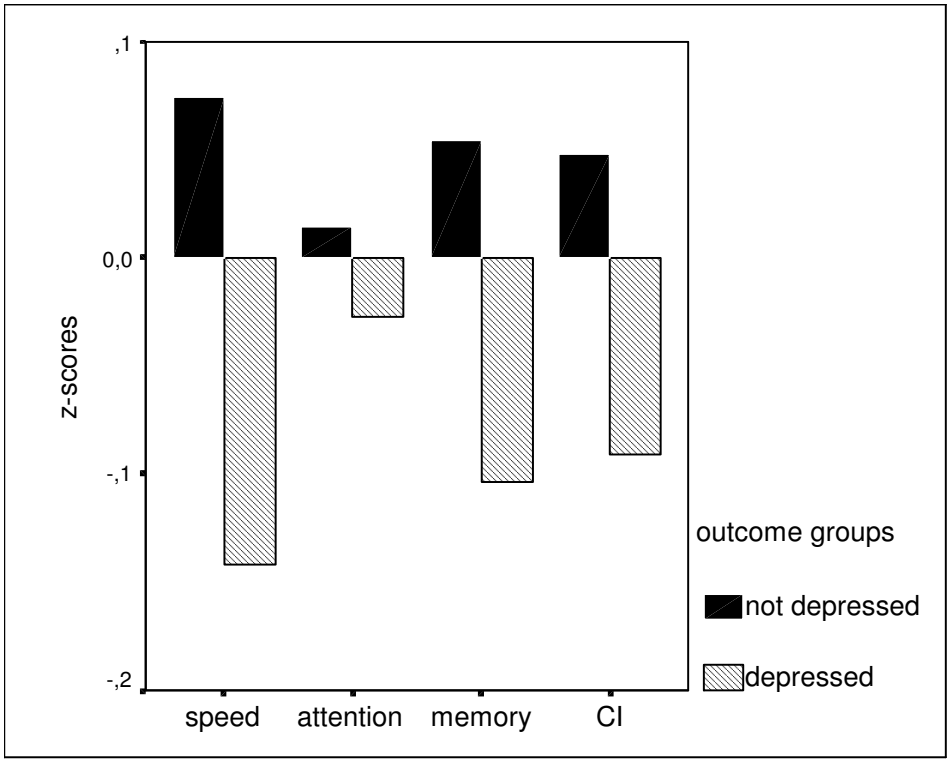

Figure 1. *Baseline mean z-scores for outcome groups*

Table 2. *Results of logistic regression analysis for each cognitive variable separately: effects of baseline cognitive measures on later depressive symptoms, before (left) and after (right) adjustment for marital status, physical health and mental health*

	Unadjusted results		Adjusted results	
	OR	95% CI	OR	95% CI
Cognitive speed	1.40*	1.09-1.81	1.65**	1.18-2.30
Attention	1.09	0.82-1.44	0.89	0.61-1.29
Memory	1.22	0.96-1.55	1.30	0.96-1.76
Cognitive Index	1.52*	1.06-2.17	1.58*	1.00-2.49

* $p<0.05$
** $p<0.01$

Table 3 shows the relative contribution of cognitive speed and the covariates in the predictive model. Physical health (IADL, change -2LL=7.4), mental health (baseline depressive symptoms, change -2LL=97.6), and cognitive speed (change -2LL=8.7) made a significant contribution to later depressive symptoms. In the predictive model no effects were found for marital status (change -2LL=0.1), somatic disorders (change -2LL=0.2), and recent bereavement (change -2LL=0.4). Similar results were obtained for the cognitive index (results not shown).

Table 3. *Relative contribution of variables and cognitive speed in the predictive model for depressive symptoms: stepwise forward logistic regression analysis*

block	variable	-2LL	change –2LL	p-change –2LL	model χ^2	Nagel-kerke R^2	correct classified
	Constant	455.0					
Demography	Marital status	454.9	0.1	0.724	0.13	0.00	66.3%
Physical health	Somatic disorders	454.7	0.2	0.619	0.37	0.00	66.3%
	IADL	447.3	7.4	0.007	7.72	0.03	68.0%
Mental health	Baseline depressive symptoms	349.7	97.6	<0.001	105.35	0.36	78.1%
	Recent bereavement	349.3	0.4	0.532	105.74	0.36	78.9%
Cognition	Cognitive speed	340.6	8.7	0.003	114.43	0.38	79.8%

-2LL=-2 Log Likelihood. Change in –2LL is the one unit change from the foregoing model (step).

To test which variables together best predicted depressive symptoms at follow-up, a stepwise forward conditional logistic regression analysis was performed. The variables cognitive speed, attention, memory, overall cognitive index, age, sex, education, IQ, marital status, somatic disorders, IADL, baseline depressive symptoms, and recent bereavement were entered in the analysis. Results are summarised in Table 4. Outcome was best predicted from a model including baseline depressive symptoms and cognitive speed. The other variables did not improve the model significantly. The overall predictive value of the model in predicting depressive symptoms was 79.2%. Especially the specificity (the correctly predicted percentage of patients who did not have depressive symptoms) was very high at 93.6%; the sensitivity (the correctly predicted percentage of patients with depressive symptoms) was 50.8%. Within

the model, cognitive speed primarily affected the sensitivity of the model, adding 4.2% to sensitivity.

Table 4. *Stepwise forward conditional logistic regression analysis of outcome*

step	variable	-2LL	change in –2LL	p-change in –2LL	model χ^2	Nagel-kerke R^2	correct classified
0	constant	455.0		0.00			66.3%
1	+ baseline depressive symptoms	352.6	102.4	0.00	102.4	0.35	78.1%
2	+ cognitive speed	341.3	11.3	0.01	110.3	0.37	79.2%

-2LL=-2 Log Likelihood. Change in –2LL is the one unit change compared to the foregoing model (step)

Discussion

In this study, we investigated whether an impairment of a particular aspect of cognitive performance may be a determinant for the later development of depressive symptoms in subjects aged 50 years and older. The results showed that subtle changes in cognitive performance and especially lower cognitive speed indeed predicted later depressive symptoms. Even after adjustment for variables that are suspected to have an influence on depression (i.e. marital status, physical health, and mental health), the results remained the same, indicating that cognitive dysfunction is an independent determinant of depressive symptoms. A model including baseline depressive symptoms and cognitive speed best predicted depressive symptoms. The finding that baseline depressive symptoms are predictive of future depressive symptomatology is in line with earlier findings [9 22 125]. Especially in older individuals, there is convincing evidence that reduced cognitive speed is cross-sectionally related to depressive symptoms [7 86 115]. It is generally assumed that lower cognitive speed is secondary to depressive symptoms. However, there is evidence that reduced cognitive speed could act as a trait marker for relapse of depressive disorder [22]. Our finding that a reduced cognitive speed is a small determinant of later depressive symptoms in the general population is a new and potentially interesting finding that provides more direct evidence for a possible reversed causality mechanism. The contribution of cognitive speed to the prediction of later depressive symptoms was modest, but nonetheless robust for adjustment of variables that have an effect on depressive symptoms (i.e. physical health and mental health). The finding that a small subclinical cognitive deficit in a healthy population is an independent determinant of later depressive symptoms might be important for our understanding of the pathogenesis of depression.

With respect to a possible mechanism underlying the effect of cognitive speed on depression in elderly individuals, at least three levels have to be considered. At a neurological level, De Groot et al. [76] recently found evidence that a decrease in speed is related to periventricular white matter lesions in older healthy individuals, aged 60-90 years. They also found that older individuals with white matter lesions had a three to five times increased chance of depressive

illness [126]. Other studies also found a relationship between white matter lesions and depression in the elderly (for example [127 128]). Brain structures are also related to depression and speed. In normal older individuals, Van der Werf et al. [122] found a relationship between reduced cognitive speed and reduced total volume of the thalamus, a relationship that was stronger than, and independent of, the decrease in total brain volume. The thalamus is also involved in depressive disorder [129]. Furthermore, the prefrontal cortex is related to both depression [130 131] and speed of information processing [104]. At a neurobiological and neurochemical level, in a review Sheline reported that glial loss in the brain could produce excitotoxic damage [132]. Glial cells transport glutamate, maintain metabolic homeostasis, and produce brain-derived neurotrophic factor. She argued that a loss of glial cells could increase vulnerability to neurotoxic damage and may be involved in volume loss in white and gray matter of the limbic-cortical-striatal-pallidal circuit. At a cognitive level, the group of Salthouse [36 45] argues that speed of information processing should be considered a resource for cognitive functioning. Slower processing not only causes a quantitative delay in higher cognitive processing, but also affects the quality of higher information processing. This could be because end products of basic processing are sometimes no longer accessible when they are needed for higher cognitive processing. A decrease in speed thus might cause a deterioration of higher information processing. In addition to the theory of Salthouse, we suggest that individuals probably have to invest more effort to try to compensate for reduced cognitive speed. As a result mental fatique may develop, which has a further negative effect on cognitive processing. It is possible that the emerging vicious circle eventually leads to depressive symptoms.

Findings from the literature thus are consistent with the notion that a reduction in the structural integrity of white and gray matter and/of in the efficiency of neurotransmission in these structures may result in a decreased speed of information processing and in an increased risk for depressive symptoms. Findings from our study suggest that an increased risk of depressive symptoms is probably at least in part a consequence of a decreased speed of information processing. This might be explained by the need to invest more effort to compensate for cognitive problems, which indirectly might have a negative effect on both cognitive processing and mood state. The proposed mechanism includes a component of coping or subjective psychological reaction to the experience of deteriorating cognitive functioning. Continuing problems with information processing can lead to a reduction in the ability to cope with environmental demands, which may cause a sense of fear. An example is the evolving fear for the development of a true cognitive disorder, such as dementia. Individuals who are able to cope with the reduced cognitive ability are probably less likely to develop depressive symptoms. Moreover, individuals who have a greater ability to invest more effort to compensate for slower information processing, for example because they already had more brain reserve capacity [42], are probably less likely to develop depressive symptoms. More research is needed to investigate these possibilities in depth.

Generalization from the present findings must be made cautiously. Since a depressive syndrome may have a long-lasting effect on cognitive function, it is preferable to study individuals without a history of depressive disorder. Therefore, we studied depressive symptoms in individuals from the general population, who did not have a history of depressive disorder. However, we cannot be completely certain that a depressive disorder has

the same etiological factors as subclinical depressive symptoms. A dedicated study in patients with a first-ever depressive episode should be performed in order to find whether a generalization from the present findings is possible. The findings apply to people aged 50 years and over. Since we only studied middle-aged and older individuals, the findings cannot be generalised to younger individuals. It is quite possible that the etiology and underlying mechanisms of depressive symptoms in younger individuals are different, for example because the brain volume is usually not reduced in younger individuals. Finally, the cognitive deficits are very subtle, as can be expected in a normal, healthy population. This implicates restrictions for use in clinical practice.

In summary, the results showed that subtle changes in cognitive function, particularly slower speed, are a small independent determinant of depressive symptoms in the general population. Thus, cognitive dysfunction does not only seem to be a consequence of depressive mood: this study argues if favour of a 'reverse causation' mechanism.

CHAPTER 7

Impairment in cognitive performance predicts non-remission of depressive disorder. A prospective study in non-demented middle-aged to older patients [*]

ABSTRACT

It is generally assumed that cognitive dysfunction is secondary to depressive disorder, but studies suggest that it could also be a risk factor for depressive disorder. This prospective study examined whether impaired cognitive performance might be a determinant for diagnosis of depressive disorder. 49 patients with depression were followed up through 2.5 years. The predictive value of baseline cognitive performance for the diagnosis 'depression' at follow-up was tested by logistic regression analysis. A second evaluation involved a similar analysis in 46 subjects who had normal mood at baseline. Reductions in cognitive speed, attention and memory in depressed patients in part predicted non-remission of depressive disorder at follow-up, even after adjustment for former psychiatric treatment, medication, age, sex, education, and intelligence. Depression at follow-up in subjects with initial normal mood state was not predicted by impaired cognitive performance. Cognitive performance seems a determinant of non-remitting depressive disorder.

[*] H.M. den Hartog, P.J. Visser, L. Krabbendam, F.R.J. Verhey & J. Jolles: submitted.

Introduction

Depressive disorder is usually accompanied by cognitive dysfunction. There is evidence for dysfunctions in information processing including deficits in cognitive speed [7 119], attention [30 133], memory [28 44 56 134], and executive function [31 135]. So far, the general idea is that these deficits are a direct consequence of depressive disorder and that they will disappear with remission of the depression. Interestingly, recent publications have actually falsified the idea that cognitive dysfunction always clarifies with remission of depression [5-8]. This may indicate that it takes more time for cognitive function to recover. Alternatively, it may be possible that cognitive dysfunction acts as a determinant or a vulnerability factor for depressive disorder, instead of merely being a secondary phenomenon. There is some evidence in support of the latter theory, in that Roberts et al. [9 10] demonstrated that subjective cognitive problems predicted the development of depressive disorder one year later. Furthermore, Van Os et al. [11 12] have demonstrated that childhood general cognitive ability is an independent risk factor for the development of depressive illness in adulthood. These results lend credibility to the hypothesis that in adults, cognitive deficits might be a determinant for depressive disorder. In the present longitudinal study, this hypothesis was studied according to a controlled design.
So far, studies on risk factors for depression have indicated that one of the most important predictors of depressive illness is prior depression [9 20-23]. Therefore, the major objective of this longitudinal study was to investigate whether impairments in cognitive performance in depressive patients might predict non-remission of depressive disorder. Cognitive performance was studied in subjects who were 2.5 years later diagnosed with or without depressive disorder. Some other variables that could have an influence on outcome were taken into account (former psychiatric treatment, use of medication, age, sex, intelligence, and education). For evaluation of cognitive function, we measured cognitive speed, attention, search in working memory, and verbal memory. The notion that impaired cognitive functioning may predict depression in patients with normal mood was evaluated exploratively in a subgroup with normal mood state at the time of the cognitive assessment.

Methods and materials

Subjects and procedure
This study is performed according to a prospective design with a baseline and 2.5 years follow-up measurement in outpatients referred to a specialised clinic for age-related cognitive and affective problems in Maastricht, the Netherlands (see for description of this population [136 137]). 95 patients fulfilled all criteria. All subjects underwent a standardised assessment, which included a detailed history, neuropsychological, psychiatric, neurological, and physical examination, as described in Verhey et al. [136]. The detailed history included information about psychiatric treatment before the baseline assessment and information about use of medication. Depressive disorder was diagnosed following DSM-IV criteria for minor and major depression. The 17-item Hamilton Depression Rating Scale (HDRS) [138] was used as a symptom checklist and a measure of severity of depression. Exclusion criteria were progressive cognitive decline (e.g. Parkinson's disease), psychiatric disorders other than depressive disorder, and somatic disorders that are known to affect cognition or depression

(e.g. thyroid dysfunction). Subjects with dementia at follow-up (MMSE<24 [121] and/or clinical diagnosis of dementia) were excluded from the cohort. Furthermore, to avoid the effects that ischemic neurological events can have on both depression and cognitive function, we excluded subjects with a positive score on one of the four relevant Hachinski Ischemic Scale items 'sudden onset', 'stroke/tia', 'focal neurological symptoms' or 'focal neurological signs'.
The total sample of 95 subjects was divided into four subgroups according to their diagnosis at baseline and at follow-up. Group 1 consisted of 21 patients who were characterised by the diagnosis 'depressive disorder' at baseline and at follow-up. The patients in group 2 (N=7) had a normal mood state at baseline but were depressed at follow-up. Group 3 (N=28) was the group of subjects who were depressed at baseline but normal at follow-up and group 4 (N=39) was normal at both baseline and follow-up. In order to compare the subjects with depression at follow-up (groups 1 and 2; N=28) to those who had normal mood state at follow-up (groups 3 and 4; N=67) these groups were matched on the baseline variables age (depressed group age 54.2 vs. control group age 54.6, p=0.87), sex (depressed group 64.3% women vs. control group 56.7% women, p=0.49), intelligence (depressed group IQ 111.5 vs. controls IQ 112.6, p=0.96) and education (depressed group 4.3 on a 8-point scale [68] vs. control group 4.2, p=0.90).

Assessment
Educational level was indexed on an 8-point scale, ranging from unfinished primary school (1) to university degree (8) [68]. To obtain a measure of general intelligence (IQ), the Groninger Intelligence Test [92] was used, which is a widely used instrument for this purpose in the Netherlands.
To assess memory storage and memory retrieval, we used the *Auditory Verbal Learning Test* (AVLT) [64]. In this test, fifteen words were read aloud and the subject was asked to recall as many words as possible. This procedure was repeated five times. The total amount of recalled words after five trials was used as a measure of memory encoding. Retrieval of the information was tested after 20 minutes with delayed recall.
To study the search in working memory, the paper & pencil *Memory Scanning Test* (MST) [56] was given to the subjects, which is based upon the Sternberg-paradigm [63]. In this measure one to four letter had to be memorised and crossed out on sheets containing matrices of letters. The extra time needed to complete a test, is a measure of the ease at which information is processed in working memory. In this study the subtests with one letter (MST-1) and two letters (MST-2) were used.
As a measure of visual conceptual and visuomotor tracking an improved version of the *Trail Making Test* (TMT) [139] was used [61]. Part A consisted of 25 consecutively numbered circles that had to be connected (the trail) as fast as possible. In Part B 25 circles with letters had to be connected. In part C the subject had to alternate between circles with numbers and letters (1-A-2-B-etc). Part A and B both reflect cognitive speed of automatic information processing, and were combined into a mean value of cognitive speed ('TMT-speed'). The percentage difference between TMT-C and TMT-speed reflects the percentage of slowing due to shifting between concepts (interference).
The *Stroop Colour Word Test* (SCWT) [62] is a measure of selective attention. The test involves three cards displaying colour names (SCWT-1), coloured patches (SCWT-2), and colour names printed in incongruously coloured ink (SCWT-3). On the first card the colour

names had to be read aloud as fast as possible and on the second card the colour of the patches had to be read aloud. On the third card irrelevant but very salient information (reading of colour name) needed to be discarded in favour of a less obvious aspect (naming colour of ink). SCWT-1 and SCWT-2 both reflect the cognitive speed of automatic information processing, and were combined into a mean value of cognitive speed (SCWT-speed). The percentage difference between SCWT-3 and SCWT-speed reflects the percentage of slowing due to suppression of the dominant response (interference).

Data reduction and statistical analysis

To reduce the number of measures and therefore minimising the chance of multiple testing false-positive errors, four compound variables were created, which measure the constructs of cognitive speed (TMT-speed and SCWT-speed), attention (TMT-interference and SCWT-interference), memory (AVLT-immediate recall and AVLT-delayed recall), and search in working memory (MST-1 and MST-2). The cognitive compound scores were created by transforming each cognitive variable into a normalised z-score, where after a mean value was created. Z-scores for cognitive speed, attention, and search in working memory were inverted, in order to assure an unambiguous interpretation, with lower z-scores reflecting worse performance. A dichotomous variable was created to indicate the presence of former psychiatric treatment. Information about use of medication at the baseline assessment was transformed into a nominal variable with four medication categories (none, psychotropic, somatic and both).

Prior to analysis, all variables were examined through various SPSS-programs for missing values and outliers. Outliers were replaced by the most extreme value within the normal distribution [70]. In order to include all subjects in the analyses, missing data were substituted. Missing values that counted for less than 5% of the variable were replaced by the mean value. Missing data in the variables TMT-speed and TMT-C accounted respectively for 9.4% and 10.4% of the variables and appeared to be of random order. Missing values of TMT-speed and TMT-C were estimated from the other variables. The estimate was based on a multiple regression analysis of data for the total study population. In this population, all variables were entered in the first step and step-forward selection was used to select variables that were significantly associated with the dependent variable. On the basis of the resulting model, an expected test score for each missing value was calculated [70]. Logistic regression analyses were performed with and without substituted data. These models yielded similar results, and therefore data from the analyses with substituted data are presented.

Statistical analyses were performed separately for the two scientific questions. The first analysis involved the predictive value of cognitive dysfunction in patients with depression at baseline (groups 1 and 3; N=49). The second analysis involved the predictive value of cognitive dysfunction in patients with normal mood state at baseline (groups 2 and 4; N=46). Between-group differences in age, IQ, and HDRS-scores were measured using Student T-tests, differences in education and medication were measured using Mann-Whitney tests and differences concerning sex and former psychiatric treatment were assessed using Chi-square tests. The effects of baseline cognitive variables on outcome (the later diagnosis of depressive disorder) were analysed using separate logistic regression analyses. To assess whether cognitive performance had a predictive value for outcome above the influence of the variables age, sex, intelligence, education, former psychiatric treatment, and medication, analyses were performed with these factors treated as covariates. When cognitive performance still predicted

outcome after adjustment for these factors, it was tested which variables predicted outcome best. Therefore a forward stepwise conditional logistic regression analysis was used. The improvement of the model after addition of a predictor variable was tested using the change in -2 Log Likelihood (-2LL). Generally, outcome measures were expressed as odds ratios and their 95% confidence intervals (CI). Two-tailed probabilities of 5% or less were considered significant. Statistical tests were performed by using the SPSS statistical package for Windows, version 9.0 (SPSS, Inc. Chicago).

Results

Predictive value of cognitive performance in patients who are depressed at baseline

The initial depressed group that was later classified as 'depressive disorder' was at baseline comparable to the initial depressed group that was later classified as 'no depressive disorder ' in age, sex, education, IQ, and medication (see table 1a). However, there were significant differences in percentage former psychiatric treatment and HDRS-scores, reflecting more subjects with former psychiatric treatment (52.4% vs 14.3%) and higher HDRS-scores (17.1 vs 12.5) in the group later classified as 'depressive disorder'.

Table 1a. *Baseline demographic data for groups with initial depressive disorder*

	outcome depressive disorder	outcome no depressive disorder	test	p-value
Number	28	21		
Age (mean; sd)	54.5; 9.3	53.5; 10.4	t= -0.36	0.72
Sex (percentage female)	52.4%	50.0%	χ^2 =0.03	0.87
Education (mean; sd)	4.2; 1.6	4.1; 1.2	z= 6.61	0.36
IQ (mean, sd)	109.7; 12.4	113.2; 15.0	t= 0.87	0.39
Baseline HDRS-score	17.1; 5.1	12.5; 4.3	t= -3.45	0.00
Percentage former psychiatric treatment	52.4%	14.3%	χ^2 =8.20	0.01
Percentage medication use: none/psychotropic	15.8/ 42.1	59.3/ 7.4		
somatic/ both	36.8/ 5.3	25.9/ 7.4	z= -1.89	0.06

Regarding the predictive value of cognitive performance on outcome, in separate logistic regression analyses cognitive speed (OR=2.28 CI=1.08-4.82) and attention (OR=2.56 CI=1.02-6.43) significantly predicted outcome. Furthermore, a trend for memory was revealed (OR=1.94 CI=0.97-3.87, p=0.06). Performance on search in working memory did not distinguish both groups (OR=1.45 CI=0.75-2.79). Figure 1 shows z-scores of cognitive performance for the later 'depressed' group. The mean performance of the later 'no depressive disorder' group is used as reference group for calculation of the z-scores.

After cognitive performance was adjusted for former psychiatric treatment, age, sex, education, intelligence, and medication, performance on cognitive speed (OR=6.29 CI=1.30-30.45), attention (OR=5.23 CI=1.19-22.95), and memory (OR=2.55 CI=1.00-6.47) significantly predicted the development of depressive disorder. Later classification was best

predicted from a model including former psychiatric treatment (change -2LL=8.34, p=0.01) and cognitive speed (change -2LL=9.06 p=0.00). The classification rate of this model was 75.5% and the model explained 40.1% variance of classification outcome.

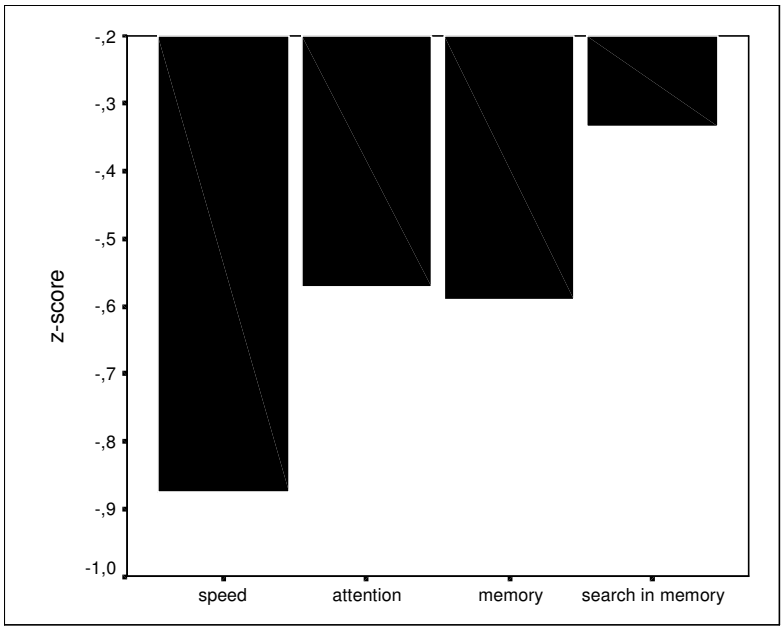

Figure 1. *Mean difference in z-scores of cognitive performance of the initial depressed group that is later classified as 'depressive disorder'*

Predictive value of cognitive performance in patients with normal mood state at baseline
Table 1b shows that the group with initial normal mood state that was later classified as 'depressive disorder' was comparable to the initial group with normal mood state that was later classified as 'no depressive disorder' in age, education, IQ, and medication. However, there were significant differences in sex, former psychiatric treatment, and HDRS-scores, reflecting more women (100% vs. 56.5%), more subjects with former psychiatric treatment (71.4% vs. 23.1%) and higher HDRS-scores (8.5 vs. 5.5) in the group later classified as 'depressive disorder'.

Regarding the predictive value of cognitive performance on outcome, separate logistic regression analyses showed that cognitive performance did not predict outcome (cognitive speed OR=1.41 CI=0.60-3.32; attention OR=0.34 CI=0.08-1.37; memory OR=0.65 CI=0.27-1.54; search in working memory OR=1.10 CI=0.50-2.42). After cognitive performance was adjusted for former psychiatric treatment age, sex, education, intelligence, and medication, cognitive performance still did not predict later outcome (results not shown).

Table 1b. *Baseline demographic data for groups with initial normal mood state*

	outcome depressive disorder	outcome no depressive disorder	test	p-value
Number	7	39		
Age (mean; sd)	53.2; 11.1	55.3; 9.9	t= 0.52	0.61
Sex (percentage female)	100.0%	56.5%	χ^2 =4.00	0.05
Education (mean; sd)	4.2; 1.8	4.9; 2.3	z= 9.21	0.33
IQ (mean, sd)	116.9; 20.0	112.2; 13.0	t= -0.82	0.42
Baseline HDRS-score	8.5; 3.6	5.5; 3.5	t= -2.10	0.04
Percentage former psychiatric treatment	71.4%	23.1%	χ^2 =6.55	0.01
Percentage medication use: none/psychotropic	50.0/ 0	35.3/ 5.9		
somatic/ both	50.0/ 0	44.1/ 14.7	z= -0.80	0.42

Discussion

The aim of the present study was two-fold. The first question evaluated whether cognitive dysfunction in depressed patients predicts non-remittance of the condition at 2.5 years follow-up. The second question evaluated the predictive value of cognitive dysfunction in patients with normal mood at baseline for diagnosis of depression at follow-up. This way, it was possible to differentiate between cognitive performance as a determinant for sustaining or relapsing depressive disorder (question 1), and cognitive performance as a vulnerability factor for the development of depressive disorder in patients with normal mood (question 2). Results showed that impaired cognitive performance in initial depressed patients was predictive for non-remittance of the depressive disorder. Even after adjustment for former treatment, medication, age, sex, education, and intelligence, subjects with deficits in cognitive speed, attention, or memory, had a 2.6 to 6.3 increased risk for non-remittance of depressive disorder. The best predicting model included impaired cognitive speed and former psychiatric treatment. This indicates that impaired cognitive performance, and especially slower cognitive speed, in part determines the continuation or relapse of depressive disorder. Other studies have also suggested that cognitive performance may predict depression. Videbech [8] reported in his review of neuro-imaging studies in depression a negative correlation between prefrontal blood flow and psychomotor retardation, which they consider a trait marker for depression. Thus, support that cognitive dysfunction can be a determinant or risk factor for depression is increasing, and our results of the analysis in depressed patients add to it.

Our results suggest that particular aspects of cognitive performance -notably reduced cognitive speed- can be predictive of depressive disorder in subjects who are already depressed. This finding is of interest in relation to other studies on reductions in information processing speed and mood disorders. Quite some studies have suggested that effective sensory information processing, and effective comparison with information that is contained in long-term memory stores, is essential in order to cope with the demands of normal life. Prolonged periods of reduced speed of information processing could lead to impairments in the ability to cope with these demands, and eventually may lead to depressed mood [56].

Interestingly, theorists on the domain of cognitive aging have suggested that speed of information processing could be considered a resource for cognitive functioning [36 45]. Slower processing does not only cause a quantitative delay in higher cognitive processing, but it has an effect on the quality of higher information processing as well. Higher cognitive operations are hampered by slower processing, for instance because end products of earlier (basic) processing are sometimes not accessible any more by the time they are needed for higher cognitive processing. A decrease in speed thus causes degradation of higher information processing. The present findings strengthen the notion that depressed subjects most likely have to invest more effort to try to compensate for reduced cognitive speed. Depressed patients are also characterised by diminished ability to allocate effort or 'mental energy' [37]. As a result mental fatigue might increase dramatically, which has a further negative effect on cognitive processing. It is possible that the emerging vicious circle makes it very hard to recover from depressive disorder and thus leads to sustainment of depression.

In the subjects with initial normal mood state, cognitive measures did not predict later depressive disorder. After adjustment for former treatment, medication, age, sex, education and intelligence, cognitive performance still did not predict later depressive disorder. This result would imply that cognitive performance could not be marked as a vulnerability factor for depressive disorder in subjects with a current normal mood state. However, this finding must be regarded as tentative, in view of the small number of subjects that were later classified as suffering from depressive disorder. Further research in larger groups is needed to study cognitive vulnerability factors in initially not depressed subjects. With respect to the generalization of the findings, we studied attendants to an outpatient clinic specialised in age-related cognitive and affective problems, and generalization to other populations might not be legitimate. This study needs to be replicated in unselected samples and normal samples.
Summarizing, this study shows that impairments in cognitive performance -notably cognitive speed, attentional performance and memory- in depressed patients partly predicts sustaining or relapsing depressive disorder. More research is needed for reliable information about cognitive vulnerability factors for depressive disorder in subjects with normal mood.

CHAPTER 8

Concluding Remarks

This thesis addressed the relationship between cognitive functioning and depression in young, middle-aged, and older subjects. The chapters describe clinical studies with groups of patients suffering from major depressive disorder and subjects with relatively mild complaints about moodwho were otherwise healthy. It is well known that various cognitive deficits may be present in depression. Our first aim was to search for unifying or integrative factors that are central to cognitive impairment in depression. The studies described in this thesis suggest that a core feature of impaired cognitive functioning in this condition is a reduction in the speed of information processing.

A second aim was to test the hypothesis that cognitive impairment can be a determinant of depression. Indeed, we found arguments in favour of this hypothesis, since cognitive slowness partly predicted depressive symptoms in a healthy population (chapter 6), and predicted sustainment of depressive disorder in a population with initial major depressive disorder (chapter 7). Results in chapter 7 suggested that cognitive slowness did not predict the development of major depressive disorder in a population that initially had a normal mood. However, this last finding was probably caused by the fact that only a very small number of individuals developed a major depressive disorder.

A third aim was to test the effects of older age, and the aspecific effects of the factor ‘compromized health’, and cortisol levels on cognitive impairment in depressive disorder. Older age did not appear to be a prerequisite for cognitive impairment (chapters 2, 3), nor was it likely that cognitive impairment was caused by the aspecific effects of being unhealthy (chapters 2, 4). Interestingly, although depressive disorder was characterised by altered cortisol levels during the day and by cognitive slowness, the two phenomena did not seem to be causally related to each other, but were mediated by depressive symptoms (chapter 5).

The findings in the present studies strongly suggest that slowness in information processing might be a primary cognitive problem in depression, at least in the age groups which were investigated. Slowness of information processing seemed inherent to depression, and was not caused by alterations in cortisol levels, aspecific effects of disease, or older age. More in-depth investigations are needed to find out whether the findings in the present study in outpatients can be generalised to other depressive populations, for example to depressive inpatients, depressive individuals with psychotic features, geriatric patients with depression, and depressive patients with other characteristics.

With respect to the role of cognitive functioning in depression, some more general remarks can be made. The following sections will address two major aspects, namely the nature of a possible core cognitive deficits in depression and the issue that cognitive dysfunction may precede depression.

Is cognitive slowness a core feature of the cognitive impairment in depression?
In our search for central mechanisms of cognitive impairment in depressive disorder, two hypotheses were tested (chapter 3). The first hypothesis stated that the core impairment in depression is a decrement in the performance on tasks involving speed of information processing. The second hypothesis stated that there is a disproportionately greater impairment in subjects with depression in their performance on tasks involving effortful processing when compared to performance on other tests. The hypotheses were tested in young to middle-aged outpatients who did not use psychotropic medication. The choice for this group was made in order to avoid the possible confounding effects of the factors 'advanced age' and 'psychotropic medication' on cognitive function. Results were in favour of the cognitive speed hypothesis. Cognitive slowness as assessed by cognitive tests was also parallelled by subjective cognitive complaints (chapter 2): complaints of cognitive slowness were more strongly related to depressive symptoms than were complaints of memory and attention.
Interestingly, the findings underline the importance of cognitive slowness in depression, but it is a clinical observation that depressed patients also complain about cognitive problems that are related to memory, attention, and executive functioning. In addition, cognitive impairments in these cognitive domains are quite visible in patients with depression, as is clearly evident from the description of a depressive state given by Widlöcher [2], cited in the introduction of this thesis. Studies on cognitive functioning in depression also report these impairments [28 29 133]. Thus, although we argue that cognitive slowness is a central cognitive impairment in depression, deficits in higher cognitive functions may also be present. If so, could there be an impairment in the higher cognitive functions, which is related to a deficit in slowness of information processing?

Salthouse and others [36 45] provide a theoretical background for the relation between cognitive slowness and higher cognitive impairments in the field of normal aging. Although they certainly do not deny the possibility of higher cognitive impairments in the process of aging, they present strong arguments in favour of the notion that a reduction in the speed of information processing is the basic impairment. In this theory, Salthouse et al. argue that cognitive operations must be executed within a limited time, and that slowed cognitive speed can make it impossible to complete operations successfully (due to a 'limited time mechanism'). Thus, a slower speed of information processing will lead to inefficient mental operations. To illustrate this rather abstract mechanism, imagine a student who has to make notes of an ongoing lecture on an unfamiliar topic. Writing down the lecture verbatim would be best for later reconstruction of the content, because all the information given in the lecture would be present. However, the student writes too slowly for verbatim reproduction. Thus, because there is only limited time to write down the words verbatim, a slower speed of information processing (in the example slower writing) makes this operation impossible. The student will probably take more global notes, which will represent the content of the lecture less completely than verbatim representation would have done.
Salthouse et al. further argue that a reduced processing speed can be responsible for the loss of early processing products by the time that they are needed for later processing (the 'simultaneity mechanism'). For example, the above-mentioned student needs to reconstruct the content of the lecture several weeks later. Since he was unable to take notes verbatim, he made more global notes. Immediately after listening to the lecture the content was rather clear to him, but when he reads the global notes of the lecture several weeks later, he is no longer

able to fully reconstruct the content of the lecture and its details. On the basis of the notes, he is not able to grasp the essence of the lecture. This example illustrates how a reduced speed (resulting in incomplete notes) is responsible for a loss of early processing products by the time that this is needed for later processing (later reconstruction of the lecture). This loss of information may affect higher processing as well. In the example, when the essence of the lecture is no longer available, the student will also have problems in explaining the material to other students, or in applying the information in an essay on a related subject.
The simultaneity mechanism may lead to a reduction of the amount of information that can be simultaneously processed within a short time frame. This may lead to a reduction in the efficiency of mental operations in working memory. Reductions in basic speed can thus lead to reduced attentional functions, memory, or executive functioning. Through the working of the limited time mechanism and the simultaneity mechanism, slowed cognitive processing can lead to impairments in higher cognitive functioning, which can be considered to be secondary to the reduced speed. Although the theory of Salthouse was initially designed to explain the effects of normal aging on cognitive functioning, we state that the theory can be quite well applied to the field of cognitive deficits in depression. We suggest that, in depression, factors that negatively affect the speed of information processing are likely to have further negative effects on cognitive function and might result in impairments in higher cognitive processing. Aging is a relevant factor in this respect, as well as some psychotropic medications, and particular risk factors such as brain infarcts and other biological factors which compromise brain function. Thus, in depression, impairments on several cognitive domains may be present, but the reduced speed of information processing may lie at the root of these impairments.

It is important to consider the fact that the population of patients examined consisted of non-psychotic outpatients. As inpatients [28] and depressive patients with psychotic features [48 140] represent more severely ill populations, it is possible that our findings do not apply to these more severely ill depressive patients Consequently, a slowness of cognitive speed may not be the central problem in the cognitive impairment in these populations. However, there are arguments in favour of the notion that compromised cognitive speed is important to consider in these populations as well. Although usually more extensive cognitive impairments are reported in depressive inpatients [33 50] and in psychotic depressive subjects [48 141], only about half of the studies have found a relationship between severity of depressive disorder and cognitive impairments [29]. This may indicate that the broader impairments of cognitive function are caused by factors other than the severity of illness. For example, an imbalance in neurotransmission in depressive disorder [142], may possibly affect the extent of cognitive impairments. Furthermore, psychotropic medication, older age, or more recurrences of depressive episodes in the past might also affect cognitive impairments in depression. Thus, even if the effects of psychotropic medication or older age are avoided in these samples (e.g. [48]), a more severe depressive illness does not necessarily imply that the speed of information processing is proportionately more impaired. In our opinion, the extent to which slower cognitive speed is present, and not the severity of the mood changes per se, determines the extent of cognitive impairment. It might even be possible that in some cases, the degree of cognitive slowness in part determines the severity of the depression, although this interesting possibility has not yet been investigated.

Future research into cognitive mechanisms in depression may benefit when it considers the notion that there is a core deficit in speed of information processing. In clinical settings, relevant knowledge may be obtained when the evaluation of processing speed in various cognitive domains is taken into consideration in neuropsychological assessment. Another clinical application has to do with the possible effects of medication on information processing speed. The findings of this thesis suggest that medication that negatively affects speed of information processing is suspected to have a negative effect on depression. Although for example sedative-hypnotic drugs are prescribed very frequently to depressed people [17 72 143], one wonders whether such a drug may lead to a reduction in the efficiency with which the subject processes incoming information and information from long term memory and thus leads to a further problem in coping with environmental demands. Further research should be devoted to an evaluation of this notion.

Reduced cognitive speed as determinant of depression

Up till now, it is generally assumed that cognitive impairment is secondary to depressive illness. Suggestions that cognitive impairment could also have an other relation to depression come from studies showing that cognitive impairment does not invariably reverse with remission of depression [4-8]. Other studies suggested that cognitive problems might even be a determinant for the later development of depressive disorder [9-12]. These studies suggest that the relation between cognitive impairment and depressive illness is more complex than is generally assumed. The research described in this thesis, investigated whether cognitive deficits can act as a predictor of the development of depression in certain individuals. Our intention was to refine the general idea of the causal relationship between cognitive impairment and depressive illness (and not to replace it).

We hypothesised that cognitive deficits may be one factor in the development of mood changes which can eventually lead to depression. To avoid a situation in which cognitive deficits can only be measured as epiphenomenona of depressive disorder, we assessed subjects who had never been diagnosed with depressive disorder, but who had developed depressive symptoms over three years after initial assessment (chapter 4). The results of this study suggested that a decreased cognitive speed in part predicts the development of depressive symptoms. However, when we extended this study to depressive disorder (chapter 5) and studied patients who were initially healthy but who developed a depressive syndrome over the same time span, cognitive speed did not predict the diagnosis of depressive disorder. Although this result may be attributed to the small number of initially healthy subjects who developed depressive disorder, it is also possible that cognitive slowness is only a determinant of depressive syndrome in particular subjects who bear a vulnerability factor or riskfactor. Some support for this hypothesis can be found in the same study (chapter 5), which showed that cognitive slowness was one predictor of non-remission of depressive disorder in initially depressed individuals.

To date, it is recognized that the presence of a depressive episode is a major determinant for the development of later depressive episodes [23 24 144 145]. Having experienced a depressive episode seems to make subjects more vulnerable for later depressive episodes. It may be possible that cognitive slowness interacts with this vulnerability in determining non-remission of depressive disorder. The mechanism mentioned above, where cognitive slowness leads to reductions in the efficiency of mental operations could be relevant in this respect.

The physiological basis for the mechanisms proposed may have to do with reductions in 'brain reserve capacity' [42]. In normal aging people, reductions in the amount of white and grey matter of the brain are reported, already in middle-aged subjects (e.g. [76 122 146]). In normal aging individuals, a reduced cognitive speed is a prominent cognitive feature [45 76], which might be explained by a gradual reduction in neuronal connections and reduced efficiency of neurotransmission. Probably, some people are better able to cope with reduced cognitive speed than others. In line with the brain reserve theory of Satz [42], some individuals may have advantages that render them more able to compensate for small alterations. Such an advantage might consist of a higher density of neuronal connections in the brain, which may possibly be the basis for a greater brain reserve capacity. A greater brain reserve capacity is sometimes reflected in a higher education, or higher intelligence [147]. When cognitive speed is reduced, people need to invest more effort to accomplish the same tasks. For example, a person working in a big office space with several co-workers is usually able to focus his or her attention selectively at the current job and to filter environmental noise as 'irrelevant'. This process of selective attention is a form of controlled processing, which is expensive in terms of the investment of mental energy or 'resources' [37]. This investment can lead to mental fatigue or tiredness. Ignoring major distractions takes more effort and leads to more tiredness than focusing on a task when there are few distractions. When speed of information processing is reduced in a case in which there is reduced brain reserve capacity, it is likely that disproportionally more effort has to be invested to finish a job, which probably will lead to earlier exhaustion. Being tired, it is harder to block out distractions and to focus on the job. According to this theory, mental fatigue will further decrease the ability to compensate for reduced cognitive speed, reflecting a secondary negative effect on cognition. A vicious circle will then develop. The subjective experience of reduced cognitive abilities may cause a variety of subjective feelings, ranging between mild worries to profound fear of dementia, which has a major influence on the qualitiy of life. Ellis et al. [37] argued that worrying and feeling down further decreases the capacity to allocate effort to cognitive tasks. In our opinion, it is conceivable that this downward spiral of events may negatively affect mood. Factors that negatively influence the brain reserve capacity, such as the aging process, or a lower intelligence, might negatively affect the ability to cope with reduced cognitive speed. This may suggest that older people with a smaller brain reserve capacity, who experience reduced cognitive speed, might be especially vulnerable to the vicious circle of events that can lead to depression.

In conclusion

If the proposed mechanism of action described in the preceding paragraphs is correct, it may have implications for clinical practice and research. If a slower cognitive speed is a central cognitive deficit in depression and if –in some circumstances- it is a causal factor in the development of mood changes and depression, it will be interesting to develop treatment interventions which aim at increasing cognitive speed and/or improve the efficiency of cognitive processing. Such therapies might be of value to reduce cognitive deficits in depression or to prevent depression in certain vulnerable individuals. That there are biological as well as environmental vulnerabilities to depression is recognized. Biological vulnerabilities may consist of alterations in the functioning of several brain structures (such as the hippocampus, amygdala, and medial frontal cortex [129]), disturbances of the neurotransmitter system [148], and disturbances of the hypothalamus-pituitary-adrenal axis [149]. Other factors

that are related to a greater vulnerability to depression are female sex [19], external locus of control [150], neuroticism [77 151], negative life-events [152], low social support [77], and earlier episodes of depression [24]. The relation between reduced cognitive speed and the various vulnerability factors for depression needs to be investigated. For clinical practice, it may be fruitful to identify individuals who complain of a reduced cognitive ability and who worry about it. If neuropsychological assessment suggests that reduced cognitive abilities are merely a reflection of normal aging in these individuals, psycho-education may prevent further worries and the possible vicious circle leading to disturbed mood may be prevented. The combination of neuropsychological assessment and psycho-education may be carried out in specialised clinics for cognition-related problems (e.g. memory clinics like the Maastricht Memory Clinic [136]). A recent study in the Netherlands [137] showed that over 30% of non-demented subjects who were referred to a memory clinic actually suffered from depressive disorder. This population may possibly represent a fraction of the worried people who ended up in the hypothetical vicious circle that might lead to depression.

Thus, in addition to the possibility that cognitive deficits can be secondary to depression, we propose that for some individuals cognitive impairment, and especially reduced cognitive speed, is likely to be a part of the process that precedes mood changes and is a risk factor for the development of depression. This 'reversed causation mechanism' does not claim to replace the idea that cognitive impairments are secondary to depression and further in-depth studies are necessary to determine the specificity of this mechanism. An important question in this respect is: 'which people are most vulnerable?' Other questions that still need to be answered relate to the exact nature of the vulnerability, the clinical features of the depression, and mediating factors, to name but a few.

References

1. A.P.A. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. Washington DC., 1994.
2. Widlöcher D.J. Psychomotor retardation: clinical, theoretical, and psychometric aspects. *Diagnosis and Treatment of Affective Disorders* 1983;6:27-40.
3. Albersnagel F.A., Emmelkamp P.M.G., Van den Hoofdakker R.H. *Depression: theory, diagnostics, and treatment [Depressie: theorie, diagnostiek en behandeling]*. Houten/Zaventum: Bohn Stafleu Van Loghum, 1989.
4. Trichard C., Martinot J.L., Alagille M., Masure M.C., Hardy P., Ginestet D., Feline A. Time course of prefrontal lobe dysfunction in severely depressed in-patients: a longitudinal neuropsychological study. *Psychological Medicine* 1995;25:79-85.
5. Paradiso S., Lamberty G.J., Garvey M.J., Robinson R.G. Cognitive impairment in the euthymic phase of chronic unipolar depression. *Journal of Nervous and Mental Disease* 1997;185:748-754.
6. Dietrich D.E., Kleinschmidt A., Hauser U., Schneider U., Spannhuth C.W., Kipp K., Huber, T. J., Wieringa B.M., Emrich H.M., Johannes S. Word recognition memory before and after succesful treatment of depression. *Pharmacopsychiatry* 2000;3:221-228.
7. Nebes R.D., Butters M.A., Mulsant B.H., Pollock B.G., Zmuda M.D., Houck P.R., Reynolds III C.F. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychological Medicine* 2000;30:679-691.
8. Videbech P. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. *Acta Psychiatrica Scandinavica* 2000;101:11-20.
9. Roberts R.E., Kaplan G.A., Shema S.J., Strawbridge W.J. Does growing old increase the risk for depression? *American Journal of Psychiatry* 1997;154:1384-1390.
10. Roberts R.E., Shema S.J., Kaplan G.A., Strawbridge W.J. Sleep complaints and depression in an aging cohort: a prospective perspective. *American Journal of Psychiatry* 2000;157:81-88.
11. Van Os J., Jones P., Lewis G., Wadsworth M., Murray R. Developmental precursors of affective illness in a general population birth cohort. *Archives of General Psychiatry* 1997;54:625-631.
12. Van Os J., Park S.B.G., Jones P.B. Neuroticism, life events and mental health: evidence for person-environment correlation. *British Journal of Psychiatry* 2001;178:s72-s77.
13. Verhey F.R., Honig A. Depression in the elderly. In: Honig A., Anseau, M., Praag van, H.M., editors. *Recent advances in affective disorders*: Willey & sons, 1997.
14. Judd L.L., Paulus M.P., Wells K.B., Rapaport M.H. Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. *American Journal of Psychiatry* 1996;153:1411-1417.
15. Copeland J.R., Beekman A.T., Dewey M.E., Hooijer C., Jordan A., Lawlor B.A., Lobo A., Magnusson H., Mann A.H., Meller I., Prince M.J., Reischies F., Turrina C., De Vries M.W., Wilson K.C. Depression in Europe. Geographical distribution among older people. *British Journal of Psychiatry* 1999;174:312-321.
16. Beekman A.T., Copeland J.R., Prince M.J. Review of community prevalence of depression in later life. *British Journal of Psychiatry* 1999;174:307-311.

17. Lépine J.P., Gastpar M., Mendlewicz J., Tylee A. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). *International Clinical Psychopharmacology* 1997;12:19-29.
18. A.P.A. Practical guideline for major depressive disorder in adults. *American Journal of Psychiatry* 1992;150:1-26.
19. Piccinelli M., Wilkinson G. Gender differences in depression. *British Journal of Psychiatry* 2000;177:486-492.
20. Cui X.-J., Vaillant G.E. Does depression generate negative life events? *Journal of Nervous and Mental Disease* 1997;185:145-150.
21. Kendler K.S., Gardner C.O., Prescott C.A. Clinical characteristics of major depression that predict risk of depression in relatives. *Archives of General Psychiatry* 1999;56:322-327.
22. Kivela S., Viramo P., Pahkala K. Factors predicting the relapse of depression in old age. *International Journal of Geriatric Psychiatry* 2000;15:112-119.
23. Solomon D.A., Keller M.B., Leon A.C., Mueller T.I., Lavori P.W., Shea M.T., Coryell W., Warshaw M., Turvey C., Maser J.D., Endicott J. Multiple recurrences of major depressive disorder. *American Journal of Psychiatry* 2000;157:229-233.
24. Keller M.B., Lavori P.W., Rice J., Coryell W., Hirschfeld R.M.A. The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: a prospective follow-up. *American Journal of Psychiatry* 1986;143:24-28.
25. Smith G.E., Petersen R.C., Ivnik R.J., Malec J.F., Tangalos E.G. Subjective memory complaints, psychological distress, and longitudinal change in objective memory performance. *Psychology and Aging* 1996;11:272-279.
26. Jorm A.F., Christensen H., Korten A.E., Jacomb P.A., Henderson A.S. Memory complaints as a precursor of memory impairment in older people: a longitudinal analysis over 7-8 years. *Psychological Medicine* 2001;31:441-449.
27. Zakzanis K., Leach L., Kaplan E. On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 1998;11:111-119.
28. Burt D.B., Niederehe G., Zembar M.J. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin* 1995;117:285-305.
29. Austin M., Mitchell P., Goodwin G.M. Cognitive deficits in depression. *British Journal of Psychiatry* 2001;178:200-206.
30. Lemelin S., Baruch P. Clinical psychomotor retardation and attention in depression. *Journal of Psychiatric Research* 1998;32:81-88.
31. Veiel H.O.F. A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology* 1997;19:587-603.
32. Purcell R., Maruff P., Kyrios M., Pantelis C. Neuropsychological function in young patiens with unipolar major depression. *Psychological Medicine* 1997;27:1277-1285.
33. Fossati P., Amar G., Raoux N., Ergis A.M., Allilaire J.F. Executive functioning and verbal memory in young patients with unipolar depression and schizophrenia. *Psychiatry Research* 1999;89:171-187.
34. Williams R.A., Hagerty B.M., Cimprich B., Therrien B., Bay E., Oe H. Changes in directed attention and short-term memory in depression. *Journal of Psychiatric Research* 2000;34:227-238.
35. Grant M.M., Thase M.E., Sweeney J.A. Cognitive disturbance in outpatient depressed younger adults: evidence of modest impairment. *Biological Psychiatry* 2001;50:35-43.

36. Kail R., Salthouse T.A. Processing speed as a mental capacity. *Acta Psychologica* 1994;86:199-225.
37. Ellis H.C., Ashbrook P.W. Resource allocation model of the effects of depressed mood states on memory. In: Fiedler K., Forgas, J., editors. *Affect, cognition and social behavior*. Toronto: Hogrefe, C.J., 1988:25-43.
38. Hasher L., Zacks R.T. Automatic and effortful processes in memory. *Journal of Experimental Psychology* 1979;108:356-388.
39. Holsboer F. Neuroendocrinology of mood disorders. In: Bloom F.E., Kupfer, D.J., editors. *Psychopharmacology: the fourth generation of progress*. New York: Raven Press Ltd., 1995:957-969.
40. Sapolsky R.M. Potential behavioral modification of glucocorticoid damage to the hippocampus. *Behavioural Brain Research* 1993;57:175-182.
41. Lupien S.J., Nair N.P.V., Brière S., Maheu F., Tu M.T., Lemay M., McEwen B.S., Meaney M.J. Increased cortisol levels and impaired cognition in human aging: implication for depression and dementia in later life. *Reviews in the Neurosciences* 1999;10:117-139.
42. Satz P. Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology* 1993;7:273-295.
43. Sliwinski M., Buschke H. Cross-sectional and longitudinal relationships among age, cognition, and processing speed. *Psychology and Aging* 1999;14:18-33.
44. Brand A.N., Jolles J., Gispen-de Wied C. Recall and recognition memory deficits in depression. *Journal of Affective Disorders* 1992;25:77-86.
45. Salthouse T.A. The processing-speed theory of adult age differences in cognition. *Psychological Review* 1996;103:403-428.
46. Feehan R.G., Knight R.G., Partridge F.M. Cognitive complaint and test performance in elderly patients suffering depression or dementia. *International Journal of Geriatric Psychiatry* 1991;6:287-293.
47. Hartlage S., Alloy L.B., Vazquez C., Dykman B. Automatic and effortful processing in depression. *Psychological Bulletin* 1993;113:247-278.
48. Schatzberg A.F., Posener J.A., DeBattista C., Kalehzan B.M., Rothschild A.J., Shear P.K. Neuropsychological deficits in psychotic versus nonpsychotic major depression and no mental illness. *American Journal of Psychiatry* 2000;157:1095-1100.
49. Alexopoulos G.S., Meyers B.S., Young R.C., Kalayam B., Kakuma T., Gabrielle M., Sirey J.A., Hull J. Executive dysfunction and long-term outcomes of geriatric depression. *Archives of General Psychiatry* 2000;57:285-290.
50. Murphy F.C., Rubinsztein J.S., Michael A., Rogers R.D., Robbins T.W., Paykel E.S., Sahakian B.J. Decision-making cognition in mania and depression. *Psychological Medicine* 2001;31:679-693.
51. DeLuca J., Johnson S.K., Beldowicz D., Natelson B.H. Neuropsychological impairments in chronic fatigue syndrome, multiple sclerosis, and depression. *Journal of Neurology, Neurosurgery, and Psychiatry* 1995;58:38-43.
52. Juniper E.F., Guyatt G.H. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clinical and Experimental Allergy* 1991;21:77-83.
53. Bousquet J., Bullinger M., Fayol C., Marquis P., Valentin B., Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *Journal of Allergy and Clinical Immunology* 1994;94:182-188.

54. Kremer B., Klimek L., Bullinger M., Mosges R. Quality of life assessment in allergic rhinitis: the role of generic and disease specific quality of life scales. *Allergy* 2001;56:957-963.
55. Besner D., Stolz J.A. Unconsciously controlled processing: the Stroop effect reconsidered. *Psychonomic Bulletin & Review* 1999;6:449-455.
56. Brand N., Jolles J. Information processing in depression and anxiety. *Psychological Medicine* 1987;17:145-153.
57. Crowe S.F. Decrease in performance on the verbal fluency test as a function of time: evaluation in a young healthy sample. *Journal of Clinical and Experimental Neuropsychology* 1998;20:391-401.
58. Beck A.T., Steer R.A. *Manual for the Beck Depression Inventory*. San Antonio: Psychological Corporation, 1993.
59. Jolles J., Houx P.J., Van Boxtel M.P.J., Ponds R.W.H.M. *Maastricht Aging Study: determinants of cognitive aging*. Maastricht: Neuropsych Publishers, 1995.
60. Van Boxtel M.P.J., Buntinx F., Houx P.J., Metsemakers J.F.M., Knottnerus A., Jolles J. The relation between morbidity and cognitive performance in a normal aging population. *Journal of Gerontology: Medical Sciences* 1998;53A:M147-M154.
61. Vink M., Jolles J. A new version of the Trail Making Test as an information processing task. *Journal of Clinical Neuropsychology* 1985;7:162.
62. Stroop J.R. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 1935;18:421-457.
63. Sternberg S. Memory scanning: new findings and current controversies. *Quarterly Journal of Experimental Psychology* 1975;27:1-32.
64. Brand N., Jolles J. Learning and retrieval rate of words presented auditorily and visually. *The Journal of General Psychology* 1985;112:201-210.
65. Rabbitt P., Donlan C., McInnes L., Bent N. Unique and interactive effects of depression, age, socio-economic advantage and gender on cognitive performance of normal healthy older people. *Psychological Aging* 1995;10:307-313.
66. Granholm E., Chock D., Morris S. Pupillary responses evoked during verbal fluency tasks indicate semantic network dysfunction in schizophrenia. *Journal of Clinical and Experimental Neuropsychology* 1998;20:856-872.
67. Lezak M.D. *Neuropsychological assessment*. New York, Oxford: Oxford University Press, 1995.
68. CBS. *Job classification [Beroepsclassificatie]*. Voorburg: Central Bureau of Statistics of the Netherlands, 1985.
69. Wechsler D. *Wechsler Adult Intelligence Scale. Manual*. New York: Psychological Corporation, 1955.
70. Tabachnick B.G., Fidell L.S. *Using multivariate statistics*. Boston, London: Allyn & Bacon, 2001.
71. Tobiansky R., Blizard R., Livingston G., Mann A. The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. *Psychological Medicine* 1995;25:779-786.
72. Tylee A., Gastpar M., Lépine J., Mendlewicz J. DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. *International Clinical Psychopharmacology* 1999;14:139-151.

73. Christensen H., Mackinnon A.J. An analysis of diversity in the cognitive performance of elderly community dwellers: individual differences in change scores as a function of age. *Psychology and Aging* 1999;14:365-379.
74. McDonald E., Cope H., David A. Cognitive impairment in patients with chronic fatigue: a preliminary study. *Journal of Neurology, Neurosurgery, and Psychiatry* 1993;56:812-815.
75. Rourke S.B., Halman M.H., Bassel C. Neurocognitive complaints in HIV-infection and their relationship to depressive symptoms and neuropsychological functioning. *Journal of Clinical and Experimental Neuropsychology* 1999;21:737-756.
76. De Groot J.C., De Leeuw F.E., Oudkerk M., Van Gijn J., Hofman A., Jolles J., Breteler M.M. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Annals of Neurology* 2000;47:145-151.
77. Henderson A.S., Korten A.E., Jacomb P.A., Mackinnon A.J., Jorm A.F., Christensen H., Rodgers B. The course of depression in the elderly: a longitudinal community-based study in Australia. *Psychological Medicine* 1997;27:119-129.
78. Bazargan M., Barbre A.R. The effects of depression, health status, and stressful life-events on self-reported memory problems among aged blacks. *International Journal of Aging and Human Development* 1994;38:351-362.
79. Jonker C., Launer L.J., Hooijer C., Lindeboom J. Memory complaints and memory impairment in older individuals. *Journal of the American Geriatrics Society* 1996;44:44-49.
80. Ponds R.W.H.M., Commissaris C.J.A.M., Jolles J. Prevalence and covariates of subjective forgetfulness in a normal population in the Netherlands. *International Journal of Aging and Human Development* 1997;45:207-221.
81. Tylee A., Gastpar M., Lépine J., Mendlewicz J. Identification of depressed patient types in the community and their treatment needs: findings from the DEPRES II (Depression Research in European Society II) survey. *International Clinical Psychopharmacology* 1999;14:153-165.
82. Metsemakers J.F.M., Höppener P., Knottnerus J.A., Kocken R.J.J., Limonard C.B.G. Computerized health information in the Netherlands: a registration network of family practices. *British Journal of General Practice* 1992;42:102-106.
83. Derogatis L.R. *SCL-90: Administration, scoring and procedures manual-I for the R(evised) version*. Baltimore: John Hopkins School of Medicine, Clinical Psychometrics Research Unit, 1977.
84. Arrindell W.A., Ettema J.H.M. *SCL-90. Manual for a multidimensional indicator of psychopathology [Handleiding bij een multidimensionele psychopathologie-indicator]*. Lisse: Swets & Zeitlinger B.V., 1986.
85. Steer R.A., Ball R., Ranieri W.F. Further evidence for the construct validity of the Beck Depression Inventory-II with psychiatric outpatients. *Psychological Reports* 1997;80:443-446.
86. Pálsson S., Johansson B., Berg S., Skoog I. A population study on the influence of depression on neuropsychological functioning in 85-year-olds. *Acta Psychiatrica Scandinavica* 2000;101:185-193.
87. Wright A.L., Holberg C.J., Martinez F.D., Halonen M., Morgan W., L.M. T. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;94:895-901.
88. Marshall P.S., O'Hara C., Steinberg P. Effects of seasonal allergic rhinitis on selected cognitive abilities. *Annals of Allergy and Asthma Immunology* 2000;84:403-410.
89. Blaiss M.S. Cognitive, social, and economic costs of allergic rhinitis. *Allergy and Asthma Proceedings* 2000;21:7-13.

90. Kay G.G. The effects of antihistamines on cognition and performance. *Journal of Allergy and Clinical Immunology* 2000;105:622-627.
91. Van Boxtel M.P.J., Van Beijsterveldt C.E.M., Houx P.J., Anteunis L.J.C., Metsemakers J.F.M., Jolles J. Mild hearing impairment can reduce verbal memory performance in a healthy adult population. *Journal of Clinical and Experimental Neuropsychology* 2000;22:147-154.
92. Luteijn F., Ploeg van der F.A.E. *Groninger Intelligence Test. Manual [Groninger Intelligentie Test. Handleiding]*. Lisse: Swets & Zeitlinger, 1983.
93. Van Cauwenberge P., Juniper E.F., Group S.S.I. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clinical and Experimental Allergy* 2000;30:891-899.
94. Jensen A. Individual differences in the Hick paradigm. In: Vernon P., editor. *Speed of information processing and intelligence*. Norwood NJ: Ablex Publishing, 1987:101-175.
95. Landro N.I., Sletvold H., Celius E.G. Memory functioning and emotional changes in early phase multiple sclerosis. *Archives of Clinical Neuropsychology* 2000;15:37-46.
96. Maj M., Satz P., Janssen R., Zaudig M., Starace F., D'Elia L., Sughondhabirom B., Mussa M., Naber D., Ndetei D., Schulte G., Sartorius N. WHO Neuropsychiatric AIDS study, cross-sectional phase II. *Archives of General Psychiatry* 1994;51:51-61.
97. Salinsky M.C., Storzbach D., Dodrill C.B., Binder L.M. Test-retest bias, reliability, and regression equations for neuropsychological measures repeated over a 12-16 week period. *Journal of the International Neuropsychological Society* 2001;7:597-605.
98. Gold P.W., Chrousos G.P. The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. *Proceedings of the Association of American Physicians* 1999;111:22-34.
99. Deuschle M., Schweiger U., Weber B., Gotthardt U., Körner A., Schmider J., Standhardt H., Lammers C., Heuser I. Diurnal activity and pulsatility of the Hypothalamus-Pituitary-Adrenal system in male depressed patients and healthy controls. *Journal of Clinical Endocrinology and Metabolism* 1997;82:234-238.
100. Mitchell A.J. The contribution of hypercortisolaemia to the cognitive decline of geriatric depression. *International Journal of Geriatric Psychiatry* 1995;10:401-409.
101. Jameison K., Dinan T.G. Glucocorticoids and cognitive function: from physiology to pathofysiology. *Human Psychopharmacology* 2001;16:293-302.
102. Van London L., Goekoop J.G., Zwinderman A.H., Lanser B.K., Wiegant V.M., De Wied D. Neuropsychological performance and plasma cortisol, arginine vasopressin and oxytocin in patients with major depression. *Psychological Medicine* 1998;28:275-284.
103. Van Niekerk J.K., Huppert F.A., Herbert J. Salivary cortisol and DHEA: association with measures of cognition and well-being in normal older men, and effects of three months of DHEA supplementation. *Psychoneuroendocrinology* 2001;26:591-612.
104. Goodwin G.M. Neuropsychological and neuroimaging evidence for the involvement of the frontal lobes in depression. *Journal of Psychopharmacology* 1997;11:115-122.
105. Tsourtos G., Thompson J.C., Stough C. Evidence of an early information processing speed deficit in unipolar major depression. *Psychological Medicine* 2002;32:259-265.
106. Leproult R., Copinschi G., Buxton O., Van Cauter E. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep* 1997;20:865-870.
107. Spiegel K., Leproult R., Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *The Lancet* 1999;354:1435-1439.

108. Vining R.F., McGinley R.A. Hormones in saliva. *CRC Critical Reviews in Clinical Laboratory Sciences* 1986;23:95-145.
109. Gunnar M.R., Morison S.J., Chisholm K., Schuder M. Salivary cortisol levels in children adopted from Romanian orphanages. *Development and Psychopathology* 2001;13:611-628.
110. McAllister-Williams R.H., Ferrier I.N., Young A.H. Mood and neuropsychological function in depression: the role of corticosteroids and serotonin. *Psychological Medicine* 1998;28:573-584.
111. Goodyer I.M., Herbert J., Altham P.M.E., Pearson J., Secher S.M., Shiers H.M. Adrenal secretion during major depression in 8- to 16-year-olds, I. Altered diurnal rhythms in salivary cortisol and dehydroepiandrosterone (DHEA) at presentation. *Psychological Medicine* 1996;26:245-256.
112. Gunnar M.R., Vazquez D.M. Low cortisol and a flattening of expected daytime rhythm: potential indices of risk in human development. *Development and Psychopathology* 2001;13:515-538.
113. Weitzman E.D., Fukushima D., Nogeire C., Roffwarg H., Gallagher T.F., Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *Journal of Clinical Endocrinology* 1971;33:14-22.
114. Born J., Hansen K., Marshall L., Mölle M., Fehm H.L. Timing the end of nocturnal sleep. *Nature* 1999;397:29-30.
115. Beats B.C., Sahakian B.J., Levy R. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychological Medicine* 1996;26:591-603.
116. Smyth J.M., Ockenfels M.C., Gorin A.A., Catley D., Porter L.S., Kirschbaum C., Hellhammer D.H., Stone A.A. Individual differences in the diurnal cycle of cortisol. *Psychoneuroendocrinology* 1997;22:89-105.
117. Stone A.A., Schwartz J.E., Smyth J., Kirschbaum C., Cohen S., Hellhammer D., Grossman S. Individual differences in the diurnal cycle of salivary free cortisol: a replication of flattened cycles for some individuals. *Psychoneuroendocrinology* 2001;26:295-306.
118. McQuaid J.R., Stein M.B., Laffaye C., McCahill M.E. Depression in a primary care clinic: the prevalence and impact of an unrecognized disorder. *Journal of Affective Disorders* 1999;55:1-10.
119. Sabbe B., Hulstijn W., Van Hoof J., Tuynman-Qua H.G., Zitman F. Retardation in depression: assessment by means of simple motor tasks. *Journal of Affective Disorders* 1999;55:39-44.
120. Berger A., Small B.J., Forsell Y., Winblad B., Bäckman L. Preclinical symptoms of major depression in very old age: a prospective longitudinal study. *American Journal of Psychiatry* 1998;155:1039-1043.
121. Folstein M., Folstein S., McHugh P. "Mini-Mental State", a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;12:189-198.
122. Van der Werf Y.D., Tisserand D.J., Visser P.J., Hofman P.A.M., Vuurman E., Uylings H.B.M., Jolles J. Thalamic volume predicts performance on tests of cognitive speed and decreases in healthy aging. A magnetic resonance imaging-based volumetric analysis. *Cognitive Brain Research* 2001;11:377-385.
123. Radloff L.S. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement* 1977;1:385-401.
124. Beekman A.T.F., Deeg D.J.H., Van Limbeek J., Braam A.W., De Vries M.Z., Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in the Netherlands. *Psychological Medicine* 1997;27:231-235.

125. Kiloh L.G., Andrews G., Neilson M. The long-term outcome of depressive illness. *British Journal of Psychiatry* 1988;153:752-757.
126. De Groot J.C., De Leeuw F.E., Oudkerk M., Hofman A., Jolles J., Breteler M.B. Cerebral white matter lesions and depressive symptoms in elderly adults. *Archives of General Psychiatry* 2000;57:1071-1076.
127. O'Brien J., Ames D., Chiu E., Schweitzer I., Desmond P., Tress B. Severe deep white matter lesions and outcome in elderly patients with major depressive disorder: follow up study. *British Medical Journal* 1998;317:982-984.
128. Simpson S., Baldwin R.C., Jackson A., Burns A.S. Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. *Psychological Medicine* 1998;28:1015-1026.
129. Byrum C.E., Ahearn E.P., Krishnan R.R. A neuroanatomic model for depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 1999;23:175-193.
130. Baxter L.R., Schwartz J.M., Phelps M.E., Mazziotta J.C., Guze B.H., Selin C.E., Gerner R.H., Sumida R.M. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry* 1989;46:243-250.
131. Soares J.C., Mann J.J. The functional neuroanatomy of mood disorders. *Journal of Psychiatric Research* 1997;31:393-432.
132. Sheline Y.I. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. *Biological Psychiatry* 2000;48:791-800.
133. Lemelin S., Baruch P., Vincent A., Everett J., Vincent P. Distractibility and processing resource deficit in major depression. Evidence for two deficient attentional processing models. *Journal of Nervous and Mental Diseases* 1997;185:542-548.
134. King D., Caine E.D. Cognitive impairment and major depression: beyond the pseudodementia syndrome. In: Grant I., Adams K.M., editors. *Neuropsychological assessment of neuropsychiatric disorders*. New York: Oxford University Press, 1996:200-217.
135. Degl'Innocenti A., Agren H., Bäckman L. Executive deficits in major depression. *Acta Psychiatrica Scandinavica* 1998;97:182-188.
136. Verhey F., Jolles J., Ponds R., Rozendaal N., Plugge L., de Vet H., Vreeling F., de Lugt P. Diagnosing dementia: a comparison between a monodisciplinary and multidiscipinary approach. *Journal of Neuropsychiatry and Clinical Neuroscience* 1993;5:78-85.
137. Visser P., Verhey F., Ponds R., Kester A., Jolles J. Distinction between preclinical dementia and depression. *Journal of the American Geriatrics Society* 2000;15:479-484.
138. Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* 1960;23:56-62.
139. Reitan R.M. Validity of the Trail Making Test as an indication of organic brain damage. *Perceptual and Motor Skills* 1958;8:271-276.
140. Belanoff J.K., Kalehzan M., Sund B., Fleming Ficek S.K., Schatzberg A.F. Cortisol activity and cognitive changes in psychotic major depression. *American Journal of Psychiatry* 2001;158:1612-1616.
141. Mojtabai R., Bromet E.J., Harvey P.D., Carlson G.A., Craig T.J., Fennig S. Neuropsychological differences between first-admission schizophrenia and psychotic affective disorders. *American Journal of Psychiatry* 2000;157:1453-1460.
142. Mayberg H.S., Mahurin R.K., Brannan S.K. Neuropsychiatric aspects of mood and affective disorders. In: Yodofsky S.C., Hales, R.E., editors. *The American psychiatric press textbook of neuropsychiatry*. Washington D.C.: American Psychiatric Press, Inc., 1997:883-902.

143. Bouhassira M., Allicar M.P., Blachier C., Nouveau A., Rouillon F. Which patients receive antidepressants? A 'real world' telephone study. *Journal of Affective Disorders* 1998;49:19-26.
144. Lee A.S., Murray R.M. The long-term outcome of Maudsley depressives. *British Journal of Psychiatry* 1988;153:741-751.
145. Swindle R.W., Cronkite R.C., Moos R.H. Risk factors for sustained nonremission of depressive symptoms. A 4 year follow-up. *Journal of Nervous and Mental Disease* 1998;186:462-469.
146. Golomb J., De Leon M.J., Kluger A., George A.E., Tarshish C., Ferris S.H. Hippocampal atrophy in normal aging. An association with recent memory impairment. *Archives of Neurology* 1993;50:967-973.
147. Schmand B., Smit J.H., Geerlings M.I., Lindeboom J. The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. *Psychological Medicine* 1997;27:1337-1344.
148. Cummings J.L. Anatomic and behavioral aspects of frontal-subcortical circuits. *Annals New York Academy of Sciences* 1995;769:1-13.
149. De Kloet E.R. Brain corticosteroid receptor balance and homeostatic control. *Frontiers in Neuroendocrinology* 1991;12:95-164.
150. Beekman A.T.F., De Beurs E., Van Balkom A.J., Deeg D.J., Van Dyck R., Van Tilburg W. Anxiety and depression in later life: co-occurrence and communality of risk factors. *American Journal of Psychiatry* 2000;157:89-95.
151. Parker G., Hadzi-Pavlovic D., Roussos J., Wilhelm K., Mitchell P., Austin M., Hickie I., Gladstone G., Eyers K. Non-melancholic depression: the contribution of personality, anxiety and life events to subclassification. *Psychological Medicine* 1998;28:1209-1219.
152. Szádóczky E., Fazekas I., Rihmer Z., Arató M. The role of psychosocial and biological variables in separating chronic and non-chronic major depression and early-late-onset dysthymia. *Journal of Affective Disorders* 1994;32:1-11.
153. Commissaris C.J.A.M., Ponds R.W.H.M., Jolles J. Subjective forgetfulness in a normal Dutch population: possibilities for health education and other interventions. *Patient Education and Counseling* 1998;34:25-32.

Summary

Cognitive impairments are very common in depressive disorder and include deficits in the domains of psychomotor speed, attention, memory, and executive functions. This thesis focuses on the relationship between mood changes, depressive disorder and cognitive functioning. Several questions are addressed, including: (a) are depressed patients characterized by a particular pattern of cognitive impairments, (b) what is the relationship between depressive symptoms and subjective cognitive complaints in several domains, (c) are cognitive deficits in depression related to the depression itself, or are they associated with nonspecific effects of disease, (d) is there a relationship between cognitive impairments and altered cortisol levels in depression, and (e) can cognitive impairments precede depression and be a determinant for its development?

Chapter 1 provides a brief introduction to depressive disorder. The cognitive impairments of depressive disorder are described, and epidemiologic data are presented. The rationale and aims of the studies presented in this thesis are described briefly.

In *chapter 2* we investigated whether depressive disorder is characterized by a characteristic pattern of cognitive impairments. Two theories concerning patterns of cognitive dysfunction were tested: the effort theory, which states that performance on effortful tasks is disproportionately impaired compared with performance on automatic tasks, and the cognitive speed theory, which states that depression is characterized by cognitive slowness. Furthermore, we also investigated whether cognitive deficits can be specifically attributed to depressive disorder, or whether they should be ascribed to more general physical disease-related factors. Thirty non-psychotic depressive outpatients from a general psychiatric hospital in Maastricht were compared with 38 healthy control subjects and 25 patients with severe allergic rhinitis from the the Department of Otorhinolaryngology, Head, and Neck Surgery of the university hospital of Maastricht. All groups consisted of young to middle-aged adults who did not use psychotropic medication. The cognitive test battery included tasks in which information processing occurs automatically, and tasks that require mental effort. Performance on several tasks was measured in terms of time (seconds), but in others it was measured as, for example, the number of words reproduced. Age, sex, education, and premorbid intelligence were controlled for. Results showed that cognitive impairments were specific for the depressive group. Since the two control groups did not differ from each other, cognitive impairments could not solely be ascribed to more general aspecific effects of disease. The depressive group was not disproportionately impaired in more effortful subtasks than in more automatic subtasks. Results favoured the cognitive speed hypothesis and suggested that reduced cognitive speed is a central cognitive deficit in depressive disorder. A reduced cognitive speed may cause impairments in higher cognitive functioning, which can then be regarded as impairments secondary to a reduction in the speed of information processing.

In *chapter 3* we investigated the relation between depressive symptoms and subjective cognitive complaints. The relation between depressive symptoms and subjective memory

complaints has been studied intensively, but little attention has been paid to complaints in other cognitive domains. In this chapter, the relation between depressive symptoms and complaints about cognitive speed, memory, and attention was investigated in 642 younger individuals (aged 24 to 50 years) and 675 older individuals (aged 50 to 88 years) from the general population. The factors sex, education, marital status, and physical health were controlled for. Results showed that in the young group, complaints about cognitive speed, memory, and attention were related to depressive symptoms, independently of the possible confounding variables, whereas in the older group, complaints about cognitive speed and memory were related to depressive symptoms. In both groups complaints about cognitive speed were highly prevalent and strongly associated with depressive symptoms. In primary care, complaints about cognitive speed and memory in older individuals may indicate the presence of depressive symptoms.

To determine whether cognitive impairments in depression are caused by the depressive illness itself, or by more general aspecific effects of disease, in chapters 2 and 5 a depressive group from a general psychiatric hospital in Maastricht was compared with a healthy control group and with a physically ill control group. The physically ill group consisted of patients with severe allergic rhinitis from the the Department of Otorhinolaryngology, Head, and Neck Surgery of the university hospital of Maastricht. Allergic rhinitis is a chronic disease of non-neurological origin, and possible effects on cognition are not expected to be caused by allergic rhinitis itself, but merely by aspecific effects of not feeling well. In *chapter 4* the allergic rhinitis group was compared with the healthy control group, to investigate whether aspecific effects of being unhealthy were present in the allergic control group. A group of 26 people with severe allergic rhinitis was compared with a group of 36 healthy individuals, matched for intelligence, education, age, and sex. Cognitive functioning (working memory, memory retrieval, speed of information processing, and flexibility) and subjective mental well-being were studied. Results showed that the allergic rhinitis group had more mental complaints, manifested as feelings and complaints of insufficiency, somatisation, sleep, and depressive feelings. Depression scores were slightly increased, but still within the normal range. Cognitive performance was the same in both groups. Thus patients with allergic rhinitis appear to have normal cognitive functioning, but it is possible that this requires extra effort and leads to more mental fatigue than in healthy individuals. This possibility should be investigated using assessment protocols that take longer to complete. The results of this study suggest that the allergic rhinitis control group can be used to investigate aspecific effects of disease.

In *chapter 5* we investigated whether young to middle-aged depressive outpatients from a general psychiatric hospital are characterized by altered cortisol levels over the day, and whether cortisol levels are associated with cognitive impairment. Furthermore, the specificity of possible effects was studied by comparing 27 depressive patients with 36 healthy controls and 20 allergic rhinitis controls. Subjects provided saliva samples at 8 a.m., 4 p.m., and 9 p.m.. The cortisol variables studied were the cortisol curve during the day (and especially its flatness) and the mean cortisol value during the day. The relation between both cortisol variables and performance on tasks of memory and speed of information processing was studied. The results showed that, compared with the healthy control group, the depressive group was characterized by a flatter cortisol curve during the day, with significantly higher

evening values. The depressive group also had a poorer performance on cognitive speed tasks than either of the control groups. Flatter cortisol curves were associated with cognitive slowness over all subjects. However, this relationship is unlikely to be causal; after control for depressive symptoms, flatness of the diurnal cortisol curve was no longer a significant predictor of cognitive slowness. Thus, major depressive disorder and related depressive symptoms appeared to be independently associated with altered cortisol secretory patterns and with decrements in cognitive speed. It was concluded that young to middle-aged depressive outpatients are characterized by cognitive slowness and altered cortisol levels, but the two phenomena are not causally related to each other.

In *chapter 6* we studied the influence of cognitive impairment on the later development of depressive symptoms. It is generally believed that cognitive deficits are a direct consequence of depression. However, several studies have shown that cognitive impairments are sometimes still present after remission of a depressive episode. Moreover, recent findings suggest that cognitive deficits are a determinant of relapse in patients with depressive disorder. It is possible that these findings present epiphenomena of depressive disorder, or else long-term consequences of a depressive disorder. To avoid possible long-lasting influences of a depressive syndrome on cognitive function, prospective research with initially healthy individuals is important. In chapter 6 a group of 388 middle-aged to old individuals from the general population, without a history of depressive disorder was monitored for 3 years. After 3 years, 134 individuals had developed depressive symptoms, whereas 254 individuals had a normal mood. The two groups did not differ in age, sex, education, or intelligence. Using logistic regression analysis controlled for marital status, physical health, and mental health, we tested whether initial cognitive performance determines the later development of depressive symptoms. Results suggest that the development of depressive symptoms is best predicted by initial slowness in information processing and by a poorer mental health. We concluded that reduced cognitive speed seems a (partial) determinant for later depressive symptoms in healthy subjects aged 50 and over. Hypothetically, the mechanism might involve a cascade in which an age-related decrease in brain functioning may lead to reduced cognitive speed. Individuals who are less able to compensate for this decrease in cognitive speed are possibly more vulnerable to the development of depressive symptoms.

In *chapter 7* we extended the study of the previous chapter to include individuals with major depressive disorder. Subjects are middle-aged to older outpatients, referred to a memory-clinic. Two experiments were carried out to study whether cognitive impairment is a predictor of the development of depressive disorder in these subjects. In the first experiment, 48 patients with initial depressive disorder were assessed at baseline and 2.5 years later. We investigated whether baseline deficits in cognitive speed, attention, and memory predict the later presence of a depressive disorder. Analyses were controlled for former psychiatric treatment, use of medication, age, sex, education, and intelligence. Results suggested that impairments in cognitive speed, attention, and memory predict the presence of depressive disorder after 2.5 years. Outcome of depressive disorder was best predicted by the combination of cognitive slowness and former psychiatric treatment. We concluded that deficits in cognitive performance are a vulnerability factor for relapsing, or persisting, depressive disorder. In the second experiment, 46 individuals with an initially normal mood state were assessed at baseline and after 2.5 years. Results for those individuals with an initial

normal mood showed that baseline cognitive impairment does not predict the later development of depressive disorder. This result may be biased by the very small number of individuals who developed a depressive disorder. This second experiment should therefore be replicated with more subjects.

In *chapter 8* we discussed the most important findings in relation to existing knowledge concerning depression. Possible mechanisms of action and the relevance of the findings for future research and clinical practice are considered. The results of the studies in this thesis strongly suggest that a decreased speed of information processing is a central cognitive impairment in depression, at least in ambulant subjects in the age groups studied. According to the limited time mechanism (the time for the execution of cognitive processing is limited, and therefore slowed cognitive processing causes less than optimal information processing) and the simultaneity mechanism (because of cognitive slowness, the end products of earlier information processing are no longer available when needed for later processing) formulated by Salthouse, cognitive slowness might lead to other impairments in information processing. This may result in deficits in attention, memory, and executive functioning. We found arguments in favor of the possibility that reduced cognitive speed is a determinant of depression in middle-aged to older individuals, both for the development of depressive symptoms and for persisting depressive disorder. Hypothetically, a reduced efficiency in brain functioning (which may be associated with reduced brain volume) during the aging process might be responsible for a reduction in cognitive speed in these groups. Individuals with a reduced brain reserve capacity might be more vulnerable because they are less able to compensate for reduced information processing, which is measured by a reduction in the speed of performance on particular cognitive tasks.
Individuals with a reduced brain reserve capacity might be vulnerable because they are less able to compensate for cognitive slowness. These individuals might end up in a vicious circle, in which reduced cognitive functioning may cause mental fatigue, worries, tiredness, and secondary negative effects on cognitive functioning. Hypothetically, this may eventually lead to mood symptoms and eventually depression. Whether treatment interventions that enhance cognitive speed also positively affect depression merits investigation. Likewise, psychoactive medication with a negative effect on processing speed could in the long run also have a negative effect on the clinical picture, which is also a notion that deserves further investigation.

The studies of this thesis show that the cognitive neuropsychological approach could contribute to our theorizing around the pathogenesis of depression. The investigation of cognitive impairments in depression can provide information on behavioral disorders and problems in daily functioning that are associated with depression, and on the causal relationship between depression and cognitive impairments. The latter may contribute to the knowledge of etiological factors of this highly prevalent disorder.

Samenvatting

Bij de depressieve stoornis treden vaak cognitieve stoornissen op, o.a. op het gebied van psychomotore snelheid, aandacht, geheugen en uitvoerende controlefuncties. De relatie tussen cognitief functioneren en depressie vormt het onderwerp van dit proefschrift. Verschillende vraagstellingen worden behandeld, waaronder: (a) worden depressieve patienten gekenmerkt door een karakteristiek profiel in cognitieve stoornissen, (b) hoe is de relatie tussen depressieve symptomen en diverse subjectieve cognitieve klachten, (c) zijn cognitieve stoornissen bij depressie werkelijk toe te schrijven aan de depressie, of komen ze voort uit aspecifieke effecten van ziekte, (d) is er een relatie tussen cognitieve tekorten en veranderde cortisolspiegels in depressie en (e) kunnen cognitieve stoornissen voorafgaan aan depressie en er een determinant van zijn.

Hoofdstuk 1 geeft een beknopte introductie over de depressieve stoornis. Op basis van de literatuur worden epidemiologische gegevens over depressie weergegeven en er wordt een algemeen beeld geschetst over cognitieve tekorten bij de depressieve stoornis. De rationale en doelen van de verschillende studies in dit proefschrift worden kort uiteengezet.

In *hoofdstuk 2* werd onderzocht of er sprake is van een kenmerkend profiel van cognitieve stoornissen bij de depressieve stoornis. Past het profiel beter bij de hypothese die stelt dat disproportionele tekorten voorkomen bij taken die meer mentale inspanning vereisen, of beter bij een specifieke stoornis in de snelheid van informatieverwerking? Voorts werd onderzocht of cognitieve stoornissen toegeschreven kunnen worden aan de depressieve stoornis, of dat zij wellicht veroorzaakt worden door aspecifieke effecten van ziekte. Dertig niet-psychotische depressieve poliklinische patiënten uit een algemeen psychiatrisch ziekenhuis werden vergeleken met 38 gezonde controlepersonen en met een controlegroep van 25 poliklinische patiënten met een ernstige vorm van allergische rhinitis, afkomstig van de KNO-afdeling van een academisch ziekenhuis. Proefpersonen waren jong- tot middelbaar van leeftijd en gebruikten geen psychotrope medicatie. De cognitieve taakbatterij was samengesteld uit taken die worden opgedeeld in subtaken waarbij informatieverwerking vooral automatisch plaats vindt en subtaken waarbij meer mentale inspanning vereist is. Sommige taken werden gemeten in snelheid, en anderen in niet-snelheidsgerelateerde eenheden (zoals. het aantal gereproduceerde woorden). Er werd gecontroleerd voor een aantal factoren die van invloed kunnen zijn op cognitieve prestatie, en wel leeftijd, geslacht, opleiding en premorbide intelligentie. Uit de resultaten bleek dat een prestatievermindering op cognitieve taken specifiek optrad bij de depressieve groep. Omdat beide controlegroepen niet van elkaar verschilden, konden cognitieve stoornissen niet zonder meer worden toegeschreven aan aspecifieke effecten van ziekte. De depressieve groep vertoonde geen disproportionele tekorten op taken die meer mentale investeringen vereisten, vergeleken met taken die automatisch verwerkt werden. Resultaten pasten veel meer bij de cognitieve snelheidshypothese en suggereerden dat een centrale cognitieve dysfunctie bij de depressieve stoornis bestaat uit een verminderde snelheid van informatieverwerking. Dit kan ook leiden

tot stoornissen in hogere cognitieve functies, welke in dat geval als secundair kunnen worden gezien aan de algehele vertraging van informatieverwerking.

In *hoofdstuk 3* werd een relatie gelegd tussen depressieve symptomen en subjectieve cognitieve problemen. In de literatuur is wel de relatie tussen depressieve symptomen en geheugenklachten geobjectiveerd, maar klachten op andere cognitieve gebieden zijn onderbelicht gebleven. Bij 642 jongere mensen (leeftijd 24 tot 50 jaar) en 675 oudere mensen (leeftijd 50 tot 88 jaar) uit de normale populatie werden depressieve symptomen gerelateerd aan klachten over cognitieve snelheid, geheugen en aandacht. Er werd gecontroleerd voor geslacht, opleiding, huwelijkse staat en lichamelijke gezondheid. Binnen de jonge groep bleken klachten over snelheid, geheugen en aandacht, onafhankelijk van de mogelijke storende factoren, geassocieerd met depressieve symptomen. Binnen de oude groep was er een associatie tussen depressieve symptomen en klachten over snelheid en geheugen. In beide groepen waren met name klachten over cognitieve snelheid hoog prevalent en het sterkst geassocieerd met depressieve symptomen. Er werd gesuggereerd dat binnen de eerstelijnszorg, de aanwezigheid van cognitieve klachten over cognitieve snelheid en geheugen bij ouderen een aanwijzing kan zijn voor de aanwezigheid van depressieve symptomen.

Om te kunnen onderzoeken of cognitieve tekorten bij depressie kunnen worden toegeschreven aan de depressieve stoornis, of dat deze wellicht het gevolg zijn van aspecifieke effecten van ziekte in het algemeen, werden in de hoofdstukken 2 en 5 een poliklinische depressieve groep uit een APZ vergeleken met een gezonde groep en tevens met een fysiek zieke groep. Voor deze laatste groep werd gebruik gemaakt van patiënten met ernstige allergische rhinitis van de afdeling KNO van een academisch ziekenhuis. Allergische rhinitis heeft geen neurologische oorsprong en daarom mag verwacht worden dat mogelijke effecten op cognitief functioneren het gevolg zijn van aspecifieke effecten van ziekte, zoals bijvoorbeeld de stress die gepaard gaat met onwelbevinden. In *hoofdstuk 4* werd de allergische groep vergeleken met de gezonde groep, om na te gaan of aspecifieke gevolgen van ziekte überhaupt aanwezig waren in de allergische groep. Een groep van 26 patiënten met allergische rhinitis werd vergeleken met een gezonde groep van 36 personen, gematcht op intelligentie, opleiding, leeftijd en geslacht. Cognitief functioneren (werkgeheugen, ophalen van informatie uit het geheugen, snelheid van informatieverwerking en flexibiliteit) en subjectief psychisch welzijn werden onderzocht. De groep met allergische rhinitis bleek meer psychische klachten te hebben, wat met name tot uiting kwam in gevoelens van insufficiëntie, lichamelijke klachten, klachten over slaap en depressieve gevoelens. Beide groepen verschilden niet in cognitieve prestatie. Het zou mogelijk kunnen zijn dat patiënten met allergische rhinitis in staat zijn om kortdurend meer energie te investeren, wat zou kunnen resulteren in een normale cognitieve prestatie gedurende het onderzoek, maar tevens in snellere vermoeidheid. Dit dient nader onderzocht te worden door meer langdurige onderzoeksprotocollen te gebruiken. De resultaten van dit onderzoek wijzen er op dat de controlegroep met allergische rhinitis een aanvaardbare controlegroep is om aspecifieke effecten van ziekte te testen.

In *hoofdstuk 5* werd onderzocht of poliklinische depressieve patiënten uit een APZ in de jong- tot middelbare leeftijd gekarakteriseerd worden door een veranderde cortisolproductie over de dag, en of er een verband is tussen cortisolproductie en cognitieve stoornissen. Voorts werd de specificiteit van dit verband onderzocht, door een groep van 27 depressieve patiënten te

vergelijken met 36 gezonde controles, alsmede met 20 patiënten met symptomatische allergische rhinitis. De primaire cortisolvariabelen waren het verloop van de cortisolcurve over de dag en met name de vlakheid ervan en de gemiddelde cortisolwaarde over de dag. De variabelen waren gebaseerd op cortisolspiegels in speeksel dat verzameld is om 08:00 uur, 16:00 uur en 21:00 uur. Beide maten voor cortisol werden geassocieerd met de prestatie op een geheugentaak en snelheid van informatieverwerking. Uit de resultaten bleek dat de depressieve groep, vergeleken met de gezonde controlegroep, gekenmerkt werd door een vlakkere cortisolcurve over de dag, met significant hogere waarden in de avond. De depressieve groep presteerde ook slechter op cognitieve snelheid vergeleken met beide controlegroepen. Over alle proefpersonen was een vlakkere cortisolcurve geassocieerd met cognitieve traagheid. Deze relatie was hoogstwaarschijnlijk niet causaal van aard, want na correctie voor depressieve symptomen was vlakte van de dagelijkse cortisolcurve niet langer een significante voorspeller van cognitieve traagheid. Depressie leek dus onafhankelijk geassocieerd te zijn met veranderde cortisolsecretie patronen en met tekorten in cognitieve snelheid. Geconcludeerd werd dat poliklinische depressieve patiënten van jonge- tot middelbare leeftijd gekenmerkt worden door cognitieve vertraging en een veranderde cortisolproductie, maar dat beide fenomenen geen causaal verband hebben.

In *hoofdstuk 6* werd een onderzoek beschreven over de invloed van cognitief functioneren op de latere ontwikkeling van depressieve symptomen. In het algemeen wordt verondersteld dat cognitieve problemen secundair zijn aan depressie. Er is in de literatuur echter reeds naar voren gekomen dat cognitieve tekorten niet altijd opklaren na herstel van depressie. Bovendien wordt gesuggereerd dat cognitieve tekorten een determinant van terugval in depressie kunnen zijn. Het is mogelijk dat zulke cognitieve tekorten toch een epifenomeen, of lange termijn gevolg van een depressieve stoornis zijn. Prospectief onderzoek met initieel gezonde mensen kan uitsluitsel geven. In hoofdstuk 4 werd een groep van 388 mensen uit de normale bevolking in de leeftijd van 50 tot 80 jaar gedurende 3 jaar gevolgd. Na 3 jaar bleken 134 depressieve symptomen te hebben, terwijl 254 een normale gemoedstoestand hadden. Beide groepen verschilden niet in leeftijd, geslacht, opleiding, of intelligentie. Met behulp van logistische regressie-analyse werd getoetst of het cognitief functioneren aan het begin van het onderzoek een determinant was voor de latere ontwikkeling van depressieve symptomen, gecontroleerd voor huwelijkse staat, fysieke gezondheid en mentale gezondheid. Resultaten suggereerden dat de ontwikkeling van depressieve symptomen het best voorspeld werd door initiële cognitieve traagheid en een initieel slechtere mentale gezondheid. Er werd geconcludeerd dat snelheid van informatieverwerking mede een determinant lijkt te zijn voor latere ontwikkeling van depressieve symptomen, in gezonde mensen die ouder zijn dan 50 jaar. De hypothese werd gesteld dat het werkingsmechanisme zou kunnen bestaan uit een cascade waarbij een leeftijdsgerelateerde vermindering in hersenfunctie kan leiden tot verminderde cognitieve snelheid, waarbij personen die minder goed in staat zijn te compenseren voor deze cognitieve achteruitgang, een risico lopen voor de ontwikkeling van depressieve symptomen.

De studie van *hoofdstuk 7* vormde een uitbreiding van het vorige hoofdstuk, waarbij nu individuen met een depressieve stoornis werden geïncludeerd. Proefpersonen waren middelbare- en oudere poliklinische patiënten, verwezen naar een geheugenpolikliniek. D.m.v. twee experimenten werd onderzocht of cognitieve stoornissen een voorspeller kunnen

zijn voor de ontwikkeling van een depressieve stoornis bij deze mensen. In het eerste experiment werden 48 patiënten met een depressieve stoornis onderzocht op het moment dat ze depressief zijn, alsmede 2,5 jaar later. Er werd onderzocht of tekorten in cognitieve snelheid, aandacht en geheugen de latere uitkomst van een depressieve stoornis voorspelden. Analyses werden gecontroleerd voor eerdere psychiatrische behandeling, medicatie, leeftijd, geslacht, opleiding en intelligentie. Resultaten suggereerden dat cognitieve stoornissen in snelheid, aandacht en geheugen determinanten zijn voor de aanwezigheid van een latere depressieve stoornis. De uitkomst werd het best voorspeld door cognitieve snelheid en eerdere psychiatrische behandeling. Er werd geconcludeerd dat tekorten in cognitieve prestatie een kwetsbaarheidsfactor vormen voor terugval in, of een aanhoudende, depressieve stoornis. In het tweede experiment werden 46 patiënten met een initieel normale gemoedstoestand 2,5 jaar later nogmaals onderzocht. Bij deze mensen bleek de initiële cognitieve prestatie geen voorspeller te zijn voor de ontwikkeling van een depressieve stoornis, wat waarschijnlijk veroorzaakt werd door het zeer kleine aantal mensen binnen deze groep dat een depressieve stoornis ontwikkelde. Dit tweede experiment dient herhaald te worden in een grotere studie.

In *hoofdstuk 8* werden de belangrijkste bevindingen ingebed in bestaande kennis over depressie, er werd aandacht geschonken aan mogelijke achterliggende werkingsmechanismen en aan de betekenis van de bevindingen voor toekomstig onderzoek en voor de klinische praktijk. Bevindingen wijzen er sterk op dat een verminderde snelheid van informatieverwerking een cognitief kerntekort is in depressie. Cognitieve traagheid zou kunnen leiden tot andere stoornissen in informatieverwerking, bijvoorbeeld tot dysfuncties in aandacht, geheugen en uitvoerende controlefuncties. De verklaring hiervoor steunt op twee cognitieve werkingsmechanismen, welke zijn geformuleerd door Salthouse. Ten eerste het ‘gelimiteerde tijdmechanisme’: doordat tijd voor de uitvoering van cognitieve processen gelimiteerd is, kan cognitieve traagheid leiden tot incomplete/inefficiënte informatieverwerking. Ten tweede het ‘simultaniteitsmechanisme’: door cognitieve traagheid zijn eindproducten van vroege verwerkingsprocessen niet altijd meer beschikbaar op het moment dat ze nodig zijn voor latere verwerking. Beide mechanismen kunnen leiden tot dysfuncties in hoger cognitieve processen. Er zijn tevens argumenten gevonden dat een verminderde cognitieve snelheid een determinant is van depressie in middelbaar tot oudere mensen, zowel voor de ontwikkeling van depressieve symptomen als voor het niet herstellen van een depressieve stoornis. Hypothetisch zou een verminderde efficiëntie van hersenfuncties (bijvoorbeeld samenhangend met een verminderde efficiëntie van neurotransmissie en verminderde connecties tussen hersencellen) gedurende het ouder worden verantwoordelijk kunnen zijn voor een afname in cognitieve snelheid in deze groepen. Mensen met verminderde hersenreservecapaciteit zijn mogelijk een kwetsbare groep die minder goed in staat is tot compensatie. Mogelijk komen zij hierdoor uiteindelijk in een vicieuze cirkel, waarbij het verminderde cognitieve functioneren leidt tot mentale uitputting, zorgen, moeheid en secundaire negatieve effecten op het cognitief functioneren. Wellicht kan dit uiteindelijk tot depressieve symptomen leiden. Dit suggereert dat het zinvol kan zijn om onderzoek te verrichten naar behandelinterventies die leiden tot een vergroting van de efficiëntie van informatieverwerking. Het is relevant om te onderzoeken of interventies die cognitieve snelheid vergroten, ook een positief effect hebben op depressie. Voorts is het relevant om in overwegen te nemen dat medicatie welke de snelheid van informatieverwerking vermindert, uiteindelijk een negatief effect kan hebben op de

mogelijkheden van de patient om efficiënt om te gaan met omgevingsprikkels, in het bijzonder in situaties waarin veel eisen worden gesteld aan informatieverwerkingscapaciteit.

De onderzoeken in dit proefschrift laten zien dat de cognitief neuropsychologische invalshoek een potentieel relevante bijdrage zou kunnen leveren aan de kennis over depressie. Onderzoek naar de cognitieve stoornissen geeft informatie over mogelijke stoornissen in gedrag en problemen in het dagelijks functioneren en over de causale relatie tussen depressie en cognitieve stoornissen. Dit laatste kan vervolgens bijdragen aan de kennis over etiologie, maar uiteindelijk ook aan de ontwikkeling van behandelinterventies voor depressie.

Dankwoord

Dit proefschrift is het bewijs dat een samenwerking tussen een algemeen psychiatrisch ziekenhuis, een academisch ziekenhuis en een universiteit mogelijk is en vruchtbaar kan zijn. Zonder de inzet van de medewerkers van PMS Vijverdal, de capaciteitsgroep Psychiatrie en Neuropsychologie van de Universiteit Maastricht, de geheugenpolikliniek en de afdeling KNO van het academisch ziekenhuis Maastricht, en van de afdeling Psychiatrie van het Maaslandziekenhuis te Sittard was het tot stand komen van dit proefschrift niet mogelijk geweest. Dit geldt ook voor de patiënten en proefpersonen die belangeloos mee hebben willen werken aan het onderzoek; zonder deze bereidwilligheid zou wetenschappelijk onderzoek onmogelijk zijn. Ik bedank al deze mensen, die zich met volle overtuiging hebben ingezet om gezamenlijk aan het doel te werken om meer kennis te vergaren over depressie.
Ik wil nog een klein aantal mensen speciaal bedanken. Jelle Jolles, promotor, je hebt me opgeleid tot wetenschapper. Je gaf me voldoende ruimte om plannen te ontwikkelen en uit te voeren. Ik heb het bijzonder gewaardeerd dat je achter me stond. Mayke Derix, jij hebt me het vak van klinisch neuropsycholoog geleerd. Ik heb altijd kunnen vertrouwen op een kritische blik en complimenten, zelfs van afstand. Lex van Bemmel, bedankt voor je gedrevenheid, enthousiasme en vertrouwen: jouw opmerkelijke onderhandelingstechnieken zijn bijzonder leerzaam geweest. Bernd Kremer, jouw betrokkenheid, eerlijkheid en vriendelijkheid hebben onze samenwerking bijzonder prettig gemaakt. Nancy Nicolson, Lydia Krabbendam, Hans Bosma, Pieter-Jelle Visser, Martin van Boxtel en Frans Verhey bedank ik voor de kritische commentaren en bijdragen aan het verbeteren van manuscripten. Sanne Tinga en Nathalie Bougie: bedankt voor de praktische hulp bij het uitvoeren van het onderzoek.
De AAN-tjes van PMS Vijverdal wil ik bedanken voor hun medeleven, support en prettige werksfeer. Edith Korten bedank ik speciaal voor haar luisterend oor, support en humoristische blik op allerhande zaken. Zonder jou waren de afgelopen jaren duidelijk minder prettig geweest. Ook mijn collegae van de capaciteitsgroep Psychiatrie en Neuropsychologie van de Universiteit Maastricht ben ik dankbaar. Door het uitstekende executieve functioneren van Elsa Misdom werd het samenwerkingsverband praktisch haalbaar. Nico Roozendaal, dank voor je oneindige bereidheid tot hulp bij allerhande zaken omtrent computers, databases, formules, etc. De vaste kroegploeg hielp bij het ontladen van wetenschappelijke spanning: Petra Hurks, Jeroen Schmitt, Edwin Klinkenberg, Brenda Jorissen, Wim Riedel, Sven Stapert, Marjolein de Vugt, Pauline Aalten, Daniëlle Tisserand: we blijven het glas heffen op de wetenschap. Jeroen Schmitt bedank ik nog speciaal voor de tijdrovende, maar boeiende en soms frustrerende wetenschappelijke discussies over allerlei onderwerpen, maar vooral over depressie-gerelateerde zaken. Ik hoop dat we het over de meeste zaken nooit eens zullen worden. Voorts Petra Hurks: je wist me altijd opnieuw te verbazen, je bent zoveel meer geworden dan een collega en je bood steun op alle mogelijke terreinen: bedankt! Petra en Stephan Planthof: ik ben bijzonder blij dat jullie het paranimfschap wilden accepteren!
Pa en ma, jullie hebben het in de diepste zin van het woord voor mij mogelijk gemaakt om te komen waar ik nu ben. Marc, bedankt voor al je liefde, steun, vertrouwen, flexibiliteit en humor. Zonder jou was alles zeker minder de moeite waard geweest.

Curriculum vitae

Mariska den Hartog is geboren op 10 april 1973 in Utrecht. In Zeist werd de openbare lagere school doorlopen, gevolgd door het Atheneum op R.S.G. Schoonoord. Deze opleiding werd in 1991 gevolgd door de opleiding Nederlandse Taal- en Letterkunde. Na behaling van de propedeuse werd in 1992 bewust gekozen voor de opleiding Psychologie aan de Rijksuniversiteit Utrecht. Tijdens de studie werd de stageperiode vervuld op de afdeling Taalstoornissen van revalidatiecentrum De Hoogstraat in Utrecht. De literatuurscriptie richtte zich op het effect van geïsoleerde- en multipele lacunaire infarcten op het cognitief functioneren. Het afstudeeronderzoek was gericht op de gevolgen van normale veroudering op de visuele organisatie en woordvinding, waarbij normering plaats vond voor de 'Hooper Visual Organisation Test' en de 'Boston Benoemingstaak'. Gedurende de studie is Mariska mede-oprichter geweest van studie-vereniging DISP (Doctoraal Studenten Interactie Programma), later herdoopt tot "Brainwave". Eind 1997 is zij afgestudeerd bij de vakgroep Psychonomie, met als hoofdrichting Cognitieve Functiestoornissen. Aansluitend voglde de aanstelling als Assistent In Opleiding bij Psychomedisch Streekcentrum Vijverdal en de vakgroep Psychiatrie en Neuropsychologie van de Universiteit Maastricht, waar het voorliggend onderzoek werd opgezet, uitgevoerd en opgeschreven. Vanaf juni 2002 is zij als neuropsycholoog ten behoeve van gezondheidszorg en wetenschappelijk onderzoek verbonden aan afdeling Vesalius van Altrecht, locatie Den Dolder, waar zij zich richt op volwassenen van jong- tot middelbare leeftijd die strijden met de gevolgen van niet-aangeboren hersenletsel.

Aantekeningen