

Chapter 1

General Introduction

Cognitive performance and cognitive decline

The human brain is the neural control centre of our bodies. It controls many functions and is responsible for our movements, behaviour, feelings and cognitive functioning. Cognitive functioning is a broad concept, referring to a variety of functional domains such as learning, memory, intelligence, attention, concentration, language, information-processing and executive functions. Contrary, for instance, to crystallized intelligence and vocabulary, our memory and speed of information-processing are sensitive to decline with ageing.

In our ageing society, many older persons suffer from cognitive decline (1-5). In some elderly people cognitive abilities decline to the level of serious impairment, and specifically dementia.

Alzheimer's disease (AD) is the most common cause of dementia, and is responsible for approximately 72% of all cases of dementia in the Netherlands (5;6). AD is a neuro-degenerative disease of the central nerve system, affecting several areas of the brain, such as the hippocampus. AD can cause a decline in short and long-term memory, disturbed abstract thinking, disturbed judgement, aphasia, or a change in personality. A slow onset and a progressive course of the disease are characteristic for AD (7). The prevalence of AD is high, and is estimated at 5% for people aged 65 years and older. With increasing age, however, the prevalence rises; in 90 year-old elderly people, the prevalence is estimated at 30% (8;9).

Cognitive decline, and possible accelerating or protecting variables, have been the subject of research over the past decades. There is some evidence that neuropsychiatric symptoms such as anxiety and depression may influence cognitive performance and cognitive decline, and might also accelerate the process of normal cognitive decline.

Previous studies on late life depression have shown that depression is associated with cognitive decline in the elderly, and that it can co-occur with mild dementia (10-15). However, research on the association between anxiety and comorbid anxiety and depression and cognitive decline is still scarce (15). It is still not known whether anxiety has an adverse effect on the brain in older persons. If so, mixed anxiety/depression might even have more consequences for cognitive functioning than pure anxiety or pure depression.

Moreover, if these symptoms influence cognitive decline, could symptoms of anxiety and depression be predictive of future cognitive decline and dementia?

Anxiety

Anxiety is a basic human emotion. It is a reaction that is intended to warn us in a threatening situation, preparing us for fight or flight. Clinical anxiety is indicated when anxiety occurs in situations in which there is no real danger, or when the intensity of the emotional response is disproportionate to the actual danger (16). This occurs in 10% to 30% of the general population (17). In elderly people with AD the prevalence of anxiety symptoms is reported to be between 50% and 70% (18;19), whereas clinically relevant levels of anxiety symptoms are reported in 20 to 38% (18-22).

A distinction is made between anxiety symptoms and anxiety disorders. Anxiety symptoms are phenomena that are characteristic of anxiety, such as feeling tense, anticipatory fear, worrying, inability to relax, physical tension, restlessness, and panic. An anxiety disorder is a syndromal classification of various anxiety symptoms, and its prevalence in the people aged 65 or over lies between 0.7% and 12% over a 1-6 month period (23;24). The most important anxiety disorders in older persons are specific phobia, social phobia, agoraphobia without panic, panic disorder without agoraphobia, panic disorder with agoraphobia, and generalised anxiety disorder (GAD).

There are several reasons to assume an association between anxiety and cognitive performance. Anxiety might be a psychological reaction to decreasing cognitive abilities (25) or a precursor to dementia (26). In the previous decades, several theories have been developed that assume an association between anxiety and cognitive performance. Firstly, Sapolsky provides an explanatory theoretical model for a possible association between anxiety symptoms and cognitive performance. Sapolsky's glucocorticoid cascade hypothesis assumes that prolonged high levels of glucocorticoids, which are the adrenal steroids that are secreted during stress, can lead to neurotoxicity in the brain and, in particular, in the hippocampus (27;28), which has a large number of glucocorticoid receptors and plays a critical role in memory function. People with anxiety suffer from long-term stress, and are suspected of having prolonged elevated levels of stress hormones in the brain (29). According to Sapolsky's theory, this can lead to poorer memory performance.

Yerks and Dodson (30) provide a second possible explanatory model for the association between anxiety and cognitive functioning. The Yerkes-Dodson law states that there is an inverted U-shaped relationship between arousal and cognitive performance.

Cognitive performance is best when an individual is under some optimal stress or in a state of arousal, above or below which performance levels drop. A certain amount of arousal helps us to perform cognitive tasks optimally. However, severe arousal can narrow our attention and cause a decline in cognitive performance.

Eysenck's processing efficiency theory (31) is a third explanatory model. This model assumes that anxiety interferes with cognitive performance by pre-empting some of the processing and storage resources of the working memory system. It states that anxiety produces worry and other intrusive thoughts, which are verbal and therefore intrude in the working memory.

Little research has focussed on the association between anxiety and cognitive functioning in older persons. Koenders et al. (32) found no association between anxiety and memory performance or the severity of dementia. However, Wetherell et al. (15) found that anxiety was associated with poorer performance in some cognitive domains, such as working memory and executive functioning of verbal information, providing some proof for Eysenck's processing efficiency theory.

Co-morbid anxiety and depression

Co-morbidity of anxiety and depression is quite highly prevalent, and probably even elevated in later life (33). Depressive symptoms include, for instance, depressed mood, worrying, loss of appetite, feelings of worthlessness, inappropriate guilt, diminished ability to concentrate, and fatigue. Beekman et al. (34) examined the co-morbidity of major depressive disorder and anxiety disorders in later life. Their results showed that co-morbidity was highly prevalent: 47.5% of people with a major depressive disorder also met the criteria for anxiety disorders, whereas 26.1% of those with anxiety disorders also met the criteria for a major depressive disorder.

Although previous research has investigated the influence of depression on cognitive functioning (35), the influence of comorbid anxiety and depression on cognitive performance has not yet been studied intensively, and needs to be paid more attention in future scientific research.

Benzodiazepines

In addition to the selective serotonin reuptake inhibitors (SSRI's), benzodiazepines are frequently prescribed in the treatment of anxiety and depression. However, benzodiazepines

have several adverse effects, such as tolerance, dependence, increased risk of falls and hip fractures, and risk of car accidents (29;36;37).

Further, despite the generally accepted advice to keep treatment short, benzodiazepines are often prescribed for long periods of time, particularly for the elderly (29). There have been many developments in the field of benzodiazepines over the past decades, and although it is common belief that benzodiazepines have an inhibiting effect on cognitive performance, the influence of long-term use on cognitive performance has not yet been established.

Aims of this thesis

Both anxiety and mixed anxiety/depression are common in later life, and may influence quality of life to a great extent. Their effect on cognitive functioning and cognitive decline is still unclear, and there is a need for further investigation. The outcome of the present study may elucidate this association and may provide valuable information that can help us to improve the well-being of older people.

Research questions:

- (1) Is there a cross-sectional relationship between anxiety and cognitive functioning?
- (2) Is there a prospective relationship between anxiety and cognitive functioning?
- (3) What is the influence of depression on the relationship between anxiety and cognitive functioning?
- (4) What trends exist in benzodiazepine use, and what is their effect on cognitive functioning?

The main objective of the present thesis was to investigate the relationship between anxiety and comorbid depressive symptoms, on the one hand, and cognitive performance and decline on the other hand. We investigated the relationship between anxiety/depression and cognitive domains that are sensitive to decline with aging, in older persons with normal cognitive functioning and in older persons suffering from early stage dementia. Furthermore, we focused on the use of benzodiazepines, and their influence on cognitive performance was also investigated.

Study populations

The objectives of this thesis were studied within the context of the Longitudinal Aging Study Amsterdam, and use was also made of collected data on older patients with AD.

The Longitudinal Aging Study Amsterdam

The Longitudinal Aging Study Amsterdam (LASA (38;39)) is an ongoing study of changes in autonomy and well-being in the aging population (> 55 years) in the Netherlands. In the prospective longitudinal design, from 1992 onwards, data on social, cognitive, emotional and physical functioning were collected every 3 years. To assess cognitive performance, LASA includes a variety of cognitive tests, measuring general cognitive functioning, fluid intelligence, information-processing speed, and memory. Because it also studies a large range of possible confounding variables, LASA provides a unique opportunity to investigate the effects of anxiety and comorbid anxiety and depression on cognitive functioning. LASA also provides extensive information on the use of prescribed drugs, by recording the medication directly from the drug containers in the home of the respondents. In this way, information on the duration, dose and frequency of benzodiazepine use has been recorded since 1992.

The study was initiated by the Dutch Ministry of Health, Welfare and Sports at the Vrije Universiteit in Amsterdam. The Vrije Universiteit supports the study by supplying research staff, accommodation and research facilities.

Population with Alzheimer's disease

Since LASA provides no data on older persons diagnosed with dementia, a specific sample of older persons in an early phase of AD was recruited. This specific group is important for our study because we are interested in the possible accelerating influence of anxiety and depression on cognitive decline. Patients who were diagnosed with AD were recruited in several general hospitals and mental health care institutes in the Netherlands: the Memory Clinic of the GGZ Buitenamstel in Amsterdam, the VU Medical Center in Amsterdam, meeting centers for older persons in Amsterdam and surrounding areas, the Tweesteden Hospital in Tilburg, the Medical Center in Alkmaar, the Slotervaart Hospital in Amsterdam, and the Sint Jacob nursing home in Amsterdam. Patients were included in the study if they met the following criteria: 1) diagnosis of AD, 2) a score on the Mini Mental State Examination ≥ 17 , 3) a score on the Clinical Dementia Rating of 1 (mild dementia), 4) age ≥ 65 , 5) adequate command of the Dutch language, 6) able to sign an informed consent form at

the start of the study, and 7) availability of a first-degree relative or a care giver in close contact with the patient.

The respondents were interviewed and scored for anxiety and depression, and their cognitive abilities were assessed at two measurement points with a follow-up period of one year.

Outline of the thesis

In Chapter 2 we investigated the cross-sectional relationship between anxiety and cognitive functioning in older persons, taking comorbid depression into account. Chapter 3 reports on the relationship between anxiety symptoms and cognitive decline in older persons over a nine-year period, and Chapter 4 describes the occurrence of anxiety and depression in different phases of cognitive decline. In Chapter 5 we investigated whether symptoms of anxiety and depression predict a decline in memory function in older persons in the early stage of AD.

In Chapter 6 we investigated trends in benzodiazepine use over a period of 10 years, and in Chapter 7 we investigated the effects of benzodiazepine use on cognitive performance in a longitudinal study. In Chapter 8 all the results are summarized and discussed.

Chapters 2 to 7 were written as separate articles, which have either been published or submitted for publication in scientific journals. Therefore, there is some overlap, especially in the description of the methods. However, all chapters can be read independently.

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