Summary and general discussion

In our aging society, cognitive decline and dementia will influence the lives of a rapidly growing number of older persons and their support system. Symptoms such as anxiety and depression, that might influence the rate of cognitive decline are being studied with much interest. In this thesis we present the results of our study on the influence of anxiety and comorbid anxiety and depression on cognitive performance and cognitive decline.

Furthermore, as benzodiazepines are widely used by older people (1-5) for the treatment of anxiety, nervousness and sleeping problems, their influence on cognitive performance is also under investigation. We have studied the trends in benzodiazepine use and the effect of long-term benzodiazepine use on cognitive performance. The results of these studies are also presented in this thesis.

The main findings of our studies are summarized below, after which the study methodology is discussed. Subsequently, the implications of the study for public healthcare and clinical practice are discussed, followed by recommendations for further research and an overall conclusion.

Main findings

In Chapters 2 and 3 we investigated the relationship between anxiety and depression on the one hand, and cognition in cognitively healthy older people on the other hand. Taking confounding variables into account, we found a cross-sectional curvilinear relationship between anxiety symptoms and cognitive performance. We found that mild anxiety symptoms seem to be beneficial for cognitive performance up to the generally accepted cut-off score on the anxiety symptoms scale (6), whereas severe anxiety negatively influences cognitive performance. However, in a longitudinal design anxiety symptoms were not predictive of cognitive decline 3 years later, and thus we found no evidence that anxiety has lasting effects on cognitive functioning.

These findings support Eysenck's processing efficiency theory, in which he states that anxiety interferes with cognitive performance by pre-empting some of the processing and storage resources of the working memory system. Moderate levels of anxiety can have an arousing function that services performance, but when the anxiety symptoms become severe they will overwhelm information processing resources. The results presented in this thesis also support the Yerkes-Dodson law, which states that there is an inverted U-shaped relationship between arousal and cognitive performance (7;8). A certain amount of arousal

helps us to perform optimally on cognitive tasks, whereas severe arousal can narrow our attention, and can worsen cognitive performance.

However, this finding indicates that the effect of anxiety on cognitive decline is a state effect, which does not support Sapolsky's hypothesis, in which he postulates that prolonged levels of stress and therefore chronic high levels of stress-hormones irreversibly impair cognitive performance (9). It may well be that in our study the self-reports of anxiety did not correlate with glucocorticoid release, and could therefore not have tapped the stress response.

Because symptoms of depression negatively influence cognitive functioning, we found that the relationship between anxiety symptoms and cognitive performance was strongly influenced by the presence of depressive symptoms. Adjusting for depressive symptoms in the statistical models changed the effect of anxiety symptoms on cognitive performance from negative to positive in most cognitive performance tests, indicating that comorbid anxiety and depression negatively influence cognitive performance. Depressive symptoms might overshadow the effect that anxiety symptoms have on cognitive performance, but older patients suffering from comorbid anxiety and depressive symptoms could also suffer from more serious symptoms.

In Chapter 4 we investigated how often anxiety symptoms, depressive symptoms, and comorbid anxiety and depressive symptoms occur in different phases of cognitive decline. We studied this by comparing older persons in different phases of cognitive decline from a community-based sample (LASA) and older people with a diagnosis of Alzheimer's disease (AD). There seems to be an increase in anxiety and depressive symptoms as cognitive performance levels drop from average to moderate, and a decrease in symptoms as cognitive functioning declines to the level of poor cognitive functioning. Older people with AD reported less anxiety symptoms than older persons who did not have AD. It may well be that persons with AD have less anxiety symptoms in this phase of the disease, but this finding could also be due to information bias, as a consequence of a lack of insight and memory problems that are characteristic for AD. Furthermore, the presentation of anxiety may be different in AD patients than in older people who do not have dementia (10). Alzheimer patients can experience sudden feelings of panic and fear, but they do not seem to experience continuous feelings of anxiety, as experienced by older persons who do not have dementia.

In Chapter 5 we investigated whether anxiety and depressive symptoms would result in an accelerated decline in memory function in patients in the early stages of AD. Symptoms

of anxiety and depression were generally mild in these patients, and did not seem to effect the rate of decline in memory function. On the contrary, we found that anxiety symptoms were associated with less decline in memory function. The enhanced memory function resulting from mild anxiety symptoms is probably caused by an arousing function that services performance (11).

In Chapter 6 trends in benzodiazepine use were investigated. We found that benzodiazepine-use remained almost stable over ten years in the 55-65 year-old community sample, and also in people with physical and mental health problems. In benzodiazepine users with a low income and sleeping problems there was an increase in benzodiazepine-use in the previous ten years**.**

In Chapter 7 we investigated the influence of benzodiazepines on cognitive performance in cognitively healthy older persons. We found that benzodiazepine-use caused a decline in cognitive performance, although the effect sizes were very small. With regard to the effect of cumulative exposure to benzodiazepine on cognitive performance, we found a similar small negative effect, which was significant for most cognitive performance tests. Cumulative exposure to benzodiazepines seems to have more negative effects than that of equivalent dosage which might imply that the duration of benzodiazepine-use has a greater negative effect on cognitive performance than the dosage itself. However, all the effects were small and might not be clinically relevant.

Methodological comments

The findings reported on in this thesis have to be placed in the context of the strengths and limitations of the research. The strength of the present research is that information on anxiety and depression was obtained from both a community-based sample (LASA), and a clinical sample (the AD study) of older people, covering a large part of the spectrum of cognitive functioning and cognitive decline. LASA is a community-based prospective study, investigating large numbers of older persons, providing data on cognitive measures covering four cognitive domains, anxiety and depressive symptoms, and relevant confounders. The AD group was followed over a period of one year, providing data on decline in memory function, anxiety and depressive symptoms, and possible confounding variables.

However there are also limitations. Firstly, in a community-based study of older persons, such as LASA, selective non-response and loss to follow-up of the most frail is an

inevitable problem. This might have resulted in an under-representation of older people with cognitive problems, more severe anxiety and depressive symptoms, or high levels of benzodiazepine-use in our study, possibly causing an under-estimation of the effects of anxiety, depression and benzodiazepine-use on cognitive functioning. To reduce the bias caused by selective loss to follow-up, we used multilevel analysis in some studies, which implied that respondents were not excluded if they had missing values. Secondly, in the interpretation of the data it must be noted that in the LASA the respondents were measured over an interval period of 3 years, during which the level of the dependent variables might have fluctuated.

Collecting data from AD patients was difficult. We initially aimed to include 90 respondents with early-phase AD, and a follow-up period of 3 years. This 3-year follow-up was intended for comparison with the LASA data, which was collected in cycles of 3 years. However, due to our strict inclusion criteria, after 18 months of recruitment at many different institutes we were only able to include 66 patients with AD. Furthermore, despite frequent contact with the respondents and their family, the study suffered from a 32% drop-out of patients over a period of 1 year. This high drop-out which was due to mortality and extreme decline in cognitive abilities, caused a power problem, and we were therefore unable to continue the follow-up of the AD patients.

When interpreting the results of the analyses of data collected in the AD study, several methodological limitations must be taken into account. Firstly, impaired cognitive functioning might have influenced the assessment of anxiety and depressive symptoms, because respondents with memory complaints might not have been able to recall their mood during a previous period. To anticipate on this, a partner or a caregiver who was in close contact with the patient was present at the time of the data-collection, to provide information about the patients anxiety, depression and benzodiazepine-use. Secondly, in the AD study cognitive performance measurements suffered from a floor effect and for that reason we could not include the data collected by the Visual Association Test (12) in the analyses.

We tried to include cognitive domains that are sensitive to decline over time in the present research. However, not all cognitive domains could be included. Including, for instance, executive functioning might have provided a more complete picture of the influence of anxiety and depression on cognitive functioning.

Relevance for public health care and clinical practice

Although the influence of depression surpasses the influence of anxiety on cognitive performance, we found that severe anxiety symptoms had a negative effect on cognitive functioning. Apart from lessening the burden of the symptoms, treating these symptoms is also beneficial for the cognitive abilities of the patient.

In the past 10 years we found an increase in benzodiazepine-use in persons with a low income and sleeping problems. In clinical practice it is therefore necessary to pay special attention to benzodiazepine-users with these characteristics and problems. Although we did not find a major influence of benzodiazepine-use on cognitive functioning, treatment with benzodiazepines should be limited, because long-term use increases the risk of other negative side-effects such as addiction, falls and (car) accidents.

Recommendations for further research

Both LASA and the AD study included mainly respondents with no anxiety or depression, and older people with moderate symptoms, and less older people suffering from severe anxiety symptoms. Therefore, the influence of severe anxiety symptoms could not be studied extensively. The results of our study indicated that severe symptoms have a negative effect on cognitive functioning, so therefore we expect to find greater influence of severe symptoms on cognitive functioning in a clinical sample. Further research should therefore study the influence of severe anxiety symptoms in a clinical sample of patients with anxiety and depression. This also implies to benzodiazepine-use. The influence of high doses of benzodiazepines on cognitive performance are expected to be clinically relevant, and this should receive more attention in further research with a clinical sample.

Due to the large drop-out of respondents in the AD study we were not able to continue the follow-up of the AD patients. Collecting data on patients with AD over a period of 3 years or more might have provided more information about the influence of anxiety and depression on long-term cognitive performance and decline, and would also have provided a good opportunity to compare this influence on cognitively healthy older persons in the LASA and older people with a diagnosis of AD. Future research on the development of anxiety and depression in people with AD and the influence of anxiety and depression on cognitive functioning must therefore focus on a larger number of older persons with AD.

The large drop-out also limited us in studying the agreement between anxiety and depressive symptoms reported by the patient and their proxy. Studying the agreement and changes in agreement during the process of cognitive decline could help to determine when

the information provided by a proxy should be used in the assessment of the patient's anxiety an depression.

The cognitive performance measurements included in the AD study were chosen to enable comparison between the AD study and the LASA. However, all measurements suffered from a floor effect, with patients scoring extremely low. In some cognitive performance tests it was therefore not possible to established any clinically relevant decline in functioning. Further research on cognitive decline must therefore include cognitive performance measurements with a greater range of performance levels.

The suggestion that depression and anxiety may have a different role in adapting to stress is potentially very important, and should be investigated in future research.

Conclusion

The main objective of this 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. Research questions addressed in the thesis were: 1) Is there a cross-sectional relationship between anxiety and cognition? We found that severe anxiety negatively influenced cognitive performance, whereas mild anxiety symptoms seemed to be beneficial for cognitive performance. 2) Is there is a prospective relationship between anxiety and cognitive decline? We found no such relationship. 3) What is the influence of depression on the relationship between anxiety and cognition? We found that the negative effect of depressive symptoms on cognitive performance overshadows the positive effect of mild anxiety symptoms on cognition resulting in a negative effect of comorbid anxiety/depression on cognitive performance. 4) Does benzodiazepine-use influence cognitive performance? We found that benzodiazepine-use in older persons remained almost stable over a period of ten years. However, even though benzodiazepines caused a decline in cognitive performance, their influence is small, and does not seem to be clinically relevant.

Although anxiety influences the quality of life of older persons in many ways, a negative effect on cognitive functioning seems to be limited to persons with severe anxiety problems and to persons with comorbid anxiety/depression. Elderly people will benefit from the treatment of their anxiety and depressive symptoms and the knowledge that has been gathered in scientific research.

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