



# Summary

## Summary

This thesis focuses on cognitive function in elderly patients with bipolar disorder. **Chapter 1** provides background information on the topic, first an introduction to the relevance of bipolar disorder in late life followed by a brief history on the field of bipolar disorder and cognition. Nowadays, a growing number of patients with a bipolar disorder reach an older age. This has important implications for the delivery of health service to this group. The last ten years many studies have demonstrated that patients with bipolar disorder have impaired functioning across a range of cognitive domains, even when they are stable. Imaging studies have shown that the anterior limbic network seems to be involved that may be responsible for the core mood symptoms but also for cognitive functioning in bipolar disorder. Still little information is available on bipolar disorder in later life. Many factors may contribute to cognitive impairment in elderly patients: illness characteristics such as age at onset and repeated mood episodes, medical comorbidity, substance use, or iatrogenic effects of medication. A neuropsychologist is confronted with a kind of jigsaw puzzle and it is often difficult to discriminate between the contribution of these different factors. In a short overview on measurement of cognitive function tests the cognitive domains are summarized that should be included in a research battery for bipolar patients; attention, verbal learning and memory and executive function, visuo-construction and verbal fluency. The research questions of this study are the following:

- Do older patients with an early onset Bipolar-I disorder in a euthymic state exhibit cognitive deficits compared with normal elderly people?
- Do older patients with bipolar disorder who are in a euthymic state exhibit cognitive deficits compared with normal elderly people?
- Do late-onset bipolar patients show more cognitive decline than early onset bipolar patients?
- How is cognitive functioning influenced by illness-related factors, medication and general health?
- Do subjective cognitive complaints predict lower scores for cognitive tests?
- Is cognitive impairment progressive among older patients?

To answer the above-mentioned questions a study was instigated in which 119 patients were recruited from outpatient clinics in four regions of the Netherlands and with help from the Dutch bipolar patients association (VMDB). Subjects were reported to be euthymic for at least three weeks by their psychiatrist, and none of the patients had a primary diagnosis of alcohol dependence or substance abuse or a clinical diagnosis of

dementia. A comparison group consisted of 78 healthy persons.

In **chapter 2** the results of our pilot study is presented. Fifteen older early onset bipolar-I patients had poorer cognitive functioning across a range of cognitive functions, including selective attention and verbal fluency (both aspects of executive functioning), verbal memory and mental effort compared to 15 matched comparison subjects without mood disorder or memory complaints. Patients were also slower than controls but although effect sizes were large, these measures did not reach level of significance. The differences between patients and controls were not attributable to symptoms of depression, severity of illness (as measured by the number of admissions in psychiatric hospitals), the occurrence of a psychotic episode in the past, or the current level of mania symptoms was not significantly correlated with cognitive performance. Although the sample size was modest, the differences between bipolar patients and comparison subjects were large enough to be statistically significant. This supports the notion that the differences between patients and comparison subjects are not only statistically significant, but also clinically relevant. A limitation of the study is that the effect of medication on test performance may have biased the interpretation of neuropsychological tests. Our findings are consistent with a growing body of evidence that bipolar patients experience cognitive deficits during mood stable episodes too and across a range of cognitive domains, including attention, executive functioning, verbal declarative memory and psychomotor speed. This may suggest a trait-related dysregulation, causing bipolar patients to have cognitive deficits, even when euthymic and regardless of their age.

In **Chapter 3** cognition and clinical characteristics of early and late onset bipolar patients were compared. We studied early (<40 years) onset bipolar patients (N=59) and late onset bipolar patients (N=60). Both bipolar groups demonstrated substantial poorer neuropsychological functioning when compared with the comparison group (N=78). Late onset bipolar patients showed poorer performances with regard to psychomotor performance, word fluency and mental flexibility. These poorer performances were not attributable to age, education or cerebrovascular risk factors. We found that early onset bipolar patients are more likely to have a family history of psychiatric illness and have more often been treated with ECT but they did not differ on other illness characteristics. The late onset bipolar patients performed less than the early onset bipolar patients of tests that suggest involvement of fronto-subcortical parts of the brain (speed and mental flexibility). This provides indirect evidence that late onset bipolar patients may have greater frontostriatal dysfunction than early onset patients, which could be due to a different neuropathology. A limitation in the study was the difficulty of ascertaining the exact age at onset and comparing our findings with those of studies with different

criteria for age of onset. Recent studies applied mostly the age at which the first mood episode that met full diagnostic criteria was reported, and this also applies to our study.

**Chapter 4** contains the study on risk factors on cognitive functioning in elderly patients with bipolar disorder. The main findings of this study show that more vascular risk factors and a greater number of hospital admissions are related to poorer outcome of cognitive functioning. Patients who are using lithium also have poorer cognitive functioning, but this can be explained by other risk factors and does not seem due to the exposure to lithium itself. Other illness factors and use of alcohol were not associated with cognitive functioning. We have used a cross-sectional design that required patients, some of whom had cognitive problems, to retrospectively recall a good deal of information. This may have biased our results. Nevertheless, the results have important implications for the treatment of elderly bipolar patients. Awareness and management of vascular risk factors and its complications are important to protect bipolar patients against cognitive dysfunction. Furthermore, relapse should be prevented by optimizing the pharmacological treatment and providing adequate psycho-education for patients and families

In **chapter 5** we examined whether subjective cognitive complaints were associated with objective neuropsychological performance and to consider the role of frontal lobe dysfunction in the awareness of cognitive impairment. Bipolar elderly patients (N=101) had the same number of cognitive complaints compared to comparison subjects (N=74), but they showed worse cognitive functioning in several domains. Nearly 60% of elderly bipolar patients who were euthymic had considerable subjective cognitive complaints. Bipolar elderly patients with less subjective cognitive complaints had worse cognitive functioning. Furthermore, a lesser awareness of cognitive deficits was associated with especially poorer performances on attention and executive tests. Impaired awareness of cognition might be a reflection of cognitive deterioration and could influence treatment. Age did not have influence on the subjective experience of cognitive dysfunction. The present study required individuals, some of which having memory problems, to retrospectively recall a good deal of information. Direct assessment of everyday functions and diary methods may be more powerful instruments to identify cognitive problems and how frequent they occur.

In the follow up part of the study (**Chapter 6**) older adults with bipolar disorder (N=65) exhibit worse cognitive dysfunction compared to healthy controls (N=42), but no greater decline in cognition over two years. Furthermore, no demographic or illness characteristics were associated with cognitive decline in attention, executive and language function.

Only manic symptoms predicted cognitive decline in memory. Unfortunately, we had not from all subjects follow up assessments. However, comparison of the baseline data of persons lost to follow up with the longitudinal sample showed only differences in the learning condition of the memory test and in one of the verbal fluency tests. This suggests that cognitive functioning in both groups were comparable. We concluded that although poorer cognitive functioning is a part of elderly bipolar disorder it seems to be rather consistent in time.

In **chapter 7** the general discussion and the principal findings of the study are summarized. Methodological issues and conceptual considerations are discussed and, finally, the clinical relevance of the findings is discussed and suggestions are made for further research. This study confirmed the importance of being aware of poor cognitive functioning in elderly bipolar patients and of the risk factors that seem to contribute to this poor functioning. Poor cognitive functioning may have a negative impact on social and occupational functioning and on the quality of life of patients. Compliance to treatment regimens could be severely compromised by poorer cognitive functioning. Because of the lack of associations between self-reported cognitive functioning and cognitive test performance it is recommended that all older bipolar patients irrespective of cognitive complaints should be objectively evaluated at least by a brief neuropsychological assessment. Future research should focus on problems that patients experience in everyday life and if neuropsychological and psychoeducational rehabilitation can help to improve functioning.