The neuropsychiatry of dementia: psychometrics, clinical implications and outcome
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Dementia is a neuropsychiatric syndrome in which impaired memory is considered to play a key role. Ever since the discovery of dementia little attention has been paid to psychiatric problems that often co-occur. These problems are referred to as neuropsychiatric symptoms (np-symptoms) in this thesis.

**Chapter 1** consists of a brief historical review of how dementia was conceptualized throughout the past 125 years. Secondly, the aims and outline of this thesis are given. Until 1880 the disorder was defined as a broad concept comprising both ‘organic’ as well as ‘functional’ psychiatric syndromes. In the second half of the 19th century, as the consequence of the rise of a biological, clinicopathological oriented psychiatry, dementia became an ‘organic’ disorder. Senile dementia was defined as a cognitive disorder and focus was on the irreversible nature and the association with age. As amnesia was thought to be the key symptom, dementia became primarily a memory disorder.

Neuropsychiatric symptoms were considered to be non-cognitive in nature, and secondary to or a result of cognitive symptoms and no longer included in the core criteria for dementia. Even Alois Alzheimer’s findings in his case study of Auguste D. (reported in 1907), a presenile form of dementia starting with neuropsychiatric symptoms besides memory and other intellectual problems, didn’t change the view on dementia in those days. On the contrary, Alzheimer’s disease became the prototype of the ‘organic’ dementias, either presenile or senile. Research during the period 1950-1980 lent further evidence supporting this hypothesis. The period after 1980 is the age of clinical epidemiological studies and psycho- and clinimetrics. This is the time when it gradually becomes clear that behavioural problems and psychiatric disorders are highly prevalent in dementia (up to 90%) and they should hold a prominent position in the diagnostic research and treatment. It is also established that these problems draw heavily upon the mental constitution of caregivers and cause early admissions to institutions. It is this awareness of neuropsychiatric symptoms of dementia and its consequences that triggered our interest and gave rise to the questions formulated in this thesis.

Chapters 2 and 3 deal with the first question to be answered: what is the most valid and reliable method that can measure np-symptoms of dementia? In **chapter 2** the research is described into psychometric aspects (interrater reliability, convergent validity and construct validity) of the Dutch version of the Neuropsychiatric Inventory (NPI). We started our research in 1997. No validated Dutch version was available then. We made and validated a new translation, including (independent) back translation into English.
Interrater agreement was very high for the separate as well as the sum scores (kappa > .90). The instrument proved construct-valid. Besides, correlations with cognitive tests and assessments of ‘cognitive’ decline were very modest, an argument in favour of the scales’ divergent validity. The NPI had the best universal (and value free) design: it allowed the most widely differentiated spectrum of neuropsychiatric symptoms to be registered, and it was designed for a broad inclusion of dementia syndromes. Most other behaviour scales were developed based on the ‘classic’ Alzheimer dementia concept. Moreover, per domain serious and systematic attention is paid to the emotional distress the phenomenon at hand causes for caregivers. The NPI therefore produces the most accurate caregiver distress picture, because, unlike the other scales, it has a ‘frequency x severity’-score per item. This renders the instrument a better predictor of distress relatedness.

The conclusion of this study is that the Dutch version of the NPI is a valid and reliable instrument to assess and evaluate neuropsychiatric symptoms of dementia. It is easily applicable in practice and has a wide range setup.

**Chapter 3** discusses validity aspects of the Dutch NPI-Q. This instrument is a short version of the NPI. It is a self rating questionnaire for caregivers, and no interview is required. Correlations found with other measures supported NPI-Q validity. Behavioural and psychiatric symptomatology showed relatively high correlations with equivalent (sub) scales of other instruments, while no correlation was found between neuropsychiatric symptoms, memory and other ‘cognitive’ domains. Caregiver distress was strongly associated with NPI-Q symptom assessment. The conclusion is that the Dutch version of the NPI-Q is valid, and supplementary to the Dutch NPI. It is particularly useful as a screening instrument for np-symptoms in dementia and associated caregiver distress. The NPI-Q is highly suitable for e.g. evaluating treatments in daily practice. Contrary to the NPI, the NPI-Q lacks a clinical interview which brings about a slight risk of under or over reporting neuropsychiatric symptoms.

Chapters 4 and 5 deal with the second research question of this thesis pertaining to the associations between neuropsychiatric symptoms of dementia and environment variables. **Chapter 4** reports on a study of neuropsychiatric symptoms in dementia outpatients and also included primary caregivers. Dementia outpatients often rely on spouses or other relatives for support. The patients are often in the mild to moderately severe stages of the disease. Potential associations were studied between the presence of np-symptoms and caregiver and environment factors. We were especially interested in the relation between np-symptoms and the emotional distress
experienced by caregivers and whether other factors influence emotional distress too. Our study showed that 52\% of the emotional impact variance could be explained by the neuropsychiatric symptoms as such. Other factors playing a role were sense of competence of the caregiver, care level required and its costs. It was concluded that emotional distress experienced by caregivers is, to a major extent, due to np-symptoms present in dementia. Depression and apathy had the highest prevalence rates. Together with agitation and irritability, caregivers experienced these symptoms as distressing the most, confirming what has been found in other (population based) studies. The study showed that caregiver distress is determined by patient, caregiver and environmental factors. The results of more recent research too show that several factors determine caregiver distress. Furthermore, if dementia comes with apathy, agitation and mood disturbances, they are important factors of caregiver distress. Also in our study it was possible to distinguish between apathy and depression and to evaluate different emotional reactions to those. The conclusion we draw in reference to this and other researched studies is that the validated Dutch NPI is an adequate instrument for detailed assessment of caregiver distress related to np-symptoms of dementia. Moreover, it appears that caregivers overall burden is only partly determined by this. Other factors too should be considered as well. As far as we know, our study is the first to examine caregiver burden by np-symptoms with the validated Dutch version of the NPI distress scale.

Chapter 5 describes the consultation study carried out among dementia patients admitted to a nursing home (n=325). The patients are in the moderate to severe stages of dementia and are cared for by professional caregivers. We were interested in the reasons why consultation was sought (at symptom level) and how this relates to prevalence data of np-symptoms in nursing home patients with dementia. As we suspected that dementia patients referred to mental health care specialists are very likely to have np-symptoms, we also wanted to know to what extent referral reasons could be adequately classified according to np-domains of the NPI. Prevalence data from another Dutch study were available. Using the NPI domains it was possible to classify more than 85\% of the reasons for consultation. So, the NPI subdomains encompassed all referrals for consultation in this dementia population. The remaining 10-15 \% mostly concerned (other) diagnostic questions or indication consultations. Large differences were found between referral reasons and normative data on symptom prevalence. Specialized mental health service was provided for agitated and disinhibited patients in particular. Chances are that this was at the expense of the apathetic, retarded and quietly ‘not causing any trouble’
patients. To our knowledge this is the first time reasons for psychiatric consultation were compared to independent prevalence estimates of np-symptoms in a large sample of nursing home patients with dementia. More research into the generalizability of our findings and the factors influencing the observed differences is needed. Especially the finding that ‘hypo-behaviours’ like apathy and retarded depressive behaviours seem a minor problem in nursing homes, while they can be experienced as a heavy burden in the outpatient population, needs to be analysed further.

Chapters 6 and 7 concern the last question of this thesis: the pathogenesis and outcome of np-symptomatology of dementia. Two prospective studies are presented. Cognitive function was monitored over a 2.5 years period in a cohort of delirious patients and matched control subjects (chapter 6). Secondly, the long term hazard risk associated with post-operative delirium was examined (chapter 7). Chapter 6 focuses on predictors for cognitive decline. A total of 71 postoperatively delirious patients was followed up, and 41 of them were matched with patients who did not develop delirium, but did have the same number of risk factors (preoperative at T=0). At follow-up 2.5 years later, patients were independently assessed using the same tests as on T=0. Dementia or Mild Cognitive Impairment (MCI) was diagnosed in 77.8% of the surviving patients with postoperative delirium and in 40.9% of the control patients (relative risk = 1.9, 95% CI = 1.1 - 3.3). In our study, care was taken that, prior to surgery, no major cognitive differences existed between patients with delirium and controls. Nevertheless, no match was found for 30/71 delirium patients because of differences in risk factor profiles at baseline (T=0). Unmatched delirium patients did worse on the MMSE than those matched, indicating more cognitive impairment. Moreover, a wide score range was observed for the MMSE (10-29). So, it is clear that some patients already had dementia or MCI before inclusion in the study. Although no conclusions on causality can be drawn from this study, it further reinforces the finding that underlying dementia may be a contributor to inpatient delirium. In conclusion, this study was carefully controlled in order to evaluate the relationship between the occurrence of postoperative delirium and long-term cognitive impairment. Dementia or MCI at follow-up is almost doubled in elderly hip surgery patients with postoperative delirium compared with at-risk patients without delirium. Delirium may indicate underlying neurodegenerative disease. Under certain circumstances, e.g. following surgery, the neuropsychiatric syndrome of delirium can be a marker of underlying cognitive decline. The relation between dementia and delirium can best be seen along a continuum of cognitive disorders, rather than two entirely separate conditions.
The aim of the second delirium follow-up study, described in chapter 7, was to examine delirium and delirium risk factors predicting mortality at two-years follow-up in elderly hip-surgery patients (n=603). Primary outcome was death during a 2 years follow-up period. Incidence of delirium was higher in patients who died (32.2%) compared with those who survived (8.8%). The effect of delirium on mortality was significant after adjusting for predefined delirium risk factors and other potential co-variables. First of all we concluded that delirium independently predicts long term mortality in elderly hip-surgery patients. Outcome for delirium is particularly poor when other risk factors are present. Risk factor stratification showed that 10% of patients with delirium and 0-1 risk factors had died, 40.7% of those with 2-3 risk factors and 59.3% with 4-5 risk factors compared to 6.1%, 13.5% and 43.1% of patients without delirium at low, intermediate and high risk of poor outcome. Prognosis of post hip-surgery delirium is reasonably good when you are relatively young and healthy. It is worse for cognitively impaired older men, who are acutely admitted to hospital and who have poor vision. The second conclusion is that vulnerability in delirium patients as expressed by presence of predisposing and precipitating factors explains excess mortality, at least to some extent. Results from the risk factor stratification analysis seem to support this hypothesis.

Developing postoperative delirium and premature death seem to share the same basis. In chapter 7, one of the conclusions was that the prognosis of post hip-surgery delirium is worse if the patient is old and cognitively impaired. It is likely that in patients developing delirium already incipient neurodegenerative processes associated with dementia were present before admission. One explanation was found in analyzing the MMSE’s, which could be carried out in both follow-up studies (chapters 6 and 7). In chapter 6 it is determined that delirium occurs mainly with low premorbid MMSE’s. Chapter 7 shows that patients in the deceased group had significantly lower average baseline scores (pre-operatively) on the MMSE than the survivors (22.1 vs. 25.8). This group consisted for 32.2% in patients with postoperative delirium. In the survivors group, this was only 8.8%, approximately a 4:1 ratio. As far as cognitive functioning is concerned, it can be concluded from the results of the two follow-up studies that delirium, as an np-syndrome highly prevalent among the elderly, can under special circumstances be the clinical manifestation of a premorbid cognitive disorder already present. In other words, there seems to be a pathogenetic relation between delirium and the premorbid presence of a cognitive disorder.

Finally, chapter 8 summarizes the main findings of this thesis and contains a general discussion about the relevance of the results, some methodological considerations
and the implications for daily clinical practice and future research. This thesis calls for attention to a broader dementia concept, in which the psychiatric phenomenology too is fully recognized. Answers were given to the three questions concerning the measurements, implementation, outcome and possible pathogenesis of the np-symptoms in dementia.