The neuropsychiatry of dementia: psychometrics, clinical implications and outcome

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This chapter summarizes the main findings of this thesis and contains a general discussion on the relevance of the results, some methodological considerations and the implications for daily clinical practice and future research.

As discussed in the general introduction of this thesis, dementia is a clinical syndrome known for centuries. Whereas until 1900 approximately, many psychiatric disorders in the elderly were included under this heading, ‘dementia’ became a syndrome in which memory and intellectual impairment were key elements. This cognitive paradigm dominated scientific research until the ’80s of the last century. Since that time psychiatric phenomenology has returned in the dementia concept, and the role of the emotional stress caused to patients and their environment, became subject of attention.

Experiences in daily psychogeriatric practice inspired the present studies based on a high prevalence of neuropsychiatric (np-)symptoms, also in the very early stages of AD.

Questions concerning the aetiology arose. Can np-symptoms be explained as a psychological reaction to developing a brain disorder or as ‘cognitive’ decline? Or are they part of the entire coordinated symptomatology related to the disease? We have been especially occupied with the latter question. The time was ripe for a dementia model considering neuropsychiatric, cognitive and behavioural symptoms as equally relevant.

The objective of this thesis is to fully integrate neuropsychiatric disorders into the dementia concept. To this end, we asked ourselves the following questions:

a. What is the most valid and reliable method that can measure neuropsychiatric symptoms of dementia?

b. How do certain neuropsychiatric symptoms of dementia relate to environment variables?

c. What is the pathogenesis of the neuropsychiatric symptoms of dementia in reference to delirium as a highly prevalent neuropsychiatric disorder in the elderly?

The first question is answered in chapters 2 and 3.

First of all, to measure neuropsychiatric disorders in dementia, we needed a valid instrument. Moreover, we preferred using a Dutch scale. In our preliminary research we came across a number of recognized English scales, frequently used already. In Chapter 2 we describe our research into psychometric aspects (interrater reliability,
convergent validity and construct validity) of the Dutch version of the Neuropsychiatric Inventory (NPI). The NPI was published in 1994 by Cummings, then still comprising 10 items. The validated 12-item version appeared in 1997, including neurovegetative abnormalities affecting appetite and sleep. We started our research in 1997 with the 12 item version. 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 translated NPI was compared to the translated and validated versions of the RMBPC (subscales) and the MMSE. The RMBPC has a different setup. Besides (a limited number of) psychiatric symptoms, it also rates memory impairment. To be certain about a possible bias due to memory disorders we also checked with the Dutch, validated MMSE. The items showed fairly high correlations with the relevant subscales of the RMBPC. Correlation with the RMBPC's emotional stress scale also supported validity of the NPI's emotional stress scale for caregivers. The instrument was proven to have construct-validity. Moreover, correlations with cognitive tests and assessments of ‘cognitive’ decline were modest at best, an argument in favour of the scales’ divergent validity. The conclusion of this study is that the Dutch version of the NPI categorizes data objectively and that it is a valid instrument to survey a wide scale of neuropsychiatric symptoms of dementia.

Our study was carried out in a time when a number of measures had already been developed to systematically register a wide range of neuropsychiatric symptoms of dementia. We opted for the NPI because it 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 and therefore applicable with the elderly, without limitations. Most other behaviour scales of that time were developed based on the ‘classic’ Alzheimer dementia concept.

As an informant-based interview the NPI can be conducted relatively quickly and it is the only one with a process of main and in-depth questions. During the neuropsychiatric interview, the instrument follows the diagnostic process in a natural manner. Moreover, per domain serious, systematic attention is paid to the emotional distress the phenomenon at hand causes 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.

Before our research started, it was already known that the (American) NPI had been tested and proven valid with a number of other brain disorders like Progressive Supranuclear Palsy, Huntington’s disease and Frontotemporal dementia. Later
studies into Parkinson’s disease with dementia, Dementia with Lewy Bodies and Cortical Basal Degeneration were published. Now, the instrument is an international standard for medication trials, caregiver distress evaluation and epidemiological and factor analytical studies. The NPI has been widely used, with the advantage that now there is a considerable body of normative data for different dementia groups.

The conclusion of chapter 2: the Dutch version of the NPI is a valid and reliable instrument to register and evaluate neuropsychiatric symptoms of dementia. It is easily applicable in practice and has a wide range setup.

As a diagnostic interview, the NPI can take a long time, especially when problems are complex (up to 45 minutes). This is not always an advantage in daily practice. Therefore we looked for an instrument approaching the NPI’s psychometric qualities as closely as possible, but with a practical setup. Our needs were met by the American NPI-Q. This scale is directly derived from the NPI that we had used already in studies. Chapter 3 discusses the findings on a few validity aspects of the Dutch NPI-Q. This variant of the NPI comprises the same 12 domains. We used the psychometric results found with the NPI version (chapter 2). The NPI-Q is a shortened version of the NPI; it is a self-rating scale for caregivers, instead of an interview with them. The scale is meant to be more like a screening instrument, with abridged main questions and no in-depth questions to objectify item presence. Furthermore, it lacks a frequency measure. This renders the NPI-Q more vulnerable, with an elevated risk on unreliable answers, since symptoms are present: yes or no. In case of doubt, therefore, it is wise to ask caregivers extra questions and give further explanation, if necessary. Rating the emotional distress of caregivers is possible.

Our research focused on several validity aspects of the Dutch version of the NPI-Q. The study was done among outpatients with dementia, almost all showing np-symptoms. Correlations found with other measures supported NPI-Q validity. Behavioural and psychiatric symptoms showed relatively high correlations with equivalent (sub)scales of other instruments, while there turned out to be no correlation between memory and other ‘cognitive’ domains. Caregiver distress was strongly associated with NPI-Q symptom assessment.

In conclusion: our preliminary results support validity of the NPI-Q Dutch form. It is a practical rating scale for assessing neuropsychiatric symptoms in dementia and associated caregiver distress. The instrument does not take much time to administer.

To our knowledge, no shortened screening versions of other broadly designed measures known at that time, like BEHAVE-AD, PBE, BRSD, MOUSEPAD, were circulating when Kaufer introduced the NPI-Q in 2000. In this sense the NPI-Q was
the obvious option. Studies on more recent measures provided no new points of view. Besides, here too it holds that the universal character of the NPI strongly favoured opting for its shortened version. As a result, the NPI-Q too could be used with many dementia types, to the (economic?) benefit of elderly psychiatry and behavioural neurology practice. The argument of better predicted stress relatedness does not hold for the NPI-Q. Unlike with the original NPI, there is no frequency measure either. The NPI-Q too is an internationally, frequently used scale by now, making study comparisons easier. Moreover, a large quantity of normative data is available as a result.

The conclusion drawn from the findings described in chapter 3 is that the Dutch version of the NPI-Q is sufficiently valid, well supplementary to the Dutch NPI. It is particularly intended as a screening instrument, highly suitable for e.g. evaluating treatments in daily practice. The assessment takes a relatively short time. There is a slightly higher risk on false answers than with the NPI, which should be taken into account.

Chapters 4 and 5 answer the second question concerning the correlation between neuropsychiatric symptoms of dementia and environment variables. We used the NPI to this purpose. Chapter 4 reports on the study among a group of dementia outpatients and their caregivers. Chapter 5 describes the study we carried out among dementia patients admitted to a nursing home.

In a study among a group of elderly with dementia living at home, we studied a possible correlation between the presence of np-symptoms and a number of caregiver- and environment factors (chapter 4). We were especially interested in the relation between np-symptoms and the emotional distress experienced by caregivers (primary outcome) and whether other factors influence this 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, 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, but that other factors too play a role.

This out-patient population consisted of patients with (very) mild to moderate stages of dementia. 83 of the 85 (98%) examined showed np-symptoms, measured/rated with the Dutch NPI version (interview). Depression and apathy had the highest prevalence rates, concurring with the findings of other studies. Together with agitation and irritability, caregivers experienced these symptoms as distressing the most, confirming what has been found in other (population) based studies. In a review Ballard et al. concluded that there was a pattern, despite the lack of a good comparison due
to the different designs that were used.\textsuperscript{40} Withdrawal, apathy,\textsuperscript{33,41} mood disturbance,\textsuperscript{42} aggression,\textsuperscript{43} and restlessness\textsuperscript{44} were the most important np-symptoms associated with caregiver burden.

Next to the NPI, we also used the Model of Determinants of Subjective Burden of Carers of Persons with Dementia by Dröes,\textsuperscript{45} which is based on the assumption that dementia patients as well as caregivers have to deal with general adaptive tasks as a consequence of the disease. A relatively great deal of attention is paid to the adaptive tasks of caregivers. Whether these tasks lead to (too much) distress or negative physical, psychological or social consequences depends mainly on the way individual caregivers cope with them,\textsuperscript{46-51} and the sense of competence they experience as a result of this.\textsuperscript{52} The latter is the perceived caregiver ability to cope with the task of caring for a dementia patient.

Using this model, our study showed that 48\% of the variance in experienced emotional distress was explained by other factors than np-symptoms as such. A low sense of competence was related to greater emotional impact on caregivers. Other studies too show that the individual experienced distress in the adaptation process is an important factor and call for this to be taken into account during treatment.\textsuperscript{53-59} A second factor was the degree of care needed by persons with dementia, which was inversely related to the emotional burden of np-symptoms, suggesting the emotional distress is largest in the early phases of the disease.\textsuperscript{60} An earlier study found the same association.\textsuperscript{61} Thirdly, we found additional financial expenditure due to care giving, such as travelling costs and costs for the use of community-based services by the person with dementia, proved to be related to a higher emotional impact on caregivers. High caregiver distress has been associated with more use of services in other studies as well.\textsuperscript{60-62}

The study discussed in this chapter showed that caregiver distress is determined by patient, caregiver and environmental factors. The results of more recent research too suggest a multifactorial influence.\textsuperscript{63-65} Furthermore, if dementia results in apathy, agitation and mood disturbances, these are important factors of caregiver burden. This finding too is supported by other research among dementia outpatients.

Measuring with the NPI gives the advantages of covering a wide range of np-symptoms and allowing caregiver distress to be rated per sub-item. Thus we could distinguish between apathy and depression and its specifically associated emotional reactions. A recent study shows that the distress associated with np-symptoms does not always depend on the frequency and severity of symptoms. Low frequencies and severity too can cause major distress.\textsuperscript{66} The NPI allows this differentiation.

Concluding from chapter 4: the validated Dutch NPI is an adequate instrument
for detailed registration of caregiver distress related to np-symptoms of dementia. Moreover, it appears that caregivers overall burden is only partly determined by np-symptoms. Other factors too should be taken into consideration. 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.

Demented outpatients often rely on support by partners or other relatives. These are generally patients with mildly to moderately severe stages of the disease. Patients with more severe stages of the disease live in nursing homes and get care from professional caregivers. Chapter 5 discusses the findings of a consultation study we did among dementia patients admitted to nursing homes (n=325). We were interested in the reasons why consultation was sought (at symptom level) and how nature and frequency of the symptoms in the referred group related to prevalence data of the np-symptoms of dementia in nursing homes. To answer the second question, we used prevalence data from another Dutch study.67 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.

Agitation, disinhibition and aberrant motor behaviour were frequent reasons for referrals (>25%). Apathy, psychotic symptoms and changed eating behaviour were infrequent reasons (<10%) for seeking consultation. Agitation and disinhibition were more often primary reasons for consultation than was expected based on normative prevalence estimates of these symptoms. In contrast, delusions, euphoria, apathy, irritability and changed eating behaviour were less often reasons for referral compared to prevalence estimates.

We concluded that there are large differences 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 quiet patients, ‘not causing any trouble’. 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.

To our knowledge this is the first time that reasons for psychiatric consultation were compared to independent prevalence estimates of np-symptoms in a large sample of nursing home patients with dementia. Therefore it is hard to comment on the generalizability of our results. However, our findings are consistent with observations
made in other countries focused on subtype and frequency of referrals, which were evaluated but lacked comparisons to prevalence estimates. The results of these studies are not entirely comparable due to differences in design, instruments used, populations selected, settings and countries where the studies were done. However, some trends concurring with our findings can be identified. The most frequently observed reasons for referral were behavioural problems (agitation/aggression, mostly followed by mood-related symptoms and psychotic features), whereas behaviours that may be considered non-disturbing, like apathy (if measured as a separate item) or retarded depressed behaviour, led to hardly any consultation request.

Nursing home staff often fail to recognize depression. Particularly quiet or retarded depressed residents may be overlooked. Also age and impairment of Activities of Daily Living predict not receiving treatment from a mental health professional. There may be other factors influencing referral patterns, like knowledge levels and availability of staff and other professionals, like psychologists, in these settings. Cohen-Mansfield et al. conclude that physicians are not always sufficiently informed about nonpharmacological interventions, leaving consultations undone and staff tempted quicker to prescribe medication themselves. Whether this also applies to Dutch nursing home physicians, who have had some specialist training in both geriatric medicine and psychiatry, is debatable.

Apart from the methodological limitations mentioned, our findings are consistent with those of others, which support the validity of our observations.

We conclude from chapter 5: This is the first study in which reasons for referral for Dutch nursing home patients with dementia were compared with normative data on prevalence of np-symptoms. Reasons for psychiatric referral and prevalence rates of np-symptoms differ. Symptom domains characterized as troublesome (‘hyper-behaviours’) were over reported, while symptoms like apathy and retarded depressive behaviour (‘hypo-behaviours’), were underrated. The NPI domains proved good tools to characterize problems requiring consultation in this patient population. More research into the generalizability of our findings and the factors influencing the discrepancies that we found is needed. Especially the finding that ‘hypo-behaviours’ seem a minor problem in nursing homes, while they can be experienced as a heavy burden in the outpatient population (see our findings in chapter 4), is worth to be analysed further.

Chapters 6 and 7 discuss the studies related to the last question of this thesis, the question of the pathogenesis and outcome of np-symptoms of dementia. A cohort of delirious patients was monitored prospectively and tested on a number of cognitive functions (chapter 6) and the pattern of mortality was described (chapter 7). Delirium
is a well defined np-syndrome, much studied over the last decade. There is growing evidence for the hypothesis that dementia and delirium represent a continuum of cognitive disorders, rather than as two entirely separate conditions.\textsuperscript{74,75} Prevalence of delirium among the elderly is high, especially among elderly patients admitted to general hospitals (up to 65\%). The cohort monitored by us was also a fairly homogenous research population with relatively little comorbidity. We studied elderly subjected to hip surgery, who developed delirium postoperatively. Patients were recruited from a patient population (n=603) of a delirium prevention study,\textsuperscript{76} a randomized placebo-controlled study for patients at risk for delirium. In this study, patients were tested on admission in the pre-delirium stage (T=0) on cognitive functioning, among other things. All patients with postoperative delirium (n=74) were eligible to participate in the follow-up studies.

Chapter 6 discusses the study on predictors for cognitive decline after 2.5 years on average. In the end, 71 postoperatively delirious patients could be included, 41 of which could be matched with patients who did not develop delirium, but having the same number of risk factors (preoperative at T=0). In the follow-up measurements after 2.5 years, patients were assessed for the same tests as on T=0, independently by a standard, neuropsychiatric, clinical interview with patients and knowledgeable informants. During the follow-up period, 54.9\% of the delirium patients had died compared to 34.1\% of the controls (relative risk = 1.6, 95\% CI = 1.0 - 2.6). Dementia or 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). Half the patients with delirium were institutionalized at follow-up, compared to 28.6\% of the controls (relative risk = 1.8, 95\% CI = 0.9 - 3.4). We concluded that the risk of dementia or MCI at follow-up for elderly hip surgery patients with postoperative delirium is almost doubled in comparison to patients with a similar risk profile but without delirium. Delirium may indicate underlying incipient dementia.

Our study shows that baseline differences between delirium patients and controls did not account for the effects found, implying that delirium independently predicts long-term adverse outcome. Six other studies also found an increased dementia risk associated with delirium at follow-up.\textsuperscript{77-82} The relative risk of cognitive disorders found in our sample is comparable to those found in the other studies. However, none of these studies, except two,\textsuperscript{81,82} examined the relative risk of dementia associated with delirium in a homogeneous, hip surgery, patient sample after checking for important, preoperatively assessed, delirium risk factors, or they did not include independent, clinical, follow-up assessments.

The strengths of our study are the primary outcome data set, inclusion of a homogeneous, hip surgery, patient sample, and use of standardized and validated
methods for diagnosing delirium, based on clinical patient interviews, pre-surgery and pre-delirium measures of predefined baseline risk factors, clinical, neuropsychiatric assessment at follow-up and subtyping of cognitive outcome.

In our study, care was taken that, prior to surgery, no major differences with respect to cognitive function existed between patients with delirium and controls. Nevertheless, we could not match 30/71 delirium patients to controls 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 processes associated with dementia may be a contributor to inpatient delirium, and that identification of underlying cognitive impairment may not be made until after an inciting event, such as major orthopaedic surgery.

Our findings are supported by others. Elie et al. conclude that dementia is the strongest risk factor for delirium among older patients. Bickel et al. found that long-term cognitive impairment was observed primarily in patients with delirium who were advanced in age and had pre-existing mild cognitive deficits. Cole et al. submit that one explanation for the poor prognosis of delirium among older hospital patients may be that many of these patients do not recover from delirium, also not after discharge from hospital. Our results do not support this hypothesis. For our study, we recruited patients from a relatively healthy population of elderly, participating in an RCT with haloperidol to prevent postoperative delirium. Delirium duration was carefully monitored in the trial and patients did not leave hospital until their delirium was over. In the fact the average stay of patients with delirium was longer than that of the patient group that did not develop delirium postoperatively. Moreover, the clinical neuropsychiatric examination at follow-up showed no delirium in any of the patients studied.

We conclude from chapter 6 that our 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 dementia. Under specific conditions, like undergoing surgical procedures, delirium, as a neuropsychiatric syndrome highly prevalent among the elderly, can be the manifestation of cognitive decline already present. 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 our second delirium follow-up study was to examine delirium and delirium risk factors predicting mortality at two-years follow-up in elderly hip-surgery patients (n=603) (chapter 7). Primary outcome was death during the 2 years follow-up period. Cox proportional hazards were estimated and compared between patients who had postoperative delirium during hospitalization and those who did not. A total of 90/603 patients (14.9%) died during the study period and 74/603 (12.3%) had postoperative delirium. 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-variates, including study intervention (adjusted Hazard risk = 1.98, 95% CI 1.24-3.17). 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. We conclude that delirium independently predicts mortality at two-year follow-up in elderly hip-surgery patients. Outcome for delirium is particularly poor when other risk factors are present.

One previous study found an increased mortality risk associated with delirium at 6 months follow-up and three studies found increased risk at 12 months follow-up or longer.81,85-87 In the Nightingale et al. study, hip-fracture patients were interviewed by a psychiatrist or psychiatric nurse between 2 and 5 days after surgery and an adjusted 2 year hazard ratio of 2.4 was found associated with delirium (CI 1.7-3.5).86 In the Edelstein et al. study 47/921 (5.1%), hip fracture patients had postoperative delirium and were more likely to have died at 1 year follow-up (unadjusted odds ratio 2.4, CI 1.1-4.9).87 Lundström et al. found that 21/29 femoral neck fracture patients with postoperative delirium died within 5 years, compared to 17/49 of those who did not have delirium (P=.001).81 The hazard ratio found in our sample is comparable to those found in the earlier studies. However, we clinically assessed patients on admission, prior to surgery, and included large numbers of patients, many of whom were not at risk for delirium. In doing so, we were able to examine the effects of delirium as well as baseline risk factors on mortality. Thus, our method represents a rigorous approach to studying the important problem of adverse, long term outcomes associated with delirium.

Advanced age and pre-existing cognitive impairment, two of the risk factors for mortality found in this study, have been identified as 2 major risk factors for prolonged delirium.88 Although some patients may have had (mild) delirium symptoms at discharge, we believe persistent delirium symptoms per se, as Cole concludes,84 are not a likely
explanation for excess mortality at follow-up. Risk factor stratification for poor outcome was examined, based on presence of delirium and other risk factors. Base rate mortality in the reference group at low risk was 6.1%. Prognosis of incident delirium was not significantly different when only few risk factors were present; all but two of the delirium patients with few risk factors survived. However, 40.7% of the delirium patients with two or three risk factors died; 59.3% died in case of four or five risk factors. So, 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.

We conclude from chapter 7 that vulnerability in delirium patients as expressed by presence of predisposing and precipitating factors explains excess mortality, at least to some extend. Results from the risk factor stratification analysis seem to support this hypothesis.

Developing postoperative delirium and earlier mortalities seem to share the same basis. In chapter 7, one of the conclusions was that the 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. This shows that there is a connection between suffering delirium and the presence of cognitive impairment with poor prognosis. 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 (chapter 6 and 7). In chapter 6 it is determined that delirium occurs mainly with low premorbid MMSE scores. Chapter 7 shows that patients in the deceased group had significantly lower average baseline values (preoperatively) 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 found in the chapters 6 and 7 that delirium (as a neuropsychiatric syndrome) is highly prevalent among elderly and that it may be a 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.
Box 1. MMSE and Cognitive outcome

In chapter 6 we conclude that dementia or MCI at follow-up is almost doubled in elderly hip surgery patients with postoperative delirium compared with at-risk patients without delirium and that delirium may indicate underlying dementia. The study shows that delirium occurs more frequently in patients with a low, pre-operative baseline value on the MMSE (<21) and that this value is also an important predictor of cognitive decline after 2.5 years. Further analysis of individual MMSE patterns between the moments t0 (on admission, pre-operatively) and t1 (2.5 yrs later) in both groups (delirium vs. no delirium), yielded the following findings (figure).

In both groups, therefore irrespective of the occurrence of delirium, at t0 MMSE values tended to be similar to or even somewhat lower than MMSE scores at t1 in most cases. Apparently, high baseline values were associated with similar scores on follow up, whereas patients showing deterioration also had relatively low scores at baseline.

One remarkable additional finding is that MMSE scores tend to increase on follow up. This raises critical questions on the use of this internationally recognized ‘golden standard’ with this type of research. Scores do not always appear to be consistent: they can improve even and sensitivity to stress seems to be of influence (see chapter 6). We have found no earlier comments on this matter in other follow up studies.
CHAPTER 8

Future research

This thesis calls for attention to a broader dementia concept, in which the psychiatric phenomenology too is fully recognized. Based on several studies on neuropsychiatric aspects of dementia we come to the following recommendations.

First of all, it is important that the neuropsychiatric syndromes found are considered as an integral part of clinical symptoms of dementia. The question whether these are merely independent psychiatric syndromes or parts of the body of symptoms of dementia disorder remains relevant. Further research into this is required. Clinical pictures with cognitive decline and associated neuropsychiatric symptoms (e.g. the psychotic symptom described with DLB) might lead to different treatment than the one needed for a psychotic disorder resembling schizophrenia, not likely to be expected during the course of dementia. This avenue has also been recommended internationally.89,90

Another, important research field for the future relates to the question whether there are specific neuropsychiatric problems in the early stages of dementia or during the Mild Cognitive Impairment (MCI) phase.30,32 As outlined in the introduction of this thesis it is not appropriate to reserve the notion of cognition exclusively to intellectual functions and to ‘ban’ perception and thinking. This also applies to the motivational aspects of dementia, like apathy. Next to attention paid to mild ‘cognitive’ symptoms, there should also be further research into profiles of early dementia, in which np-symptoms play a full, integrated role. Quoting Lishman:91 ‘Many disease processes affecting the brain will come to attention with psychological symptoms alone and well before the appearance of definite neurological signs, and it is often by the correct appreciation of these common forms of reaction that a mistaken diagnosis of non-organic (or so-called ‘functional’) psychiatric disorder will be avoided’. Analogous to the MCI concept, one could speak of Mild Affective Impairment (MAI), Mild Psychotic Impairment (MPI) and Mild Motivational Impairment (MMI).

For such a model to be applied consequentely, matching neuropsychological test examinations are indispensable. ‘Classic’ routine neuropsychological examinations were developed based on the assumption that dementia is primarily a ‘cognitive’ disorder, highly focused on testing memory and (other) intellectual functions (derived from the traditional Alzheimer concept). Full research into neuropsychiatric symptoms of dementia calls for a new sort of neuropsychological examination that integrates these problems into the whole of the findings. Currently, these phenomena are too often only discussed after extensive ‘cognitive’ profiles have been made. As a result, this inventory made might be qualified as an appendix (read by-product) with the neuropsychiatric symptoms merely as the total score of a short screening instrument.
For further characterization and differential diagnostics of neuropsychiatric phenomenology of dementia, both neuropsychiatric and neuropsychological research need to systematically pay attention to:

1. The spectrum of *affective* derangement, with attention for slight differences in grief, depression, inhibition, apathy (like diminished emotional involvement), emotional instability, fear, anxiety, agitation;
2. The spectrum comprising phenomena that have *distorted reality testing* as a key issue. One should think of paranoia, misidentifications, delusional/false perceptions, illusionary falsifications, hallucinations, delusions;
3. The spectrum of np-symptoms with *motivational aspects* at the centre: active withdrawing, avoidance, apathy (as a disorder of drive and attention), impulsive and repetitive behaviour, disinhibition and aboulia;

The following recommendations concerning future research are directly derived from the studies included in this thesis.

The findings on the emotional stress with partners of patients with dementia gave us the idea to further examine their specific characteristics. Why does apathy bother one partner more than the other? Is there a relation with coping, personality characteristics or role patterns? Eventually, this could lead to more customized care. Such research could also be useful from a system theoretical point of view. Patient-caregiver interaction crises and psychological problems in caregivers might be prevented. A recent review of predictors of nursing home admission for persons with dementia found that caregiver indicating greater emotional stress, a desire to institutionalize the care recipient and feelings of being “trapped” in care responsibilities were more likely to result in admission of patients with dementia to nursing homes. This finding underlines the importance of further research into specific caregiver characteristics in the interaction between patients and their environment.

Especially for nursing homes, the NPI could be a particularly useful instrument to initiate research into the np-symptoms of dementia that occur very frequently in this setting. One should think of agitation, apathy and repetitive behaviour. Very little is known yet about repetitive behaviour in particular. What is the relation with apathy and the dementia severity stage? How specific is this syndrome for dementia or should we conclude that it is an a-specific phenomenon, occurring in many more psycho-organic diseases or is it a sign of a (hypoactive) delirium based on (other) somatic disorders? Which interventions could be most efficient? Are not antipsychotics actually counterproductive with repetitive behaviour? The question whether this behaviour
results from growing deprivation (under stimulation) or a clinical expression of progressive brain disease, in which contact with the environment is lost more and more (disinhibition, autism, loss of contact with reality?) is also relevant too treatment. Streim et al.\textsuperscript{93} submit that ‘of all long term care settings, the nursing home has served as the most productive laboratory for the study of mental health problems of late life. Lessons from geriatric psychiatry research and practice in the nursing home have relevance to general psychiatry and to other health care settings’.

The Dutch association of nursing home physicians (NVVA) published a Guideline for Problem Behaviour. Using these guidelines may increase awareness of behavioural problems in the nursing home setting. However, the NVVA guideline approach is based on symptoms, while thorough assessment of underlying neuropsychiatric disorders seems not to be a big issue. As a consequence there is a risk for misdiagnosis and wrong treatment decisions. Neuropsychiatric assessment can help making better diagnoses, also in the nursing home setting.

In the two delirium follow up studies described in this thesis, delirium as a neuropsychiatric syndrome served as a model for research into a possible correlation between neuropsychiatric symptoms and dementia. This model lends itself well for further research into this relation. However, delirium has several clinical presentations and one might ask oneself whether there is a difference in outcome between hyper- and hypokinetic delirium and how do they relate to cognitive (and which subtype?) decline at follow up? Unlike we did in the follow up studies, measuring the course at several moments deserves recommendation, certainly when subtle differences in np-syndromes are to be distinguished. In that case several measurements during admission are also indicated, for instance to gain a better view on the course of attention disorders with the neuropsychiatric phenomenology. Beforehand, patients need to be screened more carefully for dementia. The MMSE proved a stress sensitive instrument as a screening measure in our study. It would be interesting to see how other tests would perform in this respect.

\textbf{Concluding remarks}

The aim of this thesis was to study the neuropsychiatric symptoms of dementia more closely and to contribute to the integration of these phenomena into the diagnostics and treatment of dementia.

Neuropsychiatric disorders are highly prevalent, also in very early types of dementia. They constitute major burdens on patients and on informal and professional caregivers. Neuropsychiatric symptoms need to be a full part of a modern clinical assessment in dementia. Neuropsychiatry can help to refine differential diagnosis in dementia.
Implementation of exactly these innovations will allow for the definition of new (pre-senile) dementia syndromes, development of adequate pathogenic models and possibly for more specific symptomatic treatments. Neuropsychiatric insights, carrying the concept of dementia beyond the limited cognitive paradigm, can contribute to a change of our thinking on dementia, by broadening the scope of clinical research for the benefit of patients with dementia that suffer from more than memory problems alone.


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