‘La nature n’est pas en surface; elle est en profondeur. Les couleurs sont l’expression, à cette surface, de cette profondeur. Elles montent des racines du monde’ (‘De natuur is niet aan de oppervlakte maar in de diepte. De kleuren zijn een uiting van deze diepte aan de oppervlakte; zij rijzen op vanuit de wortels van de wereld’)

Paul Cézanne

‘Dementia may result from anoxia, from trauma or from primary degenerative disease. It is therefore possible to extract important symptoms and syndromes which indicate the possibility of cerebral disorder whatever the basic pathology and despite the colouring lent by pathoplastic features. Such symptoms form the cornerstone of diagnosis in organic psychiatry and it is essential to recognise their earliest and most minor manifestations’

William Alwyn Lishman
CHAPTER 1

Introduction
Dementia is a syndrome in which impaired memory plays a key role. As long as this syndrome has been recognized, relatively little attention has been paid to psychiatric problems that may occur in association. This thesis is an attempt to answer the following questions:

1. How can neuropsychiatric symptoms of dementia be assessed in a valid and reliable manner?

2. How do certain neuropsychiatric symptoms of dementia relate to environmental variables? Which instrument is most suitable for studying these associations?

3. Is there a relation between delirium as a neuropsychiatric syndrome and dementia?

This introduction will first outline the historical framework that has led to these questions posed.

**Dementia: historical aspects**

Partly due to the influence of positivism, the nineteenth century shows the rise of a trend towards applied scientific psychiatry. Mental disorders are regarded diseases of the brain. Researchers became increasingly interested into the relationship between clinical psychiatric disorders and the neuropathological substratum. This is also the age in which neurosurgery and neuropathology are introduced. Around 1850 microscopic techniques like specimen tissue staining are applied for the first time.

The view on dementia too changed in that period. Until 1880 approximately, dementia was a broad concept, still comprising many syndromes. Their denominator was manifested psychosocial incompetence as a result of a reduced capacity to judge adequately and reason logically. Defect conditions in psychosis and mood disorders too fell under this diagnostic category. Senile dementia e.g. was seen ‘as a final common pathway to a number of chronic psychoses and organic disorders’.

With the rise of organically oriented psychiatry, a division in the originally widely defined concept of dementia came about in the second half of the 19th century. ‘Functional’ psychiatric syndromes disappeared from this diagnostic ‘entity’. Senile dementia became an ‘organic’ dementia, more focused on the irreversible nature of the disorders underlying this syndrome and the relation to age. Thus, amnesia became a key symptom and the multidimensional dementia syndrome primarily became a memory dysfunction.

This is also the time when the German physician Alois Alzheimer publishes his
findings. He was very much interested in clinicopathological research. In 1907 he
describes the clinical picture and the neuropathological findings of his patient Auguste
D. and tries to classify his diagnosis according to the brain disorder classification system
current at that time. That did not quite work: ‘Mein Fall Auguste D. bot schon klinisch ein
so abweichendes Bild, dass er sich unter keine der bekannten Krankheiten einreihen
liess’.\(^3\) With this he implied to have discovered a new syndrome. In a number of aspects,
the disorder did not resemble the criteria applying to dementia senilis at that time: the
first symptoms arose at an early age already (50 years) and, in addition to the memory
problems, psychotic symptoms and behavioural disorders were already present early
onwards. Moreover, he detected temporal-parietal phenomena like aphasia, apraxia
and agnosia early on in the course of the disease. Furthermore, he emphasized that
Auguste ‘zeigte als erste Krankheitserscheinung Eifersuchtsideen gegen den Mann’.\(^4\)
Apparently, the psychotic symptoms manifested themselves at a very early stage, even
before memory dysfunctions were evident.

This patient, originally diagnosed by him with senile psychosis, later became known
as the first Alzheimer patient. Based on their clinicopathological findings, Alzheimer and
colleagues can not but conclude, from 1910 onwards, that the difference between pre-
senile and senile forms of dementia can not be maintained. In 1911 Alzheimer submits:
‘So scheint wirklich kein stichhaltiger Grund vorhanden diese Fälle als durch einen
besondern Krankheitsprozes verursacht zu betrachten. Es sind seniele Psychosen,
atypische Formen der senielen Demenz’.\(^5\)

This equalization cleared the path for an ‘organic’ dementia concept, with emphasis
on loss of memory and intellect, irreversible in course and apparently not exclusive
to old age. The pre-senile phenomena Alzheimer found, like aphasia, apraxia and
agnosia, were included in the process, but (remarkably so) psychiatric symptoms were
not. Apparently, the latter did not fit the concept of dementia as a primarily ‘organic’
disorder, thus excluding ‘functional’ psychiatric phenomena.

This partly allowed the foundation to be laid for a view on dementia which would
last until far into the 20th century and for many until today. Clinicopathological research
into the relation between memory and intellectual disorders and the neuropathological
substratum plays a key role in this.

From the Fifties until the Seventies, it is Roth and his co-workers\(^6\) who define the
psychiatric disorders in the (pre)senium more precisely, based on their clinical and
neuropathological research. Next to the ‘organic’ dementias, which they call senile and
arteriosclerotic psychoses, ‘functional’ psychiatric syndromes like affective psychosis
and (late) paraphrenia (1955) are defined.\(^7\) Blessed et al., linked dementia severity to
the extent of pathological changes in the brain.\(^8\) In a controlled study (non-demented
versus dementia patients) Tomlinson et al. showed that non-demented patients displayed no or hardly any Alzheimer pathology,\(^8\)\(^{-10}\) and it became clear that pre-senile and senile forms of dementia do not differ neuropathologically.

Like his British colleagues, it is dementia researcher Stam in the Netherlands at that time, who is making out a course for sharp boundaries between different psychiatric clinical pictures in the elderly. He too is working with a clearly clinicopathological perspective and he studies refined and sharpened definitions within the group of dementia disorders. Following Schneider, a renowned schizophrenia researcher at that time, Stam proposes to come to so-called 1\(^{st}\) and 2\(^{nd}\) order symptoms in clinical diagnostics.\(^11\) Specific 1\(^{st}\) order symptoms are memory disorders and/or loss of (other) acquired functions. Changes in personality, mood, reality testing and behaviour are considered to belong to the 2\(^{nd}\) order.

Scientific research results in the period 1950-1980 led to further support for the hypothesis that senile dementia and Alzheimer’s disease, based on clinical pictures and especially on the major neuropathological overlap, were actually synonyms for one dementia disorder, called Alzheimer’s disease. It is noteworthy that most studies at that time were conducted among relatively young patients (< 75 years) with well defined dementia disorders and therefore not among the group with the highest dementia prevalence (75+). The result was that senile dementia was considered to overlap completely with the Alzheimer dementia concept.

This process was completed around 1980. The operationalized dementia criteria, resulting from clinicopathological research are reflected in the then existing, internationally recognized classification systems DSM-III\(^12\) and NINCDS-ADRDA.\(^13\) Symptoms concerning memory and (other) acquired functions belong to the core criteria.

**The cognitive paradigm: the devaluation of neuropsychiatric symptoms**

The result of this historical development was that the name Alzheimer was connected more and more to a form of dementia in which the irreversibility of cognitive disorders and the relation to (advanced) age play an important role. The highly characteristic other clinical phenomena that Alzheimer described in his original pre-senile case, like psychiatric symptoms and behavioural problems - in this thesis from here on referred to as **neuropsychiatric symptoms (np-symptoms)** – gradually vanished from the dementia scenario. This conceptual switch later became known as the ‘cognitive paradigm’, a term introduced by Berrios,\(^14\) which he describes as follows:

‘The current concept of dementia was constructed during the nineteenth and early
twentieth centuries. This process can be described as one of pruning down the heterogeneous clinical content of dementia. The process started before 1800 and culminated in the early 1900s in what I have called the ‘cognitive paradigm’, i.e. the view that dementia just consisted of an irreversible disorder of intellectual functions. Historical analysis shows that this view resulted more from ideology than clinical observation. For decades, the cognitive paradigm has prevented the adequate mapping of non-cognitive symptoms of dementia and hindered research.’

Now np-symptoms were considered non-cognitive symptoms, turning them into a rest group of a-specific clinical phenomena, playing a secondary role within the diagnostic criteria for dementia. One of the consequences was that diagnostic and neuropsychological instruments were developed, based on this hierarchic ranking in cognitive non-cognitive, so that these instruments detected what they were designed for, viz. memory and other ‘cognitive’ disorders. The cognitive paradigm became the leading principle in dementia diagnostics.

The term ‘cognitive disorder’ constitutes another illustration of the cognitive paradigm. Perception and thinking have fallen under the cognitive functions of psychiatric research since way back. Hallucinations and delusions are their psychopathological phenomena. By designating abnormalities of perception and thinking to the non-cognitive disorders, they resolutely disappeared from the cognitive domain of dementia research.

Dementia research primarily turned into memory research, exemplified also by the fact that care for patients with dementia is organized in ‘Memory Clinics’ throughout the world. Dementia became closely linked with ‘cognitive’ decline, as described in dementia senilis and in this sense hard to define, other than a gradual difference with progressing, ‘regular’ ageing. Where senile dementia as an ‘organic’ dementia was initially incorporated into Alzheimer’s pre-senile dementia model, this changed later and AD was chiefly related to dementia syndromes occurring in the senium.

Neuropsychiatric assessment: scales and pathogenesis

The period after 1980 is the age of clinical epidemiological studies and psycho- and clinimetrics. It is the time when one starts to realize the scale of the disease and what consequences it has for patients, society, the economy and the health care system. There is also more awareness of how much impact dementia puts on the environment and that years of clinical neuropathological research have not yet produced an adequate solution to this problem. The focus in dementia research is on studying psychiatric and behavioural problems and the interventions necessary for these. In their book ‘Dementia, a Clinical Approach’ Cummings and Benson15 say about the preceding period: ‘The
results of this research have been valuable and exciting, but a considerable gap has opened between the new information and its application in the clinical management of demented patients. Similar opinions were voiced in the Netherlands also, e.g. by Van Crevel who underlined the importance of thorough anamnesis, adequate application of support examinations and the reliability of clinical diagnoses. He stressed the use of distinguishing between cortical and subcortical dementia syndromes.

This is also the time when it gradually becomes clear that behavioural problems and psychiatric disorders are highly prevalent in dementia (up to 90%) and should hold a prominent position in the diagnostic research and treatment. It is also established that these problems draw heavily on the mental constitution of caregivers and cause early admissions to institutions. New instruments were developed to chart the psychiatric phenomenology. Examples are the CAMDEX, BEHAVE-AD, CUSPAD, NPI, and the MOUSEPAD. Also in the Netherlands studies are published on the subject matter. At first, they were conducted at the level of validating scales or surveying at symptom level, like depression and apathy or studying the mental impact of these symptoms on caregivers. Along the way, studies of a factor analytic nature appear: among patients in different settings symptom clusters (syndromes) are distinguished within the spectrum of neuropsychiatric symptoms in dementia. In many instances three factors are found time and again: a psychosis-, a depression- and a behavioural factor (too much: hyper, maniform; too little: hypo, apathetic).

So, since the Eighties and Nineties of the past century serious attention has been paid to the neuropsychiatric disorders of dementia. Initially this occurs at the levels of symptom- and syndrome diagnostics, while the classical hierarchic dementia concept, with memory disorders as key symptoms, is maintained. The past ten years shows a trend of attempts to explain these np-symptoms pathogenetically and to integrate it with defects of the memory and other (higher) cortical functions. Traditional hierarchical thinking in primary and secondary (reactive?) or cause and consequence is abandoned. The influence of the General Systems Theory is noticeable here. Alexander is the first to describe a number of brain circuits that connect (fronto)cortical with subcortical structures. This allowed explaining, for instance, behaviour, motor- and cognitive aspects within one (functional) circuit. Neuropsychiatric, neurological and neurocognitive symptoms are now equally ranked pathological phenomena within one (or several) dysfunctional fronto-subcortical circuit(s). The path was cleared for a new view on the pathogenesis of dementia, challenging the validity of the classical and hierarchical disease model (primary cognitive and secondary non-cognitive symptoms) as a product of mainly clinical neuropathological research.

One fine example of this development is the concept of dementia with Lewy
bodies (DLB), described not so long ago. The clinical picture is characterized by impaired attention, memory, perception (hallucinations) and sleeping behaviour, next to possibly occurring motor symptoms (Parkinsonism) and behavioural disorders like agitation and apathy. This clinical unity of coordinated neuropsychiatric, neurocognitive and neurological symptoms was also pathogenetically related to deficiencies in the cholinergic system.

The clinical picture of DLB resembles that of another neuropsychiatric syndrome, viz. delirium. Here too attention deficits, hallucinations, agitation, apathy and night time behavioural disturbances are found as important symptoms. There is a strong resemblance at syndrome level, while there may be differences in aetiology and impact on the brain (acute, chronic). Both syndromes show practically the same neuropsychiatric symptoms. To get a clearer view on the pathogenesis of np-symptoms of dementia, it might be useful to take delirium as an example and to study the relation between delirium and dementia more closely.

Aims and outline of this thesis
The development outlined above was the reason to study the neuropsychiatric aspects of dementia more closely and to try to integrate seriously these phenomena in the clinical diagnosis and pathogenesis of dementia. The studies carried out follow the chronology of the developments described earlier, starting off with the implementation of an adequate measure for neuropsychiatric disorders, its application in studies into np-disorders in various settings and, finally, the study into its possible meaning for the pathogenesis of dementia.

Introducing two neuropsychiatric instruments, chapters 2 and 3 deal with the first question to be answered: how can neuropsychiatric symptoms of dementia be assessed in a valid and reliable manner? The instruments are the NeuroPsychiatric Inventory (NPI) and the NeuroPsychiatric Inventory Questionnaire (NPI-Q). Psychometric research into the validity and reliability of the Dutch versions are at the centre of the discussion.

Chapters 4 and 5 try to answer the second research question of this thesis: how do certain neuropsychiatric symptoms of dementia relate to environment variables? To this purpose, the neuropsychiatric symptomatology of an ambulatory and an institutionalized population of dementia patients are classified according to the NPI domains. Chapter 4 studies both the relation between np-disorders in dementia and emotional stress experienced by caregivers and the question whether caregiver factors are of influence too. Subsequently disease related and caregiver related factors are compared. Chapter 5 is a consultation study. The NPI was used as a tool to classify referral reasons in case of psychiatric consultation. It assesses whether this scale is suitable to adequately
classify consultation questions and how neuropsychiatric disorders within the referred group relate to the prevalence of these disorders in the nursing home.

Finally, Chapters 6 and 7 describe the studies particularly focused on the relation between dementia and delirium, the third research question of this thesis. The pathogenetic aspects of neuropsychiatric symptoms of dementia are also further discussed. Both studies were conducted with a neuropsychiatric syndrome highly prevalent among the elderly, delirium. The study setting was a general hospital, the location where many elderly with delirium are found (up to 65%). We had the opportunity to follow a relatively homogeneous group of elderly, vulnerable to developing delirium. They were senior citizens admitted for hip surgery. The purpose of this first study (chapter 6) was to document the long-term course of post-operative delirium, based on the hypothesis that delirious patients would develop cognitive decline sooner than the elderly free from postoperative delirium, correcting for risk factors.

Chapter 7 reports on a second study on the course of delirium in a prospective case-control study of mortality among elderly developing postoperative delirium and its associated risk factors.

Chapter 8 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.
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