A cognitive perspective on clinical manifestations of Alzheimer s disease

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Part 1

General Introduction

In 1901 Dr Aloïs Alzheimer examined a 51- year old woman, Auguste D., with a remarkable cluster of symptoms. She presented with prominent language disturbances and behavioural disturbances; agitation, auditory hallucinations and paranoid thinking. Within five years after first examination, in April 1906, she died. The rapid decline and her young age triggered dr. Alzheimer to investigate her brain. He found that about 30% of her brain had disappeared and in the remainder of her brain he observed intraneuronal neurofibrillary 'tangles' and extracelluar amyloid 'plaques'. Later, the disease was named after dr. Alzheimer [1].

To date, dementia is a major health care problem, with estimates of over 35 million people worldwide suffering from dementia [2]. In the Netherlands currently an estimated 250.000 persons have dementia [3]. In the coming years this number will increase, as age is a major risk to develop dementia and the average age of the Dutch population continues to rise. In turn, this will increase both pressure on caregivers and costs for health care. There are more than 50 causes of dementia, of which Alzheimer's disease (AD) is the most prevalent [4].

Neuropsychological assessment

Neuropsychology studies the structure and function of the brain in relation to cognitive functioning and behaviour. Cognition is a term that generally refers to higher intellectual processes such as thought, memory and attention. To study cognition, neuropsychologists use tests that address functioning in specific cognitive domains. Together, these tests form the neuropsychological test battery. The patients' performance on every neuropsychological test is compared to the performance of a large, general population sample with a correction for age, level of education and gender. A neuropsychological test battery is assembled with the aim to cover the main cognitive domains. Impairment in two or more cognitive domains is a key feature of the diagnosis of dementia.

The VUmc Alzheimer Center employs an extensive standardized neuropsychological test battery that assesses the most important cognitive domains [5]. This test battery is assessed at baseline, when patients first visit the Center for a diagnosis, and at follow-up, so that performance on the same tests over time can be examined. The studies in this thesis incorporated the following cognitive domains:

- Memory: short-term or working memory (storage for a period of seconds to a few minutes) and long-term-memory (lifelong retention of information). Storage of

- learned information can be subdivided into episodic memory (autobiographical memory), declarative memory (facts, knowledge) and procedural memory (skills; like driving).
- Language: production of language (speaking, writing) and understanding of language (listening, reading). These two modalities depend on the mental lexicon, the dictionary in our brain. This dictionary contains information about the meaning, grammatical rules and sounds of words.
- Attention: crucial in information processing, as it divides relevant information from non-relevant information. Attention can be divided into bottom-up (passive and automatic attraction) and top-down (active and selective, defined by a person).
- Executive functioning: planning, organizing, executing and monitoring of behaviour, problem solving, initiating and regulation of targeted behaviour in complex, unstructured situations. Demands planning, error detection, conflict solving and adaptation, therefore it can hardly be done on routine.
- Visuo-spatial functioning: processing and understanding of spatial relationships or spatial imagery in order to locate objects and persons in space and to orient.
- Apraxia: is the inability to carry out learned movements, not caused by motor or sensory impairments, comprehension or cooperation. Apraxia can be subdivided in ideomotor and ideational apraxia: a patient with ideomotor apraxia knows what to do but doesn't know *how*, while a patient with ideational apraxia doesn't know *what* to do with a tool.

To assess global cognition (short) screening tests such as the Mini-Mental State Examination (MMSE) are used. These tests give a first impression of cognitive decline. The studies described in this thesis use a combination of neuropsychological tests from the standardized neuropsychological test battery. Table 1 one shows the tests we used to assess the above-mentioned cognitive domains. An example of a simple neuropsychological test is the clock drawing task. This task assesses visuo-spatial functioning and visuo-constructive praxis (drawing and placing numbers), executive functioning (planning) and memory (remembering instructions and appearance of a clock). Figure 1 shows clocks drawn by three patients with AD.

Alzheimer's disease

Traditionally, AD is hallmarked by initial memory impairment, followed by decline in other cognitive domains such as: language and executive functioning [6]. The initially impaired domain and the order of declining domains may vary however, as in a minority of patients, AD starts with impairment in other cognitive functions. It may start for example, with language or visuo-spatial disturbances followed by executive dysfunctioning or memory impairment [7].

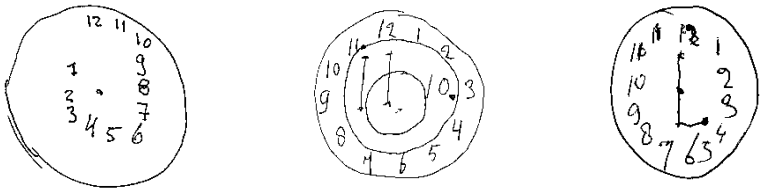

Figure 1. Clocks drawn by three patients with Alzheimer's disease. The instructions of the clock drawing test are: draw an interface of a clock, put in the numbers and place the arms on 11.10 o'clock. As shown, the same instructions lead to various results due to differences in cognitive impairment. Left clock: the numbers are written anti-clockwise and are not correctly placed in the interface. The patient also seems to have forgotten the remainder of the instructions. Middle clock: the first part of the instructions went well, however placing the arms gave some troubles. Two extra circles were drawn and the arms look like an extra '11'. Finally, the number '10' was written next to this extra '11' and two dots were drawn near 11 and 10 as some sort of last attempt to fulfil the task. Right clock: the numbers on the right side of the interface could be placed more to the flank. The patient repeated number '11' and the arms don't point at a time.

The recently revised clinical criteria for AD for the first time acknowledge these so-called non-memory presentations [8]. Three focal atypical AD variants have been described: (1) posterior cortical atrophy (PCA), (2) logopenic progressive aphasia caused by AD and (3) the frontal variant of AD [9,10]. Signs and symptoms of cortical visual dysfunction like simultanagnosia or visual disorientation characterize PCA [10]. Logopenic progressive aphasia caused by AD is characterized by word-find difficulties and impaired auditory verbal short-term memory. The frontal variant of AD is characterized by executive dysfunction or impairment of behaviour [9]. Apart from these extreme phenotypes, there is more variation in clinical presentation of AD. In a former study, we found that among young onset patients, apraxia/visuo-spatial presentation is the most common nonamnestic presentation AD [11]. Nonetheless, apraxia in AD has hardly been studied and the presence of apraxia is most often based on clinical judgment or simple bedside tests, since a validated test is lacking.

Table 1. Overview of used neuropsychological tests in this thesis.

Cognitive domain	Test
Global cognition	Mini-Mental State Examination [12]
	Cambridge Cognitive Examination [13]
Memory	Visual Association Test [14]
	Rey Auditory Verbal Learning Task (Dutch version), total immediate recall [15, 16]
	Rey Auditory Verbal Learning Task (Dutch version), delayed recall [15, 16]
Language	Visual Association Test, naming [14]
	Category fluency (animals) [17]
	Controlled Oral Word Association Test (Dutch version) letter fluency [18]
	Comparative questions
	Naming condition of the Arizona Battery for Communication Disorders [19]
Attention	Trail Making Test A [20]
	Forward condition of Digit Span (extended version) [21]
Executive functioning	Trail Making Test B [20]
	Backward condition of Digit Span (extended version) [21]
	Frontal Assessment Battery [22]
Visuo-spatial functioning	Incomplete Letters [23]
	Dot Counting [23]
	Number Location [23]
Praxis	Van Heugten test for Apraxia [24]

Factors that might influence clinical presentations in AD are: age at disease onset and the apolipoprotein (APOE) Ɛ4 allele. The APOE Ɛ4 allele is the major genetic risk factor for sporadic AD and it is known to decrease the age at onset of the disease [25]. When a diagnosis of dementia is made when a person is 65 years old or younger, it is often referred to as 'early-onset dementia'. Estimates are that 22-64% of early onset patients have an a-typical presentation of AD [7]. There are only few studies that focus on understanding heterogeneity in cognitive profile, according to neurobiological characteristics, with conflicting results. Limitations were small sample sizes and limited cognitive domains assessed as the focus was mainly on memory and executive functioning. Patients with an early onset are thought to decline faster than patients with a late onset. This effect might be accelerated by the absence of the APOE Ɛ4 allele [7,25,26]. However, the effect of age at onset of AD and

the APOE Ɛ4 allele on rate of cognitive decline on the main cognitive domains have not yet been studied.

Electroencephalogram and magnetic resonance imaging

Electroencephalogram (EEG) and magnetic resonance imaging (MRI) provide information on function and structure of the brain and can be used as ancillary investigation in the diagnostic work-up of AD. EEG and MRI are conducted as part of standard work-up at VUmc Alzheimer Center [5]. EEG is a method to measure electrical activity of cortical neurons and therefore provides a direct measure of brain function. In general, the EEG in patients with AD is characterized by diffuse slowing, but focal abnormalities are not uncommon in AD [27]. However, EEG can also be normal [28]. Some studies assessed the relationship between EEG abnormalities and cognitive impairment in AD, but most were limited to the MMSE. It is unclear if there are associations between EEG abnormalities and different cognitive profiles in AD.

With MRI, structural images of the brain can be investigated. In AD, atrophy of the medial temporal lobe (MTA), especially the hippocampus, is considered a diagnostic hallmark. MTA can be rated with a visual rating scale [29]. Relations between MTA and episodic memory impairment have frequently been shown [30]. However, not every patient with AD presents with MTA as imaging studies have revealed prominent (fronto-)parietal atrophy in AD, especially in patients with an earlier age of disease onset [31]. Earlier, a new visual rating scale for posterior atrophy (PA) has been developed by our group [32]. We hypothesized that the extent of PA is associated with impairment in non-memory domains, but this has not been studied yet.

Mild Cognitive Impairment and other types of dementia

Mild Cognitive Impairment (MCI) is considered a pre-stage of dementia. These patients have objective memory impairment, but do not fulfil the diagnostic criteria for dementia [33]. Within five years, about half of these patients progress to dementia, mostly AD [34].

In addition to AD, other common causes of dementia include: vascular dementia (VaD), dementia with Lewy bodies (DLB) and frontotemporal lobar degeneration (FTLD). These types of dementia are thought to have their own neuropsychological features [35-37]. In general, VaD is characterized by mental slowness and executive impairment. DLB is characterized by prominent attentional fluctuations, visuo-spatial disturbances and executive dysfunctioning. FTLD is a heterogeneous group of syndromes, consisting of 1) frontotemporal

dementia, that is characterized by behavioural changes and executive impairment, 2) progressive non-fluent aphasia, characterized by an effortful, non-fluent speech with grammar and phonological errors and 3) semantic dementia, characterized by a progressive loss of meanings of words.

Despite the theoretical differences in cognitive profiles, there are not many studies directly comparing different types of dementia in a large sample of patients. Moreover, trajectories of cognitive decline in various types of dementia have hardly been studied. The few available longitudinal studies mostly used global cognition as measured by MMSE as outcome measure, and are thus unable to provide information on decline in specific cognitive functions.

Aims and outline thesis

The general aim of this thesis is to investigate which neurobiological factors influence cognitive manifestations of AD. For this, we investigated:

- The associations between age at onset, abnormalities on EEG and brain atrophy as observed on MRI on the one hand and cognitive profiles on the other hand.
- The reliability and validity of a test for apraxia and risk factors for apraxia in AD.
- Patterns of cognitive decline on the main cognitive domains for several types of dementia. Besides that, we specifically investigated the influence of age at onset and APOE Ɛ4 on cognitive decline on the main cognitive domains in AD.

Chapters 2.1 till 2.4 have a cross-sectional set-up. In chapter **2.1** the difference in neuropsychological profiles between patients with early and late onset AD are studied cross-sectionally. We stratified the analyses according to dementia severity to examine differences within mild and moderately demented patients. In chapter **2.2** neuropsychological profiles in AD in relation to functional abnormalities on electroencephalogram (EEG) are investigated. In chapter **2.3** the relation between regional atrophy on magnetic resonance imaging (MRI) and cognition in AD is studied and we also took age at disease onset into account. In chapter **2.4** a new test for apraxia is introduced in our memory clinic and its reliability and validity is studied. Besides that, we investigated the risk factors for apraxia in AD.

Chapters 3.1 and 3.2 have a longitudinal set-up, in those studies we used the follow-up data of our neuropsychological assessments. In chapter **3.1** the trajectories of cognitive decline on the main cognitive domains in various types of dementia are studied. In chapter **3.2** we take a

closer look on AD and study how age at onset and APOE Ɛ4 influence cognitive decline in different cognitive domains in AD. Finally, in chapter **4** the main findings of this thesis are summarized and discussed, leading to suggestions for further research.

References

[1] Feldman HH. Atlas of Alzheimer's disease. Hampshire: Informa Healthcare; 2007.

[2] World Health Organization. Available from: http://www.who.int/mental_health/publications/dementia_report_2012/en/.

[3] Alzheimer Nederland. Available from: http://www.alzheimer-nederland.nl/informatie/wat-is-dementie.aspx.

[4] Kester MI, Scheltens P. Dementia: the bare essentials. Pract Neurol. 2009 Aug;9(4):241-51.

[5] van der Flier WM, Pijnenburg YA, Prins N, Lemstra AW, Bouwman FH, Teunissen CE, et al. Optimizing Patient Care and Research: The Amsterdam Dementia Cohort. J Alzheimers Dis. 2014 Mar 10.

[6] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939-44.

[7] Mendez MF. Early-onset Alzheimer's disease: nonamnestic subtypes and type 2 AD. Arch Med Res. 2012 Nov;43(8):677-85.

[8] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263-9.

[9] Warren JD, Fletcher PD, Golden HL. The paradox of syndromic diversity in Alzheimer disease. Nat Rev Neurol. 2012 Aug;8(8):451-64.

[10] Tang-Wai DF, Graff-Radford NR. Looking into posterior cortical atrophy: providing insight into Alzheimer disease. Neurology. 2011 May 24;76(21):1778-9.

[11] Koedam EL, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YA. Early-versus late-onset Alzheimer's disease: more than age alone. J Alzheimers Dis. 2010;19(4):1401-8.

[12] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98.

[13] Derix MM, Hofstede AB, Teunisse S, Hijdra A, Walstra GJ, Weinstein HC, et al. [CAMDEX-N: the Dutch version of the Cambridge Examination for Mental Disorders of the Elderly with automatic data processing]. Tijdschr Gerontol Geriatr. 1991 Aug;22(4):143-50.

[14] Lindeboom J, Schmand B, Tulner L, Walstra G, Jonker C. Visual association test to detect early dementia of the Alzheimer type. J Neurol Neurosurg Psychiatry. 2002 Aug;73(2):126-33.

[15] Rey A. L'examen clinique en psychologie. Paris: Presse de Universitaire de France; 1964.

[16] Saan RJ, Deelman BG. De 15-Woorden Test A en B. (Een voorlopige handleiding, in Dutch). 1986.

[17] Luteijn F, Ploeg FAEvd. GIT. Groninger Intelligentie Test (in Dutch). Lisse: Swets & Zeitlinger; 1982.

[18] Schmand B, Groenink SC, van den Dungen M. [Letter fluency: psychometric properties and Dutch normative data]. Tijdschr Gerontol Geriatr. 2008 Apr;39(2):64-76.

[19] Bayles CM, Tomoeda CK. Arizona Battery for Communication Disorders in dementia. Tucson, AZ: Canyonlands Publishing; 1993.

[20] Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills. 1958;8:271-6.

[21] Lindeboom J, Matto D. [Digit series and Knox cubes as concentration tests for elderly subjects]. Tijdschr Gerontol Geriatr. 1994 May;25(2):63-8.

[22] Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology. 2000 Dec 12;55(11):1621-6.

[23] Warrington EK, James M. The Visual Object and Space Perception Battery. Bury St. Edmunds UK: Thames Valley Test Company; 1991.

[24] van Heugten CM, Dekker J, Deelman BG, Stehmann-Saris FC, Kinebanian A. A diagnostic test for apraxia in stroke patients: internal consistency and diagnostic value. Clin Neuropsychol. 1999 May;13(2):182-92.

[25] van der Flier WM, Pijnenburg YA, Fox NC, Scheltens P. Early-onset versus late-onset Alzheimer's disease: the case of the missing APOE varepsilon4 allele. Lancet Neurol. 2011 Mar;10(3):280-8.

[26] van der Vlies AE, Koedam EL, Pijnenburg YA, Twisk JW, Scheltens P, van der Flier WM. Most rapid cognitive decline in APOE epsilon4 negative Alzheimer's disease with early onset. Psychol Med. 2009 Nov;39(11):1907-11.

[27] Jeong J. EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol. 2004 Jul;115(7):1490-505.

[28] Kowalski JW, Gawel M, Pfeffer A, Barcikowska M. The diagnostic value of EEG in Alzheimer disease: correlation with the severity of mental impairment. J Clin Neurophysiol. 2001 Nov;18(6):570-5.

[29] Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry. 1992 Oct;55(10):967-72.

[30] Rami L, Sole-Padulles C, Fortea J, Bosch B, Llado A, Antonell A, et al. Applying the new research diagnostic criteria: MRI findings and neuropsychological correlations of prodromal AD. Int J Geriatr Psychiatry. 2012 Feb;27(2):127-34.

[31] Frisoni GB, Pievani M, Testa C, Sabattoli F, Bresciani L, Bonetti M, et al. The topography of grey matter involvement in early and late onset Alzheimer's disease. Brain. 2007 Mar;130(Pt 3):720-30.

[32] Koedam EL, Lehmann M, van der Flier WM, Scheltens P, Pijnenburg YA, Fox N, et al. Visual assessment of posterior atrophy development of a MRI rating scale. Eur Radiol. 2011 Dec;21(12):2618-25.

[33] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999 Mar;56(3):303-8.

[34] Visser PJ, Kester A, Jolles J, Verhey F. Ten-year risk of dementia in subjects with mild cognitive impairment. Neurology. 2006 Oct 10;67(7):1201-7.

[35] Karantzoulis S, Galvin JE. Distinguishing Alzheimer's disease from other major forms of dementia. Expert Rev Neurother. 2011 Nov;11(11):1579-91.

[36] Reilly J, Rodriguez AD, Lamy M, Neils-Strunjas J. Cognition, language, and clinical pathological features of non-Alzheimer's dementias: an overview. J Commun Disord. 2010 Sep-Oct;43(5):438-52.

[37] Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol. 2003;54 Suppl 5:S15-9.