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Masterthesis

Memory profile in different subtypes of Alzheimer's disease based on patterns of regional brain atrophy

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Memory profile in different subtypes of Alzheimer's disease based on patterns of regional brain atrophy

ABSTRACT

Introduction: An explanation for the worldwide struggle to find a cure for Alzheimer's disease (AD) might be the underlying biological heterogeneity of the disease. In order to better understand differences in clinical manifestations that are seen in AD patients, this research focused on subtyping AD patients based on structural brain atrophy patterns and subsequently studying their corresponding memory profile. **Methods:** A population reference group (n = 27) was recruited and used for studying relationships between memory components in a population based group. A number of 229 healthy controls and 192 AD patients from ADNI were included to investigate relationships between memory, other cognitive functions and brain atrophy patterns in AD. **Results:** Three AD subtypes were identified based on atrophy in the medial temporal lobe alone (MTA), together with other brain regions (MTA+), or sparing of the medial temporal lobe (non-MTA). All memory components were impaired in the AD-subtypes compared to healthy controls. Learning and recognition was modulated by the AD subtype. The MTA+ subtype was the subtype showing worse memory profile. The non-MTA group benefited the most from external help in retrievement of learnt information. Influence of other cognitive function on memory was different in the AD subtypes as compared with the healthy controls, showing loss of specificity and disruption of normal cognitive support in AD. **Conclusions:** AD is heterogeneous and different forms of memory impairment are associated with different patterns of brain atrophy. Future research should focus on validating the categorized groups from this research by including more (biological) variables and clinical qualitative information, as well as investigating of longitudinal trajectories of the different AD subtypes.

Keywords: memory, Alzheimer's disease, regional brain atrophy, ADNI

Introduction

Alzheimer's disease (AD) is with an estimated prevalence of 44 million people worldwide the most common form of dementia and is therefore a major global healthcare challenge (Alzheimer's Disease International [ADI], 2014). Dementia has a huge impact on quality of life not only for the people who suffer from it, but also for their caregivers and families (George & Gwyther, 1986; Zarit, Reever, & Bach-Peterson, 1980). However, despite the fact that there has been a huge amount of research conducted about the clinical manifestations, there is much that still remains unclear and at the moment only 20-50% of the dementia cases are recognised and diagnosed and there is no cure found yet (ADI, 2014). An explanation for this might be that researchers have been mainly focussing on finding one pharmaceutical agent that will cover the total Alzheimer spectrum, however this might not be possible due to the underlying biological heterogeneity from the disease (Townsend, 2011).

The clarification of the biological basis of AD has made a huge progress since the first diagnostic criteria were published 30 years ago by the NINCDS-ADRDA Work Group (McKhann et al., 1984). There has been substantial improvement in identifying relevant structural and molecular biomarkers of pathology in the brain that might reflect the heterogeneity of the disease (Dubois et al., 2007). Biomarkers are physiological, biochemical or anatomic parameters that can be measured in vivo and reflect specific features of pathophysiological processes of the disease (Jack et al., 2011).

Because of some biomarkers turning out being more specific for some features of AD than others, it has been proposed to divide these biomarkers in two major categories: the first category contains the biomarkers of amyloid beta (Aβ) accumulation, which can be measured on amyloid PET imaging as well as in the cerebrospinal fluid (CSF), showing reduced levels of the $A\beta_{42}$ protein. The second category of biomarkers reflects neuronal degeneration or injury, which becomes the dominant pathological process later. Increased CSF tau and structural MRI measurements of cerebral atrophy in a specific topographic pattern are seen here especially involving the medial temporal lobe (Jack et al., 2010). These biomarkers of neurodegeneration have been proved to correlate well with severity of the clinical symptoms in AD patients (Jack et al., 2010; Vemuri et al., 2010). Therefore, biomarker evidence is expected to increase accuracy of the diagnosis by increasing certainty of the underlying disease (Jacket al., 2010; McKhann et al., 2011). Because of this, the National Institute on Aging-Alzheimer's Association (NIA-AA) conducted a revision of the NINCDS-ADRDA criteria quite recently and included the use of these biomarkers for the diagnosis of AD

(McKhann et al., 2011). However, at the moment, due to its continuous nature, biomarker evidence mainly contributes to assess the clear presence or clear non-presence of AD and there is a lack of definitive cut-off values. As a result, biomarker evidence is currently inconclusive and sometimes biomarkers profiles can even be contradictory (McKhann et al., 2011) (table 1).

Table 1

AD dementia criteria incorporating biomarkers (Obtained from: McKhann et al., 2011)

Table 1
AD dementia criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSF tau, FDG-PET, structural MRI)
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence	Intermediate	Unavailable or indeterminate	Positive
of AD pathophysiological	Intermediate	Positive	Unavailable or indeterminate
process	High	Positive	Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, ^{18}fluorodeoxyglucose; MRI, magnetic resonance imaging.

It is presumable that these inconsistencies that are present in clinical manifestations and in biomarker profiles can be associated to the different patterns of atrophy in different brain regions that are seen in AD's. Therefore, studying and categorizing AD subtypes based on these structural patterns of atrophy could help to understand the clinical heterogeneity (Ferreira et al., 2015) and therefore support disambiguating the diagnosis of AD. However, this is not well established in preceding research, or at least the association with the clinical presentations defined in the new diagnostic criteria has not been demonstrated yet.

The most common presentation of AD is the typical amnestic form, characterized by progressive episodic memory deficit that remains dominant in the later stages of the disease (Grady et al., 1988). Atrophy in the medial temporal lobe has been found to correlate with memory impairment in numerous studies and has been included in the diagnostic criteria of AD as a supportive feature (Frisoni, Fox, Jack, Scheltens & Thompson, 2010; Dubois et al., 2007). However, atrophy in other brain regions could also explain memory impairment in AD. For instance, atrophy in the frontal lobe could explain aspects related with free retrieval of the information (Cabeza & Nyberg, 2000). On the other hand the atypical non-amnestic AD presentations, described in the NIA-AA criteria of AD as executive, language and

visuospatial dysfunction, could possibly be explained by atrophy in other brain regions beyond the medial temporal lobe (McKhann et al., 2011; Ferreira et al., 2015). In further disease progression these presentations usually show amnestic deficits as well (Galton, Patterson, Xuereb, & Hodges, 2000).

Atrophy in AD can be visually assessed using validated visual rating scales of medial temporal atrophy (MTA), scoring the atrophy in hippocampus, parahippocampal gyrus, entorhinal cortex and surrounding cerebrospinal fluid spaces (Scheltens et al., 1992; Scheltens & van den Pol, 2012) and of posterior cortical atrophy (PA), focussing on scoring of atrophy in posterior cingulate sulcus, precuneus, parieto-occipital sulcus and parietal cortex (Möller et al., 2014, Koedam et al., 2011). Assessing of the frontal lobe can be done by using the frontal subscale of the global cortical atrophy (GCA-F) (Pasquier et al., 1996 Scheltens, Pasquier, Weerts, Barkhof, & Leys, 1997). Therefore, different AD subtypes can be identified based on patterns of brain atrophy (Ferreira et al., 2015). Combining the above-mentioned visual rating scale, AD patients with atrophy only in the medial temporal lobe, or in combination with atrophy in the frontal and posterior cortex can be identified. Likewise, atypical AD patients with atrophy only in the frontal lobe, only in the posterior cortex, or even without atrophy can be determined. As a result, the AD patients can be classified into eight different subtypes according to their pattern of brain atrophy: MTA, FA, PA, MTA + FA, MTA + PA, MTA + FA + PA, FA + PA and a subtype representing 'no atrophy'.

As mentioned above, memory impairment has been traditionally related to atrophy in the medial temporal lobe. However, memory is a very complex cognitive function and it is supported by other brain regions beyond the medial temporal lobe (Cabeza & Nyberg, 2000). The main aim of this project is to investigate memory profiles in different AD subtypes according to patterns of brain regional atrophy and associations with other cognitive domains. This will be tested a line of subsequent secondary aims. First, relationships between different memory components in a population reference group of cognitively normal individuals will be studied in order to understand the normal memory profile in a population based group. Different components of episodic memory (i.e. learning, delayed recall, and recognition) will be included, as well as other cognitive functions such as executive functioning and visuospatial functions and interactions between functions.

Second, keeping these results and relationships in mind, the memory profile of the healthy controls from another separate sample, the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, will be investigated. The ADNI is a large open dataset from the United States and Canada that includes a large sample of AD patients, mild cognitive

impairment (MCI) patients and healthy controls. However, the ADNI cohort has been found to be highly selected and contain participants with frequently high education, and is therefore not completely representative of the general population (Whitwell et al., 2012). Differences in performances and results between this cohort and the population reference group will be kept in mind in further steps and during results interpretation.

Third, once the normal memory profile has been studied in two independent groups of healthy controls, the same kind of analyses will be done in AD patients. Different AD subtypes will be studied according to different patterns of brain atrophy according to visual rating scales of atrophy in the medial temporal, frontal and posterior cortex. The memory profile of the AD patients from the ADNI cohort will be studied, focussing on relationships between variables in the memory profile in an integrative way, including different memory components and the influence of non-memory cognitive functions.

Hypotheses

1) In the population reference group, the different memory components will be significantly related to each other. This would show that delayed free recall and recognition, relevant for the diagnosis of AD, depend on other components such as learning, interference and working memory.

2) In the population reference group, the different memory components will be influenced by performance in other cognitive functions. In particular, executive functions will have an important influence. Other factors such as age, gender and education might also have some influence in memory performance.

3) Similar patterns as those seen in the population reference group are expected in the healthy controls from the ADNI cohort, although greater influence of executive components as part of compensatory processes are anticipated in the ADNI cohort given their higher degree of education.

4) In AD patients, variability in the memory profile will be related to different patterns of brain atrophy. For instance, AD patients with atrophy in the medial temporal lobe will show memory impairment, but this impairment will be greater in AD patients evidencing atrophy in other brain regions in addition to the medial temporal lobes.

Methods

Two cohorts were included in this study: (1) a population reference group recruited at the region of Gemeente Bernheze (The Netherlands), and (2) a large dataset including data from controls, MCI patients and AD patients from the ADNI (Alzheimer's Disease Neuroimaging Iniative) multicentre study (USA and Canada).

Population reference group

Participants

Twenty-seven subjects were recruited by the student (C.V.) at the region of Gemeente Bernheze (The Netherlands) in April 2015. The mean age was 66,15 (SD = 2,37), ranging from 49 to 88 years old. The gender distribution was around 50% (13 male, 14 female). All participants were relatives or acquaintances of the student and participated voluntarily. Informed consent was obtained from all participants. The following criteria were used to recruit 'healthy' individuals: (1) no vascular diabetes or a brain disease; (2) no diagnosis of AD or another type of dementia or neurodegenerative disease; (3) had not suffered from traumatic brain injury or cerebrovascular accident; and (4) had no history of psychological or psychiatric disorder that could influence the test results. A further overall picture of the controls daily functioning and mental health was obtained by using a clinical interview, the MMSE, GDS and the FAQ (see below for a description of these instruments). Exclusion criteria were (1) a GDS score of 6 or higher; (2) a MMSE score of 23 or less; (3) a clock drawing score of 6 or less; (4) substance abuse or alcohol abuse; (5) and visual and auditory acuity inadequate for neuropsychological testing.

Materials

The following tests and questionnaires were used in the population reference group:

1. Clinical and demographic interview (appendix). Interview that contains 20 various questions about demographic and clinical aspects.
2. Standardized Dutch version of the Mini Mental State Examination (MMSE; Kok & Verhey, 2002)
3. 15 Woorden Test [1](15-WT; Saan & Deelman, 1986)
4. Functional Assessment Questionnaire (FAQ; Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982). A Dutch translation was used (enclosed).

[1] Fifteen words test

5. Geriatric Depression Scale - 15 items (GDS; Parmelee & Katz, 1990)
6. Iowa Trail Making task (TMT; Reitan, 1944)
7. Clock Drawing Test (CDT; Agrell & Dehlin, 1998) (?)
8. Nederlandse Leestest voor Volwassenen (NLV; Lindeboom & Van Harskamp 1992).

Procedure

Participants were informed about this research and its purpose with the help of an information letter (appendix) 1-2 week before testing in order to give participant enough time to decide if they wanted to participate or not. If in the meantime any questions raised, participants were able to contact the student by phone or e-mail.

Before the volunteers started participation in this research, they had to declare that they read the information letter and had to agree with the informed consent by means of signing the informed consent form (appendix). All tests were administered in Dutch in a quiet room at the participant's house. Since the test session lasted around 50 minutes, the participant was informed about this and advised to use the bathroom before test period, switch the mobile phone off, and disconnect the doorbell/landline telephone if possible. If other people were present in the same house during the tests, they were informed about the assessment and that it was not allowed to disturb during the test period.

First, the participants were asked if they were having any problems with sight, reading or hearing problems. Subsequently if no objections arose, a standard testing procedure was started in the following order without taking breaks between tests:

1. Demographic and clinical interview questions 1-10 and 12-20 (appendix).

   Rationale: Starting with this questionnaire in order to screen the participant for inclusion/exclusion criteria as well as to establish a climate of confidence.
2. Mini Mental State Examination.

   Rationale: screening the participants on their global cognitive status. Isn question four it is chosen to let the participant 'spell WORST backwards', this option seemed the most similar to the question that is used in the ADNI cohort ('spell EARTH backwards').
3. Bloem-kroon-snor version of 15-WT (after the learning phase of the 15-WT there was a delay of 20-25 minutes. This delay was filled with other tests (non verbal or non memory tests).

   Rationale: In order to be able to fill the full 20-25 minute time gap with the remaining neuropsychological tests, the 15-WT was used at first.

4. Iowa Trail Making task
5. Clock drawing
6. Functional Assessment Questionnaire

Rationale: test 4, 5, 6 are all three non-verbal tasks and therefore useful to fill up the 20-25 minute time gap. The questionnaire was initially answered based on the participant's own opinion, but if given answers did not seem to reflect the actual physical/mental status of the participant, they were checked with the help of an informant.

7. Geriatric Depression Scale 15 items

Rationale: usually the GDS is placed at the end of the neuropsychological battery because of its possible influence on performance. However, it is assumed that this effect is not that influential on healthy people that are not depressive, so in this protocol the GDS is used to fill up the time gap. Participants are asked to not overthink the questions. The next 'test' is a test that is neither performance nor time based in order to prevent the GDS to bias any test results.

8. Demographic and clinical interview question 11 *(spare time activities/hobbies)*

Rationale: placed here in order to fill up the remaining time of the 20-25 minute gap and to decline the possible effect of thinking about GDS items by switching quickly to a more positive topic (spare time activities/hobbies). If already 20 minutes had gone by, this question was cut short within a few minutes, and finished after the delayed recall and delayed recognition of the 15-WT. Keeping the time gap more or less the same between participants was in this study of higher importance.

9. After 20 minutes: delayed recall + delayed recognition of 15-WT.
10. Nederlandse Leestest voor Volwassenen[2]

Rationale: the NLV is put after the 15-WT in order to prevent interference because of its verbal content.

All tests were administered by the student according to the official instructions. After administration of the test battery, there was a short review moment to talk about how the participant experienced the tests and to thank the participant for his/her participation.

The test procedure for the population reference group slightly differs from the procedure of the multicentre ADNI study because a larger test battery was carried out in this last. However, this should not affect to the quality of the data for the purpose of our study.

[2] Dutch Reading test for Adults

Measurements and calculations

The following cognitive variables were measured: learning, delayed recall, and recognition (15-WT), psychomotor speed (TMT A), divided attention (TMT B and the ratio between TMT A and TMT B), visual-spatial constructive abilities (CDT) and IQ estimation (NLV). Other variables that were taken into account during analyses were: independence in functional activities (FAQ), depressive symptomatology (GDS-15) and global cognitive state (MMSE). All tests were scored by the student with the help of the official material used at a daily basis by clinicians within the Universitair Medisch Centrum of Utrecht. A trainee (Nienke Slaper) at the neurological department from the UMCU, helped with the scoring of some of the tests. Since all participants were considered healthy and showed very few errors in the Clock drawing Test, the test was scored with a scale of 10 points to get a more detailed range of scores, increasing variability, useful for statistical analyses. This scoring was performed with the help of Alejandra Machado, clinician and researcher at the Department of Clinical Psychology, Psychobiology and Methodology from the University of La Laguna (Spain), and the Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society from the Karolinska Institutet (Sweden). Other variables that were included and collected with the help of the demographic and clinical interview were gender, age, education level (according to the Dutch educational classification of Verhage, 1983), years of education, subjective memory complaints, presence of diseases, psychic or psychiatric disorders, use of medicines, alcohol intake, smoking, family history of AD or other forms of dementia and preceding traumatic brain injury or cerebro-vascular accidents.

ADNI cohort

Data

Data from the ADNI cohort was downloaded from the ADNI-database. Information is available at www.adni-info.org.

Participants

The ADNI study recruited a total of 819 subjects: cognitively normal subjects (n = 229), MCI patients (n = 398) and AD patients (n = 192). Subjects age was between 55 and 90 years old. The mean age of the 3 groups was equivalent to approximately 75 years. There was an approximately equal number of men and women in the normal control and AD groups, but there were more men in the MCI group. The estimated mean of premorbid verbal IQ was high, almost 120 for the normal control subjects, 116 for the subjects with MCI, and 114 for

the subjects with AD. Inclusion criteria were: (1) a Hachinski Ischemic Score of less than or equal to 4; (2) stable medications for 4 weeks prior to screening; (3) a GDS score of less than 6; (4) a study partner with 10 hours per week of contact either in person or on the telephone and who could accompany the participant to the clinical visits; (5) visual and auditory acuity adequate for neuropsychological testing; (6) good general health with no diseases precluding enrollment; (7) six grades of education or work history equivalent; (8) and ability to speak English or Spanish fluently. Women had to be sterile or 2 years past childbearing potential. Subjects had to be able to complete a 3-year imaging study (2 years for subjects with AD). Participants having psychoactive medications believed to affect cognitive function were excluded. Subjects agreed to DNA extraction for *APOE* testing and banking and agreed to blood and urine examination for biomarkers. Subjects could not have any medical contraindications to MRI and could not be enrolled in other trials or studies.

Diagnostic procedure

Healthy subjects

With respect to memory complaints, the normal subjects had none. On the Mini-Mental State Examination (MMSE) the range was 24-30, and the CDR score 0. For the memory criterion, delayed recall of 1 paragraph from the Logical Memory II subscale of the Wechsler Memory Scale–Revised (maximum score of 25) 12 was used with cutoff scores as follows based on education: 9 for 16 years of education, 5 for 8–15 years of education, and 3 for 0–7 years of education. In addition, the normal control subjects were to be matched to the other subjects in age and could not have any significant impairment in cognitive functions or activities of daily living

AD patients

AD patients also had to have memory complaints and a scoring on the MMSE between 20-26. The rating for AD subjects on CDR was 0.5 or 1. Cut-off for scoring on the Logical Memory II of the Wechsler Memory-scale- revised were the same as for MCI patients. The subjects with AD had mild AD and had to meet the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD.

Materials

Neuropsychological tests used for the ADNI cohort:

1. Mini Mental State Examination (MMSE: Folstein, Folstein & McHugh, 1975))
2. Functional Assessment Questionnaire (FAQ: Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982)
3. Rey's Auditory Verbal Learning Test (RAVLT: Schmidt, 1996)
4. Iowa Trail Making Test A and B (TMT: Reitan, 1944)
5. Clock Drawing Test (CDT: Agrell, & Dehlin, 1998).
6. Clock copy
7. Geriatric Depression Scale 15-item version (GDS-15: Parmelee & Katz, 1990).
8. Digit forwards and digit backwards (Wechsler, 1987)
9. Category fluency task (animals version)
10. Boston naming task (Kaplan et al. 1993)
11. American National Adult Reading Test (Blair & Spreen, 1989)

MRI

All subjects received an MRI scan at 1.5 Tesla. Twenty-five per cent of the subjects also received an MRI scan at 3 Tesla. Only images from 1.5 Tesla are used for this study. Atrophy of the posterior cortex was rated with the posterior cortical atrophy visual rating scale (Möller et al., 2014; Koedam et al., 2011). Medial temporal atrophy (MTA) was measured with the visual rating scale developed by Scheltens et al. (1992) and frontal atrophy by the separate assessment of the Global Cortical Atrophy scale for the frontal lobe (GCA-F). Deviation from normality was established following a recently proposed list of practical cut-offs (Ferreira et al., 2015). In particular, medial temporal atrophy was considered when MTA scores were ≥1.5, ≥1.5, ≥2, ≥2.5 for the respective age ranges 45-64, 65-74, 75-84, and 85-94 years; and frontal and posterior atrophy was considered when GCA-F and PA scores were ≥1, irrespectively of the age range

Protocol design

The protocol design used for the ADNI cohort is attached in the appendix.

Measurements and calculations

As mentioned before, combining the three atrophy cut-off scores gives the possibility to categorize the AD-patients in 8 subtypes: MTA, FA, PA, MTA + FA, MTA + PA, MTA + FA + PA, FA + PA and a subtype representing 'no atrophy'. To simplify statistical analyses and

due to small groups sizes for some of the subtypes, these subtypes were re-categorized into the following three subtypes: MTA (representing the group with only medial temporal atrophy above cut-off), MTA+ (representing the group with medial temporal atrophy combined with frontal and/or posterior atrophy above cut-off) and non-MTA (representing the group with frontal atrophy, posterior atrophy or a combination of that above cut-off, as well as the non-atrophy group: reflecting no atrophy or atrophy below cut-off).

Data Analysis

SPSS 18.0 for windows was used for all the statistical analyses for population reference group. Pearson correlations, Spearman's Rho correlations and partial correlations were carried out to investigate relationship between two variables. Multiple linear regression was used to investigate relationship among three or more variables. For all the regression analyses, the 'backwards' method was used. Regressions were checked for multicollinearity to avoid statistical artefacts. Predictors kept in the final models because standard methodological criteria ($p<0.10$), but that were not significant (p-value between 0.10 and 0.051),are reported but were not considered in results interpretation and conclusions. ANOVA and ANCOVA were used for mean comparisons. When sphericity was not assumed Greenhouse-Geisser was used to estimate degrees of freedom. The bonferroni correction was used for the post-hoc comparisons. In order to determine which clinical cut-off (-1.5 Sd or -1.96 Sd) to use for interpretation of the performances of all the groups, crosstabs were used to calculate specifity and sensitivity values for both cut-off's, and ROC-analyses were carried out to identify the bigger area under the curve. A p-value of <0.05 was used to indicate significance in all analyses and results.

Results

Population reference group

Descriptives

The population reference group (n = 27) consists out of 14 female participants and 13 male participants with a mean age of 66.15 and age range of 49 to 88. Education level (M = 5) of the participants ranges between 2 to 7 according to the Dutch educational classification of Verhage (1983). Years of education are spread out from 7.5 to 30 years with a mean of 15.98.

Table 2

Overview of demographics of the population reference group (n = 27) in terms of means (M), standard deviation (SD), median and range.

	M (SD)	median	range
age	66.15 (2.37)	66	49-88
education level	5.00 (0.24)	5	2-7
years of education	15.98 (1.10)	15	7.5-30

Figure 1

Distribution of gender in percentage

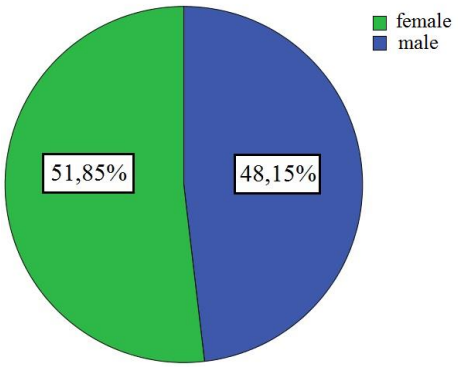


Figure 2 and 3

Distribution of age (in years) and years of education of the population reference group

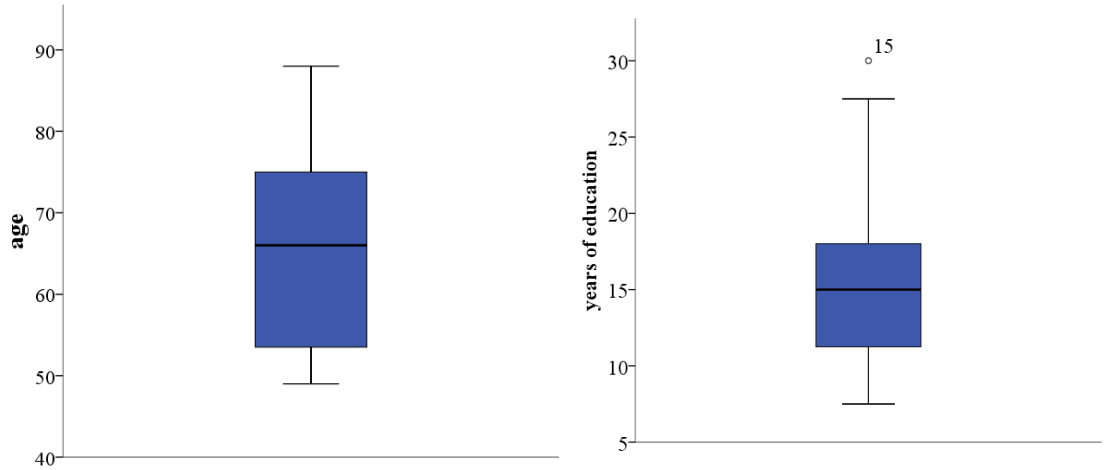
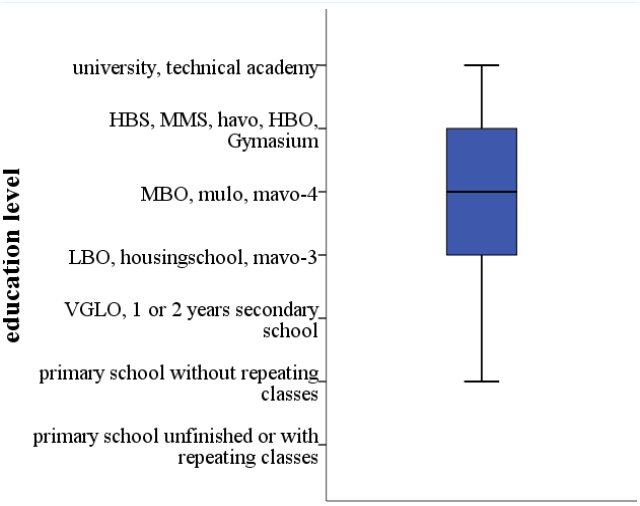


Figure 4
Distribution of education level of the population reference group according to Verhage educational classification (1983).



Cognitive performance

An overview of cognitive performance of the reference population group is shown in table 3.

Table 3.
Overview of test results of the reference population group (n = 27) in terms of mean (M), standard deviation (SD), median and range

	M (SD)	median	range
NLV IQ	104.56 (2.84)	105	72 - 126
MMSE	29.15 (0.21)	29	26-30
FAQ	0.96 (0.26)	0	0 - 4
GDS	1.59 (0.32)	1	0-7
15WT-LP	39.52 (10.65)	40	19-58
15WT recall	7.93 (3.50)	8	3-15
15WT recognition	28.33 (1.86)	29	24-30
TMT A	41.70 (20.75)	36	16-106
TMT B	114.15 (70.04)	98	38-315
B/A ratio	2.75 (0.80)	2.7	1.7-4.1
Clock drawing test	9.61 (0.64)	10	7.5-10

Relationship among memory components in the population reference group

Learning was found to have a significant strong positive correlation with recognition, r_s = 0.871 and delayed recall, r_s = 0.901; recognition was also correlated with delayed recall r_s = 0.799 (all *p*-values <0.001).

Table 4.
Correlations among memory components in the population reference group

	r_s	*p*
learning x delayed recall	0.901	<0.001
learning x recognition	0.871	<0.001
delayed recall x recognition	0.799	<0.001

Interestingly, separate analyses for two different education groups (low = education level 1-4, high = education level 5 – 7), showed no significant correlations for the 'low education' group (Table 5).

Table 5.

Correlations among memory components in the population reference group, split up in lower education level 1-4 (1) and higher education level 5-7 (2).

	1 (*n* = 18)		2 (*n* = 9)	
	r_s	*p*	r_s	*p*
learning x delayed recall	0.606	0.111	0.899	<0.001
learning x recognition	0.630	0.094	0.826	<0.001
delayed recall x recognition	0.185	0.661	0.791	<0.001

The same pattern of results was found when controlling for the influence of age, gender, years of education, education level, IQ estimation and depression.

Influence of other cognitive functions on memory

There was found a significant negative correlation between learning, delayed recall and delayed recognition and TMTA and TMT B (table 6). None of the memory variables showed a significant relationship with the clock drawing test.

Table 6.
Spearman rho's correlations and their significance between TMT A, TMT B, Clock Drawing Test and memory variables in the population reference group

	TMT A		TMT B		CLOCK	
	r_s	p	r_s	p	r_s	p
learning	-0.532	0.004	-0.578	0.002	0.344	0.079
delayed recall	-0.563	0.002	-0.527	0.005	0.352	0.072
recognition	-0.518	0.006	-0.504	0.007	0.322	0.101

These correlations were no longer significant when controlling for age and FAQ (Table 7). The other confounding variables gender, depression, IQ estimation, education level and years of education did not have any influence on the results (data not shown).

Table 7.
Correlations and their significance between memory profile variables and TMT A, TMT B and Clock Drawing Test, while controlling for age and functional activities

	TMT A		TMT B		CLOCK	
	r_s	p	r_s	p	r_s	p
age						
learning	-0.205	0.315	-0.284	0.160	0.146	0.476
delayed recall	-0.348	0.082	-0.287	0.155	0.105	0.609
recognition	-0.309	0.125	-0.285	0.158	0.113	0.582
FAQ						
learning	-0.296	0.142	-0.311	0.122	0.195	0.341
delayed recall	-0.379	0.056	-0.284	0.160	0.140	0.496
recognition	-0.310	0.123	-0.240	0.237	0.137	0.504

ADNI-cohort

Descriptives

The ADNI-cohort (n = 783) consists out of 336 female participants and 447 male participants. The healthy group (n = 230) includes 112 female and 118 male participants. Years of education are spread out from 4 to 20 years. The AD group (n = 199), consists out of 96 female patients and 103 male patients. The range of years of education is also 4 to 20 years. In both groups, mean years of education is high, around 15 years.

Table 8.
Overview of demographics of the total ADNI cohort (n = 783) in terms of means (M), standard deviation (SD), median and range.

	N	%female	age				years of education			
			M	SD	median	range	M	SD	median	range
healthy	230	48.7	75.93	5.02	75.72	59.9-89.6	16.02	2.90	16	6-20
MCI	354	36.2	75.05	7.20	75.65	55.2-88.8	15.75	2.96	16	6-20
AD	199	48.2	75.53	7.70	75.95	55.14-90.93	14.69	3.21	15	4-20
Total	783	42.9	75.43	6.78	75.71	55.14-90.93	15.56	3.04	16	4-20

Cognitive performance
An overview of cognitive performance of the ADNI cohort is shown in table 9.

Table 9.
Overview of test results of the ADNI healthy controls (n = 230) and AD patients (n = 199) in terms of mean (M), standard deviation (SD), median and range

			healthy				AD	
	M	SD	median	range	M	SD	median	range
IQ ANART	120.09	7.27	122.19	87 - 128	114.89	8.10	115.55	88-128
MMSE	29.11	1.00	29	25-30	23.28	2.04	23	18-27
FAQ	0.136	0.60	0	0-6	13.14	6.84	12	0-30
GDS	0.84	0.00	0	0-5	1,67	1,42	1	0-6
CDR	0.00	0.00	0	0-0	0.75	0.25	0.75	0.5-1.0
AVLT-learning total	43.27	9.07	43	16-69	23.20	7.74	23.20	0 - 42
AVLT- delayed recall	7.41	3.69	7	0-15	0.73	1,63	0	0-9
AVLT- recognition	12.87	2.52	14	2-15	7.23	4	7	0-15
TMT A	36.45	13.22	33.00	17-102	68.19	36.63	56	18-150
TMT B	89.31	44.33	79.00	34-300	198.97	87,12	192	35-300
B/A ratio	2.52	0.97	2.33	0.90-6.67	3.44	1.70	3.00	0.38-8.82
digit backward span	7.23	2.16	7	2.0-12.0	4.93	1,84	5	1-11
digit forward span	8.79	1.98	9	4.0-12.0	7.57	1,96	7	2-12
Clock Drawing Test	4.68	0.66	5	1.0-5.0	3.36	2,13	4	0-5
Clock Test copy	4.86	0.42	5	2.0-5.0	4.33	1,01	5	1-5
BNT	29.21	2.29	30	0-32	22.36	6,29	23	1-30
Verbal fluency	19.92	5.60	19.50	6-38	12.29	4,92	12	0-27

AD-subtypes

The AD patients were reorganized in three groups based on atrophy patterns: a group that shows atrophy only in the medial temporal lobe (MTA: *N* = 31, 54.8% female), a group that contains also other forms of atrophy in addition to atrophy in the medial temporal lobe (MTA+: *N* = 125, 40.8% female), and a group with atrophy sparing the medial temporal lobe (non-MTA: *N* = 43, 65.1% female). Main demographic and clinical characteristics are shown in table 10.

Table 10.
Overview of age, years of education (YOE), MMSE-score and CDR of the AD-subtypes

	MTA				MTA+				non-MTA			
	M	SD	median	range	M	SD	median	range	M	SD	median	range
age	71.98	6.52	71.83	55.1-84.3	77.15	6.52	77.82	59.9-89.3	73.38	10.03	75.27	56.4-90.9
YOE	14.74	2.45	15	8-20	14.75	3.21	16	4-20	14.47	3.73	15	4-20
MMSE	23.45	2.08	24	20-26	23.07	2.05	23	18-27	23.79	1.91	24	20-26
CDR	0.69	0.25	0.50	0.5-1.0	0.769	0.25	1.0	0.5-1.0	0.724	0.25	0.50	0.5-1.0

YOE = years of education

Cognitive profile overview

In order to enhance interpretation and comparison between all the cognitive variables and study groups, all the cognitive variables were transformed to z-scores and visualized in a graph (Table 11 and Figure 5). Z-scores were calculated using the healthy controls from the ADNI cohort as reference group (z-score = 0). Also the performance of the population reference group is included in the graph. In the following sections the memory profile and the influence of other cognitive functions in the memory profile across AD subtypes will be further investigated.

Table 11: Z-scores for cognitive tests with reference to healthy controls from ADNI

	healthy controls (reference)	PRG	MTA	MTA+ others	non-MTA
delayed recall	0	0.14	-1.81	-1.86	-1.67
recognition	0	0.43	-2.11	-2.43	-1,75
working memory	0	n/a	-1.211	-0.98	-1.19
TMT B	0	-0.56	-2.04	-2.67	-2.25
digitforwards	0	n/a	-0.89	-0.51	-0.73
TMTA	0	-0.40	-1.86	-2.57	-2.31
animals	0	n/a	-1.29	-1.43	-1.22
BNT	0	n/a	-1.26	-1.82	-0.65
clocktest	0	0.48	-1.51	-2.17	-1.86
clockcopy	0	n/a	-1.05	-1.44	-0.86

n/a = data not available

Note: Z-scores on learning are shown in Table 13.

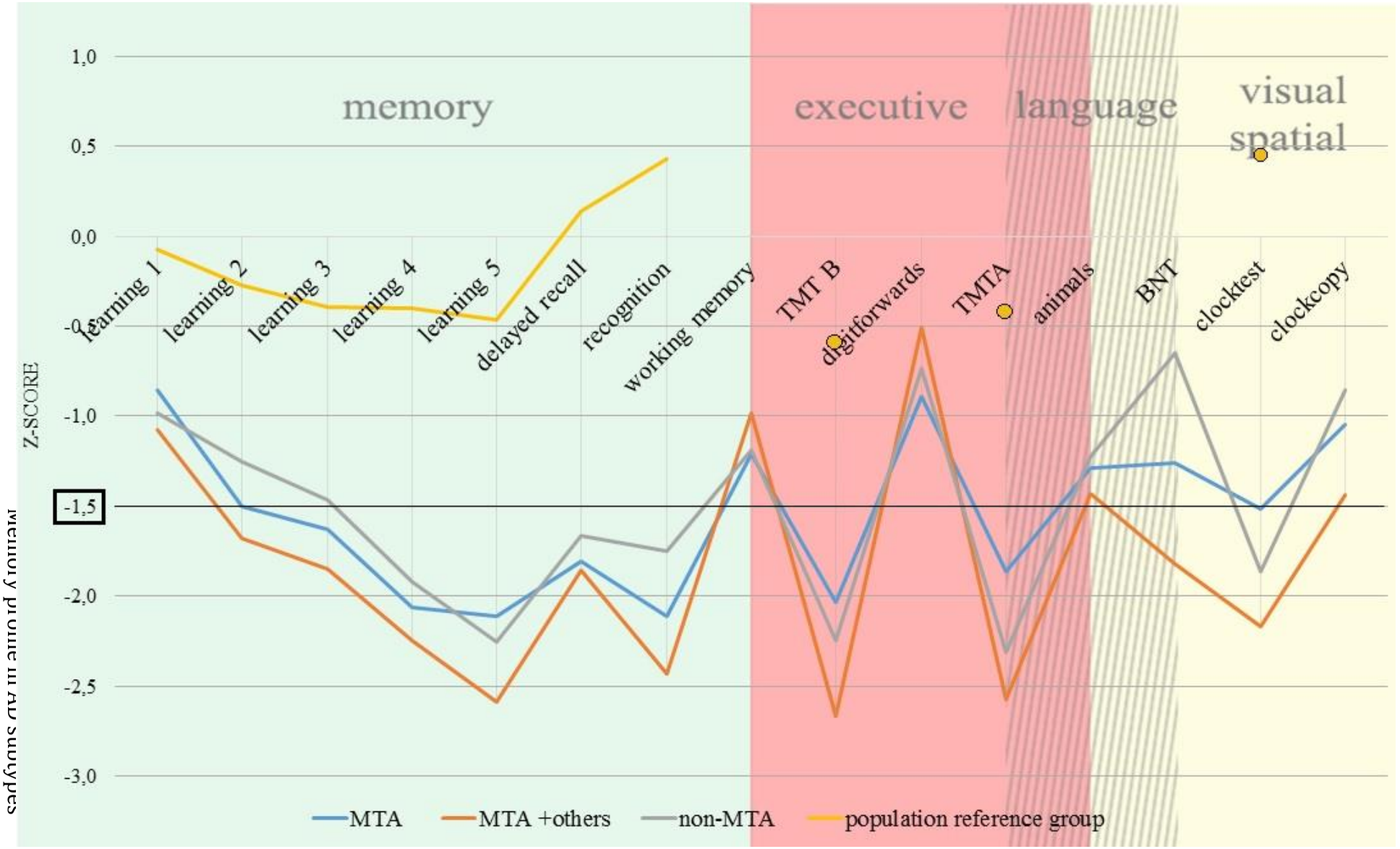


Figure 5. Z-scores for all included cognitive variables and study groups.

Memory profile

Learning curve and gain

As described above, Z-scores for the three AD subtypes were computed for all the cognitive tests, using the performance of the healthy controls of the ADNI cohort (HC) as reference group. Performance of the population reference group (PRG) is also reported (Table 12 and Figure 6).

Table 12: Z-scores for learning trials 1-5 (AVLT)

	Healthy Controls (reference)	PRG	MTA	MTA+	non-MTA
Learning 1	0	-0.07	-0.85	-1.07	-0.98
Learning 2	0	-0.27	-1.50	-1.68	-1.25
Learning 3	0	-0.39	-1.63	-1.85	-1.46
Learning 4	0	-0.40	-2.06	-2.25	-1.92
Learning 5	0	-0.46	-2.11	-2.59	-2.26
Total learning	0	-0.41	-2.03	-2.34	-1.95

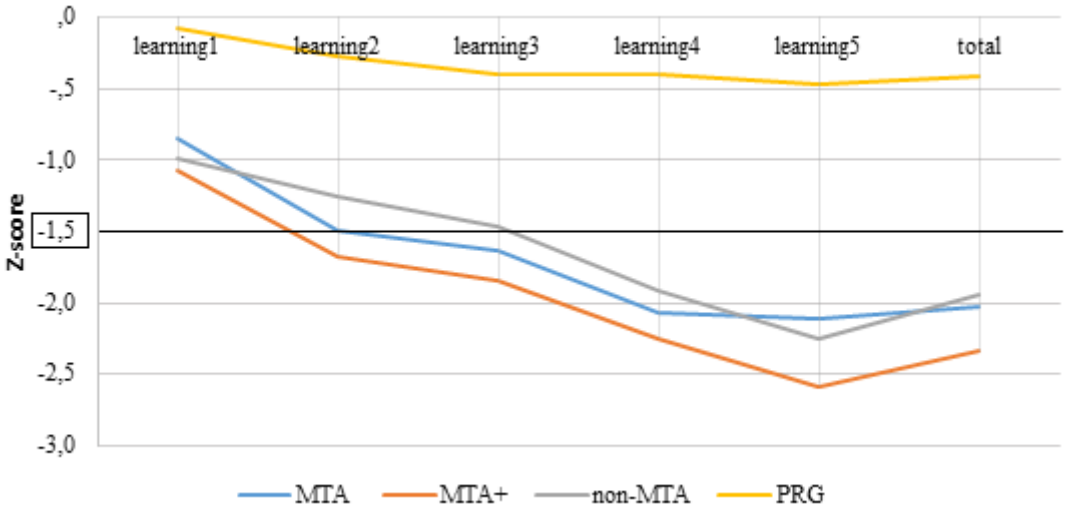


Figure 6. Z-scores on learning for AD subtypes and PRG.

All of the AD subtypes differed significantly from the healthy controls for the five learning trials and total learning, all p's < 0.001. The one-way ANOVA for the three AD subtypes showed statistical significant differences between non-MTA and MTA+ for learning trial 2 ($F_{(2, 185)} = 3.70$, $p = 0.027$), learning trial 3 ($F_{(2, 184)} = 4.14$, $p = 0.017$); and between MTA and MTA+ for learning trial 5 ($F_{(2, 183)} = 4.52$, $p = 0.012$). In all the three cases MTA+ patients performed worse. Looking at the total of recalled words during learning, MTA+ showed a significantly lower score compared to non-MTA ($F_{(2,183)} = 4.009$, $p = 0.020$). The population reference group showed no significant differences with the healthy controls from ADNI for

the learning trials 1-4. However, on learning trial 5 and total learning, performance was significantly lower, $p = 0.026$ and $p = 0.047$ respectively. Moreover, there was a statistical trend towards significance for learning trial 3 and 4, $p = 0.053$, $p = 0.057$ respectively.

In order to study the gain in learning between trial 1 and 5, data were analysed using a mixed-design ANOVA, with a within-subjects factor of learning (learning trial 1 vs. learning trial 5)) and a between-subject factor of subtype (MTA vs. MTA+ vs. non-MTA vs. ADNI healthy controls). There was found a significant interaction effect between the factors learning and subtype ($F_{(3, 408)} = 130, 45$, $p < 0.001$).

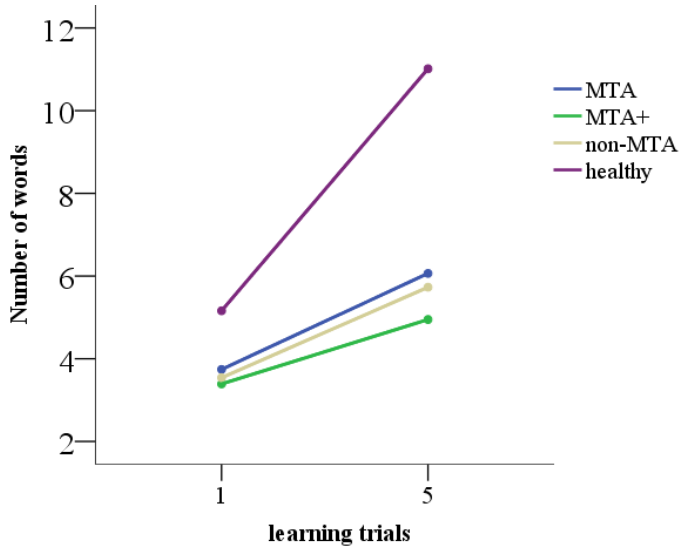


Figure 7. Learning effect in the three MTA-subtypes and healthy controls

Post hoc comparisons showed that controls performed significantly better than the other three groups in trial 1: $F_{(3,411)} = 40.00$, $p < 0.001$, and trial 5: $F_{(3, 408)} = 226.09$, $p < 0.001$. There were no significant differences found between MTA-subtypes on the learning trials.
Paired samples T-test showed that there were statistically significant differences between trial 1 and 5 for the AD subtypes (MTA: t (30) = -8.19, $p < 0.001$, MTA+: t (117) = -9.29, $p < 0.001$, non-MTA: t(36) = -7.37, $p < 0.001$), as well for the healthy controls (t (225) = -38.46, $p < 0.001$).

Despite the lack of significant differences between AD subtypes, the visual assessment of the plot suggests differences in slopes between the four groups: a stronger slope in the healthy controls, then in the MTA and non-MTA subtypes, and finally in the MTA+ subtype (Figure 3). The paired samples T-tests mentioned above were used in order to further understand the

pattern of differences in performance in trial 1 vs. trial 5 more in detail for the four diagnostic groups. The magnitude of the effects evidenced stronger learning effect in the controls (η^2 = 87%) than in the AD-subtypes, and showed differences in effect size between MTA (η^2 = 69%) and non-MTA (η^2 = 60%), and MTA+ (η^2 = 42%) (Table 13). Therefore, although learning capacity is significantly impaired in AD as compared with healthy controls, it is modulated by the subtype, with MTA+ evidencing greater learning impairment than MTA and non-MTA.

Table 13: Effect sizes for MTA subtypes on learning 1 and 5

	MTA	MTA+	non-MTA	healthy
Partial Eta Squared	0,691	0,424	0,601	0,868

An extra mixed-design ANOVA was performed to focus only on the AD subtypes. Again, there was found an interaction effect between learning and subtype ($F_{(2,183)} = 3.26$, $p = 0.040$). No significant differences between the AD-subtypes were found on leaning 1 ($F_{(2,185)} = 0,803$, $p = 0.449$) but significant differences were found on learning 5 ($F_{(2, 183)} = 4.52$, $p = 0.012$): MTA+ performed significant lower ($M = 4.95$, $SD = 2.12$) than MTA ($M = 6,07$, $SD = 2.17$).

All memory components: Learning, recognition, and working memory

Using a mixed ANOVA the possible interaction between a within-subjects factor of memory component (learning (mean of 4th and 5th trials – 1st trial) vs. working memory vs. recognition) and a between-subject factor of subtype (MTA vs. MTA+ vs. non-MTA vs. healthy controls) was analysed. There was a significant interaction between MTA subtype and memory component ($F_{(4.97, 670.84)} = 24.55$, $p < 0.001$). When doing separate ANOVA's for every memory component they showed significant differences: learning,($F_{(3, 408)} = 232,96$, $p < 0.001$), working memory ($F_{(3,411)} = 105, 79$ $p < 0.001$), recognition ($F_{(3,409)} = 44,79$, $p < 0.001$). However, these results were modulated by the subtype factor. Post-hoc comparisons showed significant differences between the healthy controls and the AD subtypes for learning, working memory and recognition (all p's < 0.001) and also a significant difference between MTA+ and non-MTA only for recognition $p = 0.025$.

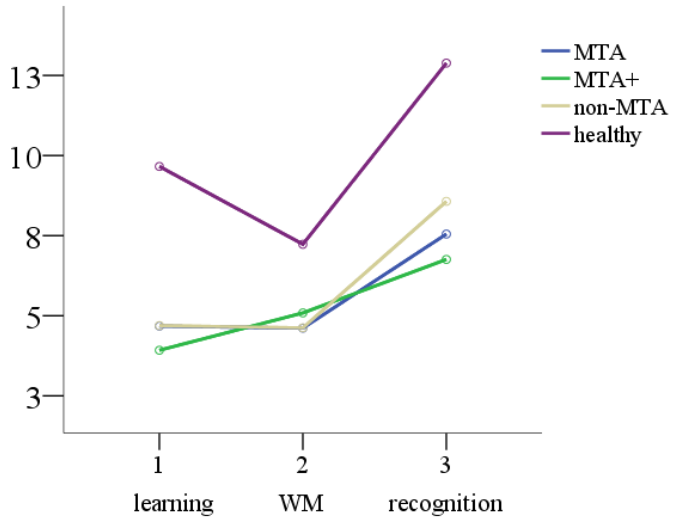


Figure 4. Learning, working memory and recognition in MTA-subtypes and healthy controls

We then wanted to further investigate the clinical meaning of these results. Percentage of AD patients that scored below a clinical cut-off on recognition and learning were computed. For calculating this cut-off, the healthy controls from the ADNI cohort were used as reference group (z-score = 0). A cut-off of -1.5 standard deviations was used according to the clinical convention (e.g. Winblad et al., 2004). Table 15 provides information about differences in performance between groups for learning and recognition, showing that for the MTA+ group a higher percentage of patients was performing under the clinical cut-off than for the other two groups for learning (MTA+: 84.00% > MTA: 80.65% > non-MTA: 74.12%) and that this also is the case for recognition (MTA+: 70.40% > MTA: 67.74% > non-MTA: 51.16%). We also calculated the variable Δ, by subtracting the recognition percentage from the learning percentage, in order to quantify benefit from additional help (recognition) when accessing stored information. The impact of this help is reflected by the biggest drop down in percentage of patients performing under the clinical cut-off (non-MTA: 22.96% > MTA+: 13.60% > MTA: 12.91%) (table 14). This means that non-MTA patients were those who had a greater benefit from external help in memory retrieving.

Table 14: Percentage of AD-patients under clinical-cut off of z-score = -1.5

	MTA	MTA+	non-MTA
learning	80.65%	84.00%	74.12%
recognition	67.74%	70.40%	51.16%
Δ	12.91%	13,60%	22.96%

Influence of other cognitive functions on memory

Learning

The influence of other cognitive functions on memory was investigated with multiple linear regression both in healthy controls and AD subtypes. It was hypothesized that learning capacity could be potentially influenced by working memory (span), attention, executive functions (strategies, flexibility, cognitive control), access to the lexicon, but not visuospatial abilities. Therefore, the following predictors were introduced into the model representing the above-mentioned aspects in the same order: digits forward span, TMT A, TMT B and verbal fluency task (animals), BNT total score, Clock Test copy. Also age and years of education were included to control for their possible confounding effects. Using the 'backwards' method, it was revealed that only the verbal fluency task (animals) was a highly significant predictor of mean learning scores ($\beta = 0.332$, $p < 0.001$) in healthy controls, accounting for 10.6% of the variance.

For analysing the AD patients, the same model as for the healthy controls was applied. The regression analysis showed that verbal fluency task, TMT B and Boston Naming task accounted for one fourth of the variance in learning performance ($R^2 = 0.255$), which was highly significant $F_{(3, 169)} = 19.27$, $p < 0.001$. Both executive tasks, word fluency ($\beta = 0.277$, $p < 0.001$) and TMT B ($\beta = -0.175$, $p = 0.013$) and the Boston naming task ($\beta = 0.210$, $p = 0.007$) demonstrated significant effects on learning performance. The influence of age and years of education was not significant in both models.

Delayed recall

The same model as in learning was used in the regression analysis for delayed recall for the healthy controls, but also learning itself was included as an independent variable, since how much is recalled in the delayed trial may depend on how much it was initially learnt. Learning ($\beta = 0.673$, $p < 0.001$), verbal fluency task ($\beta = 0.131$, $p = 0.010$) and Digit forward span ($\beta = -0.084$, $p = 0.080$), were predictors accounting for 52.2% of the variance ($F_{(3,217)} = 79.07$, $p < 0.001$). There was no influence of age and years of education.

For the AD patients the same model was used as for the healthy controls. Learning ($\beta = 0.563$, $p < 0.001$) and TMT B ($\beta = 0.240$, $p < 0.001$), resulted highly significant predictors, which were together with the confounders age ($\beta = -0.194$, $p = 0.002$) and years of education ($\beta = 0.111$, $p = 0.077$) accounting for 35,2% of the total variance ($F_{(4, 168)} = 22.86$, $p < 0.001$).

Recognition

In order to identify the predictors of recognition for the healthy controls and AD patients the same predictors as for learning were introduced into the model together with learning and delayed recall. Learning ($\beta = 0.284$, $p = 0.001$), delayed recall ($\beta = 0.252$, $p = 0.003$) and TMT B ($\beta = -0.156$, $p = 0.013$) came out to be significant predictors and together with the confounders years of education ($\beta = -0.181$, $p = 0.003$) and age ($\beta = 0.123$, $p = 0.046$) this model accounted for 27,5% of the variance for recognition in the healthy controls ($F_{(5,220)} = 16.27$, $p < 0.001$).

For the AD patients, the same regression model showed that delayed recall ($\beta = 0.312$, $p < 0.001$), learning ($\beta = 0.176$, $p = 0.037$), digit forwards ($\beta = -0.159$, $p = 0.020$), Clock Test copy ($\beta = 0.131$, $p = 0.053$) and BNT ($\beta = 0.119$, $p = 0.099$) were (significant) predictors of recognition and accounted for 26,5% of the variance ($F_{(5, 167)} = 12.02$, $p < 0.001$). There was no significant influence of confounders.

Working memory

Since it was expected working memory might depend on the influence of attention, executive functions, access to the lexicon and learning, the following predictors were included in the regression model for working memory for healthy controls: digit forward span, TMT A, TMT B, BNT, verbal fluency task (animals), learning, controlling for age and years of education. Since there was no influence expected of visuospatial abilities in working memory, the Clock Test Copy was included as a control variable in the model. Digit forward span ($\beta = 0.593$, $p < 0.001$) and learning ($\beta = 0.156$, $p < 0.004$) significantly predicted working memory performance, $R^2 = 0.392$, $F_{(2, 218)} = 70.20$, $p < 0.001$. Age and years of education did not have a significant influence on the model.

For the AD patients, the same predictors as for healthy people were included in the regression model for working memory. Digit forward span ($\beta = 0.312$, $p < 0.001$), TMT B ($\beta = -0.184$, $p = 0.011$) and Clock test copy ($\beta = 0.143$, $p = 0.044$) were significant predictors for working memory and age ($\beta = 0.176$, $p = 0.011$) was identified as a significant confounder. The model accounted for 23.4% of the variance and was significant, $F_{(4, 166)} = 12.68$, $p < 0.001$.

Discussion

The aim of this study was to investigate heterogeneity in AD by studying different AD subtypes based on atrophy patterns and studying the underlying memory profiles. In order to understand how different cognitive components are related to each other in the normal population, we studied a population reference group. We wanted to investigate if similar patterns where present in the highly selective healthy controls of the ADNI groups. This information served as a reference in order to understand the memory profile of the different AD subtypes. Our main interest was to found out if variability in the cognitive profile of the AD subtypes can be related to the different patterns of brain atrophy.

Memory profile in the population reference group: healthy controls

When looking at the relationships between memory components very strong correlations were found for the population reference group between learning, recall and recognition. This finding is in line with previous research indicating that in healthy people the amount of words recalled or recognized depends on the amount of words initially learned (Hardword and Naylor, 1969). The weakest correlation is showed between delayed recall and recognition. This could be due to the use of different brain structures: delayed recall involves more active retrieval and use of strategies, and is therefore more dependent on functioning of the prefrontal cortex (Kapur et al., 1995; Nyberg et al., 1995; Tulving et al., 1994). On the other hand, recognition is more dependent on structures in the medial temporal lobe (Yonelinas, 2002). Very interestingly, education modulated this finding. No significant correlations between memory components were found for the lower-educated part of the population reference group. Possibly, lower educated persons implement less strategies to actively retrieve information during delayed recall but have more variance in recognizing performance, leading to distorted relationship between the two.

Also other cognitive functions were of influence on learning. In particular, better executive functioning was associated with better learning capacity. Visual spatial abilities were not of influence on the memory components. This could have to do with the fact that the 15-WT assessed verbal memory and not visual memory. When the influence of executive functioning was controlled for age and for functional status (FAQ), the relationship between memory and executive functioning disappeared. The influence of age is in line with our expectations and has been found to be explained due to the association between memory and

the use of strategies during memorizing and guiding search at retrieval (West, 1996). Also, normal aging commonly shows early and more-pronounced changes in executive functioning, compared to other cognitive functions (Andrès & Van Der Linden, 2000; Libon et al., 1994). The fact that associations between memory components were no longer significant after accounting for FAQ suggests that variability in memory aligns with subclinical functional decline already in this healthy group.

The population reference group is not able to memorize as much words as the healthy controls of the ADNI cohort. Possibly this lower performance in learning could be assigned to lower education level in the population reference group, assuming that the ADNI controls have attained more learning strategies to memorize more words in a smaller amount of trials (more efficient). This is reflected by the higher performance of the ADNI controls on TMT B, representing visual search, processing speed, working memory, general intelligence and attention (Sánchez-Cubillo et al, 2009). The population reference group showed higher scores than the healthy controls from ADNI on recognition, which is in contrast to our expectations. During the recognition part of the RAVLT, the participants got the opportunity to read recognition list, instead of only getting it presented auditory as done in the 15-WT. Additionally, as mentioned before: recognition is partly explained by learning performance, which in this study is showed to be of a higher level for the healthy controls of the ADNI-cohort. However, the differences in recognition performances could possibly be explained by the differences in the delay between population reference group (20 minutes) and ADNI controls (30 minutes); and the fact that the population reference group had a younger age on average, knowing that recognition impairs with higher age. The better performance on the Clock Copy test for the population reference group is due to differences in scoring systems. It's therefore not comparable to the performance of ADNI.

Nonetheless, all the differences mentioned above are only varying between -0.5 and 0.5 standard deviations from the mean of the ADNI healthy controls, indicating subtle differences and in combination with the great disproportion of the groups' sizes that are compared to each other, they must been considered carefully. Further research could study these differences more in detail, by using a population reference group with a bigger sample size, a more corresponding average age and a neuropsychological battery that is completely complementary to the ADNI cohort battery.

Memory profile in the ADNI cohort: AD subtypes

Learning

When looking at the learning curve in the memory profile for AD, all the subtypes deviate increasingly from baseline with each learning trial, implying that the AD patients are not able to benefit from rehearsal as much as healthy controls do. However there seem to be some differences between AD-subtypes within the learning curve. MTA+ is the subtype showing greatest decline resulting in bigger deviation from baseline in all the learning trials. Since MTA+ involves atrophy in the medial temporal lobe and other brain regions, this result reflects that impaired learning is based on a dysfunctional network of brain regions rather than a result of circumscribed atrophy, which is in line with findings in the literature (Cabeza and Nyberg, 2000). MTA and MTA+ show greatest decline in the first 2 trials, while the non-MTA group performs above the clinical cut-off till the third learning trial. It also seems that MTA group flatten more in the last two trials. This could indicate that this group is able to get some benefits from repetition compared to the other groups, and can therefore be (statistically) differentiated from the MTA+ group in trial 5. Further MTA+ and non-MTA show a different pattern when comparing delayed recall and recognition: MTA+ deviating further from the healthy controls, while non-MTA stays around the same deviation. This indicates that the MTA+ group experienced more consolidation problems compared to non-MTA group.

Despite the fact that all of the AD subtypes showed some gain effect in the amount of words memorized between trial 1 and trial 5, there seem to be no clear linear relationship between the amount of words that is learned and the number of trials, since according to our results learning capacity was modulated by AD subtype. The MTA+ group was not able to memorize as much words as the other groups did at the end of the learning phase, again implying that learning seem to be relying on a more large-scale network than just one brain region.

Delayed recall and recognition

Both performance on delayed recall and recognition of the AD patients are on average below the clinical cut-off. Together with the finding that the AD patients are not able to benefit from repetition that much, as mentioned before, this is showing consistency with impaired consolidation rather than an ineffective retrieval of information, something that already is known for AD patients (Helkala, Laulumaa, Soininen & Riekkinen, 1988; Delis et al., 1991). The novel finding in this research is that impairment in consolidation is not homogeneous

across AD patients, with the MTA+ subtype showing more impairment than the non-MTA subtype.

In order to further understand the differences between AD groups for recognition and learning, we wanted to know which proportion of patients was performing on a pathological level across AD subtypes. Computed percentages representing AD patients performing under the clinical cut-offs show that the MTA+ group contain most of the clinically impaired subjects for both delayed recall and recognition, followed by MTA and then non-MTA. Of notice is that non-MTA shows the biggest drop down in percentage (see Δ-values in table 4), reflecting the percentage of patients that is able to benefit from additional help (recognition). Failure in long term storage of information is primarily associated with atrophy in the medial temporal lobe, and will therefore even with additional help not become present, simply because the information is not there to be recalled (Squire & Zola-Morgan, 1991). MTA and MTA+ showing the least benefit from additional help, is therefore in alignment with our expectations. Results on the non-MTA subtype suggest contribution of systems beyond the medial temporal lobe to the memory profile in a percentage of the patients.

Influence of other cognitive domains in learning

Learning in healthy controls was predicted by verbal fluency, which is representing cognitive control, recall strategies and mental flexibility. In addition to verbal fluency, learning in AD patients is also predicted by TMT B. Therefore, besides primary memory impairment in AD, part of decline in learning seems to be explained by failure to use executive mechanism to its full extent (Souchay, Moulin, Isingrini & Conway, 2008). Also access to the lexicon seem to play a role in learning (BNT) which seems reasonable since the RAVLT is a auditory/verbal learning test and word finding problems are acknowledged as a non-amnestic feature in AD according to the clinical diagnostic criteria (McKhann et al, 2011). Since healthy controls and AD patients are around the same mean age, this variety in word finding problems that are also a known feature for healthy elderly (Burke & Shafto, 2004), is quite unlikely to be assigned solely to normal cognitive decline.

Delayed recall is predicted in healthy controls by verbal fluency, the same predictors as for learning, and learning itself. This result is reasonable since how much is recalled in the delayed trial may depend on how much it was initially learnt, as well as some executive support. For the AD patients it is remarkable that better performance on TMT B results in lower performance on delayed recall. However, scores on TMT B are not reflecting/including the amount of errors that were made during the test. A higher score on TMT, being able to

finish the test in a shorter amount of time, may go together with more errors (inhibition). Not being able to inhibit during recall might cause problems with selecting the right words during recall resulting in a lower score. For delayed recall, age is identified as a confounder. However, since age is not influencing delayed recall for healthy controls, it could be that age in AD patients is more reflecting disease progression than actual aging: older patients reflecting further disease progression have more impairment, so also more problems in delayed recall.

Recognition in healthy controls is dependent on learning and delayed recall, as expected. Age is positive predictor (higher age, better recognition), although this result showed the lowest standardized regression coefficient in the model. Other predictors show unexpected outcomes: years of education are negative, meaning that less education goes together with better recognition. This seems contradictory since more education goes together with higher intelligence and therefore higher competence in learning because of more learning strategies in healthy persons. This result needs therefore further investigation in future research. For the AD-patients also an unexpected finding was found: lower performance on attention (digit forwards) leads to better recognition. Our hypothesis was that the more attention is paid, the better memory performance and therefore achievement in recognition. Hence, this result also needs of further investigation in future research.

Working memory is predicted by attention (digit forwards), in line with foregoing research about attention and working memory. The ability to retain information in an accessible state (working memory) is depending on the ability to selectively process information (attention). This is also acknowledged in the model about working memory of Baddeley, where the central executive, which is among other things responsible for selective attention and inhibition, plays an important supervisory role in working memory (Baddeley, Della Sala, Robbins & Baddeley, 1996*).* In the AD patients also performance on the TMT B seems to play a role. This represent among others task-switching ability, control influencing and cognitive control and might determine if the patient is able to process the chunks in time before new information comes in, reflecting workload. It might also reflect parts of working memory itself as well (Sánchez-Cubillo et al., 2009). Age is identified as a confounder, but again this might reflect disease progression more than actual aging. Of notice is that clock copy tests is identified as a significant predictor. This is against expectations since there are no visual or motoric components recruited when performing this task of working memory (digit backwards span). However, according to Price and collegues (2011), when copying a clock, there might be less demand on working memory than in the clock drawing command

condition, but there is still a need for inhibitory functions, visuoperception and visuospatial integration. Also other research has confirmed the relationship between executive functioning and visuospatial functions in clock drawing copy (Libon, Malamut, Swenson & Cloud 1996; Cosentino, Jefferson, Chute, Kaplan, & Libon., 2004). Consentino and collegues (2004) mention that patients with high white matter alterations performed worse in copy condition. This result could thus be interpreted also as large-scale alterations in AD as compared with healthy controls, and as reflected in AD subtypes including atrophy beyond the medial temporal lobe (MTA+ and non-MTA).

When integrating all the results discussed above, in almost every test, having MTA atrophy in combination with other atrophy (MTA+) seems to have the worse outcome. A relevant question here is whether this group is a different phenotype of AD or in reality is just a more progressed state of the disease, including bigger spread of atrophy through the brain. If this would be the case, one would expect this MTA+ group to have longer disease duration. However, this measure was not available for this research. Since longer disease duration usually correlates with older age, one would expect this MTA+ group to be significantly older than the other two groups. Our findings indicate that this seems to be the case. However, as said above, the ability to focus and sustain attention is usually only affected in later stages of the disease, but this does not seem the case for the MTA+ group, who are actually performing better on this test than the other groups. Our results do not allow to make a definitive conclusion and future research should focus on this, investigating disease-onset to ascertain whether the MTA+ group can be considered a different AD phenotype or simply an older expression of the disease.

Limitations

As mentioned before, the population reference group was not completely comparable to the healthy controls from ADNI due to small sample size, younger age and differences in the neuropsychological battery. However in this thesis, the population reference group fulfilled its purpose because it was not our aim to compare the population reference group directly with the ADNI cohort, but to gain some insight about memory profiles in order to hypothesize about what to expect and where to focus on in the ADNI cohort.

A more considerable limitation of this study is, as already mentioned, the high selectivity of the ADNI cohort. This has been recognized in previous studies (Brodaty et al 2014; Kawashima et al 2012). Participants had high average IQ and years of education and low average of GDS. As a result performances might be overstating compensatory

mechanisms, and understating actual reflection of impairment and there should therefore be caution in interpreting neuropsychological-structural relationships. Further, lack of longitudinal information prevented us to include valuable information that could have helped categorizing the subtypes clearer based on different trajectories along time. Also the healthy controls might show some distortion, since there could be participation bias. It sounds reasonable that the cohort might consist of a large group of people that have a family member suffering from AD, know the burden of the disease and are therefore motivated to be part of the study. As a result the group might for instance consist of a higher percentage of people that are APOE e4 positive causing the proportion of APOE e4 carriers to be unrealistic high and even influencing performances on the tests (Brodaty et al 2014; Kawashima et al 2012).

Another limitation of the study is that the patients' clinical diagnoses of AD have not been pathologically confirmed. This might raise the question if inaccuracies in diagnosis or the presence of coexisting pathology contributes or explains differences in memory profile. For example, mixed dementia is known to contribute quite often in AD (Zekry, Hauw & Gold, 2002), and as mentioned before, there could be some vascular involvement in the AD. Future research could focus on approaching the impact of vascular presence by checking white matter lesions on images when differentiating the subtypes. However, all patients met clinical criteria for AD.

A last limitation relies on the subtyping procedure for the AD patients. The rationale for subtyping AD in three groups as done in this research was due to several reasons. First of all, we had to keep in mind the data we were working with. The total AD group consisted out of fair number of participants, however when subtyping based on different atrophy patterns, very unequal and/or small group sizes appeared. Subtyping into groups based on MTA was the best option considering sample sizes and also found support in preceding research about the importance of MTA in AD (Jack et al., 1997; Decarli et al., 2007) and about categorizing MCI-patients in amnestic single and multiple domain as well as non-amnestic patients (Winblad et al. 2004). However, other subtyping strategies could be performed in which the focus can be more on other types of atrophy (e.g. frontal subtypes), or even on using other types of variables as a foundation for the subtyping. One example of another way of subtyping in this way, is as recently published in an article from Scheltens and colleagues (Scheltens et al., 2015). They subtyped their AD patients based on cognitive performance and explored the relationship with demographical and neurobiological characteristics. However, categorizing based on underlying biological characteristics might be of greater practicality

when searching for a cure for AD, since a potential medicine might possibly act upon them, rather than directly upon cognition. When in the future more data is available, research should focus on categorizing AD patients on other AD combinations, for example by focussing on frontal atrophy groups in addition to the MTA groups or focusing on just 'pure' AD forms (only frontal atrophy or only posterior atrophy). Further, as a first approach we used quantitative data, while qualitative data should also be used in future to possibly better understand the different phenotypes in the subtypes. For instance, information about learning should not be restricted to the number of errors made, but also the nature of the errors observed by the clinician. Errors could be due to perseverations or more based on phonological mistakes. Another example that can happen when not taking errors or qualitative information into account is that there could be a group of AD patients that in the recognition phase just say 'yes' to every word that is on the list and therefore are perceived as having a good recognition while this particular group could be suffering from an inhibition problem. Of course this approach goes together with his own restrictions, but it is something to take into consideration when trying to better understand the AD-subtypes. It might give extra valuable information that could also be of great importance to the clinicians.

Conclusion

In this research AD patients were subtyped based on their patterns of brain atrophy. Three subtypes were defined: the MTA subtype, reflecting a group of patients with only medial temporal atrophy; the MTA+ subtype, with not only medial temporal, but also frontal and posterior atrophy; and the non-MTA subtype, reflecting atrophy in brain regions other than in the medial temporal lobes. Strong relationships were found between the different memory components in healthy controls from both a population reference group and the highly selected ADNI cohort. However, greater influence of executive components were found in the ADNI cohort, possibly as part of compensatory processes, given the higher degree of education in ADNI as compared with the population reference group. Moreover, these associations are less specific in AD patients than in healthy controls, showing influence of other functions such as lexical access and visuospatial functions. Likewise, more functions and confounders play a role in delayed recall and recognition than in learning. Regarding the three AD subtypes, different memory profiles were found. The MTA+ subtype was the one showing worse learning capacity, with MTA and non-MTA subtypes evidencing comparable memory impairment. Differences between subtypes are magnified in recognition with the non-MTA performing better, then MTA and finally MTA+. Performance in working memory

was comparable. Finally, the non-MTA patients were those who had greater benefit from external help in memory retrieving. These findings shed new light on clinically different AD subtypes and might be of relevance for diagnosing AD, showing which cognitive variables are more impaired in which subtypes. Studying patterns of performance looking at multiple neuropsychological variables as well as influences between them might be of more clinical and research interest, rather than looking at performance in separated cognitive tests. As a result differentiation between subtypes can be done only when there is a full cognitive profile available. Focussing on other atrophy combinations and including qualitative information and more biological variables could give extra information in future research.

Implications

There is no cure found for AD yet, which might be due to the fact that AD is highly complex and shows heterogeneity across AD patients. Being able to subtype AD patients based on brain atrophy or other neurobiological factors is a step towards disambiguating the diagnosis of AD and finding a cure that acts upon different underlying biological characteristics of AD. This information will be necessary when developing personalised medicines or therapies in the future, but is also of importance for the understanding of the disease.

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Appendix

Demografisch en klinisch interview *Participantnr:*

1. Leeftijd
2. Geslacht
3. Geboorteplaats
4. Heeft u kinderen
5. Wat is uw hoogste opleidingsniveau? Heeft u dit afgerond?

6. Aantal scholingsjaren:

7. Volgt u een cursus of onderwijs op het moment?

8. Huidige baan/laatste baan:

9. Hoeveel uur per week:
10. Opleiding van ouders:
11. Wat doet u in uw vrije tijd? (cognitief stimulerend bezigheden die worden uitgevoerd buiten werktijd of onderwijs)

Voor de onderzoeker:

- Intellectuele activiteiten, sociale activiteiten, fysieke activiteiten.,
- Eventueel helpen met voorbeelden:
  lezen (hoeveel boeken per hoeveel tijd?), huiswerk, sudoko's, kaarten, gaan naar lokale evenementen, langsgaan bij vrienden/vrienden laten langskomen, autorijden, gebruik van nieuwe technologieën, tuinieren, handwerk, zorgen voor ouderen of kinderen, vrijwilligerswerk, artistieke activiteiten (muziek, schilderen), exposities/conferenties/concerten, vakantie, zorgen voor huisdieren, eigen boekhouding doen, andere bezoeken.
  Frequentie in termen van nooit, soms, vaak, altijd of in aantal keer per week/maand/jaar
  Voor hoeveel jaar doet u dit al?

12. Heeft u het gevoel dat u geheugenproblemen heeft? Voor hoe lang bestaan deze al? Is dat langer dan 6 maanden?

13. Hoe is uw algemene gezondheid? Zijn er ziektes bij uw gediagnosticeerd of heeft uw ziektes in het verleden gehad? (hersenziektes?)

14. Heeft u een geschiedenis van psychologische of psychiatrische problemen? Bent u daarvoor behandeld?

15. Gebruikt uw medicijnen? Zo ja welke?

16. Drinkt u alcohol? Zo, ja hoe veel en hoe vaak?
17. Gebruikt u drugs?
18. Rookt u? Hoe vaak?
19. Is er een geschiedenis van Alzheimer of een andere vorm van dementia aanwezig in uw familie?

20. Heeft u ooit traumatische hersenletstel gehad door een klap op het hoofd of een herseninfarct of bloeding gehad?

Functional Activities Questionnaire

Testafname

Bevraag de informant om de patiënt zijn of haar vaardigheden te beoordelen volgens het volgende scoringssysteem:

- Afhankelijk = 3
- Vereist enige assistentie = 2
- Heeft moeite, maar doet het zelf = 1
- Normaal = 0
- Heeft de activiteit nooit gedaan, maar zou het wel kunnen doen nu = 0
- Heeft de activiteit nooit gedaan, maar zou er nu moeite mee hebben = 1

1. Betalen van rekeningen, boekhouding bijhouden	
2. Het samenvoegen van belastingbrieven, werkzaken of papieren	
3. Alleen winkelen voor kleding, huishoudelijke noodzakelijkheden of boodschappen	
4. Een spel spelen of een hobby uitvoeren	
5. Water koken, koffiezetten, de oven of het gas uitzetten na gebruik	
6. Het klaarmaken van een gebalanceerde maaltijd	
7. Bijhouden van huidige gebeurtenissen	
8. Aandacht hebben voor, het begrijpen of bediscussiëren van TV, boeken of tijdschriften	
9. Het onthouden van afspraken, familie gebeurtenissen, vakanties en medicijnen	
10. Het verlaten van de buurt, zelf rijdend of het regelen van vervoer daarvoor	
Totale score:	

Evaluatie

Tel de scores op (variërend van 0 - 30). Cut-point van 9 (afhankelijk in 3 of meer activiteiten) is aangeraden om verslechterde functie en mogelijk cognitieve verslechtering aan te kunnen duiden.

Nederlandse vertaling van:

Pfeffer, R.I., Kurosaki, T.T., Harrah, C.H. Jr., Chance, J.M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *Journal of Gerontology, 37*(3), 323-329.

Informatiebrief: Het verband tussen (geheugen)klachten in verschillende vormen van Alzheimer en de toestand van de hersenen.

Beste vrienden, familie en/of kennissen,

Met behulp van deze informatiebrief zal u worden ingelicht over de inhoud van een onderzoek, waaraan ik u graag wil vragen om mee te doen. Mocht u aan het einde van deze brief nog vragen hebben, neemt u dan contact met mij op via telefoon (06-55936012) of e-mail (c.verhagen@students.uu.nl). Zoals u misschien al weet, moet ik voor mijn masteropleiding Neuropsychologie aan de Universiteit Utrecht een onderzoek opzetten en uitvoeren. Hiervoor zal ik onder andere een aantal maanden (04/05 – 04/08) naar Zweden vertrekken. Het onderzoek zal gaan over de ziekte van Alzheimer. Een ziekte die kwaliteit van leven voor zowel patiënt als omgeving erg kan beperken. Ik wil graag een gezonde groep mensen testen op een aantal vaardigheden, zodat ik die kan vergelijken met de vaardigheden van Alzheimer patiënten. Deze brief zal u hierover verder inlichten.

Doel van het onderzoek
Een van de kenmerken van de ziekte van Alzheimer is dat er uitdunning van de hersenen plaatsvindt (ook wel atrofie genoemd). Dit gebeurt op specifieke plekken. Waar deze uitdunning plaats vindt, verschilt per patiënt. U kunt zich voorstellen dat wanneer er uitdunning voor in het hoofd plaatsvindt, dit andere gevolgen voor iemands gedrag zal hebben dan wanneer het achter in het hoofd plaatsvindt. Met dit onderzoek wil ik een verband zoeken tussen de (geheugen)klachten die Alzheimerpatiënten hebben en de toestand van de hersenen op basis van hersenscans.

Waarom ik het erg fijn zou vinden als u mee wilt doen
Voor mijn onderzoek moet ik zelf neuropsychologische tests afnemen bij mensen. Neuropsychologische tests zijn tests die de relatie tussen de werking van de hersenen en het gedrag onderzoeken. Een voorbeeld van een neuropsychologische test is bijvoorbeeld een natekentest om te controleren of uw zicht nog goed is. Ik wil een aantal van deze soort tests in Nederland afnemen, bij een gezonde groep van ongeveer 25 deelnemers in de leeftijdscategorie 55-90 jaar. Ik wil daarvoor u, als gezonde deelnemer graag testen. De tests die ik bij u af zal nemen zijn: een woordentest, een aandachtstest en een test waarbij u zal moeten tekenen. Verder zal ik een aantal vragenlijsten bij u afnemen. Ik kom de tests bij u thuis afnemen in een rustige ruimte, zodat u nergens naar hoeft af te reizen. Het afnemen van de tests zal ongeveer een uur in beslag nemen. Mocht u tijdens het afnemen

van de tests om welke reden dan ook niet meer door willen gaan, dan mag u zich terugtrekken uit de deelname. U hoeft hiervoor geen reden aan te geven. Stoppen mag dus altijd.

Anonimiteit
Uw gegevens en uw resultaten uit de tests worden anoniem verwerkt. Dat klinkt natuurlijk raar omdat ik weet wie u bent. Anonieme verwerking houdt in dat vanaf het moment dat de resultaten in de computer worden gezet, uw naam wordt losgekoppeld van uw gegevens en resultaten. U wordt hierdoor eigenlijk enkel een cijfertje. Dit cijfertje is niet meer terug te herleiden aan uw naam. Er staat dan bijvoorbeeld: dit zijn de resultaten van nummer 18 en **niet**: dit zijn de resultaten van Jantje Jansen of Betje van Boekel.

Op de volgende pagina staan nog een aantal vragen die bij het lezen van deze brief eventueel bij u opgekomen kunnen zijn. Neem deze nog even rustig door. Lees daarna het toestemmingsformulier. Hierop staan een aantal stellingen waarmee u akkoord moet gaan voordat ik u mag meedoen aan mijn onderzoek. Ik neem over ongeveer een week contact met u op om te vragen of u mee wilt doen. Mocht u voor die tijd nog vragen hebben, neemt u dan gerust contact met mij op.

Ik hoop graag binnenkort uw formulieren in ontvangst te mogen nemen. Alvast bedankt voor uw moeite en tijd,

Met vriendelijke groet,

Chloë Verhagen
Telefoonnr.: 06-55936012
E-mailadres: c.verhagen@students.uu.nl

Vraag en antwoord:

1. *Wat ga je precies met mijn resultaten doen?*

Ik zal uw resultaten gaan vergelijken met de resultaten van Alzheimer patiënten. Om te kunnen zeggen dat iemand ziek is (Alzheimer patiënten) moet ik namelijk ook weten wanneer iemand gezond is (in dit onderzoek bent u dat). De resultaten van de Alzheimer patiënten zijn al verzameld. Het is onderdeel van een heel groot resultatenarchief (ADNI: Alzheimer 's Disease Neuroimaging Iniative). Deze is speciaal samengesteld zodat onderzoekers die kunnen gebruiken bij hun eigen onderzoek naar de ziekte van Alzheimer. Ook ik zal hier dus gebruik van gaan maken voor mijn masteronderzoek.

2. *Er wordt in de informatiebrief gezegd dat er gekeken zal worden naar verschillen in de hersenen met behulp van hersenscans. Heb je geen hersenscans van mijn hersenen nodig?*

Ik gebruik alleen hersenscans van de hersenen van Alzheimerpatiënten. Ik heb geen scans nodig van uw hersenen. Op basis van de resultaten van de tests en vragenlijsten die ik bij u zal gaan afnemen, neem ik aan dat u goed functioneert en hoogstwaarschijnlijk geen ziekte van Alzheimer heeft. Hierbij neem ik aan dat u over een gewoon gezond stel hersens bezit.

3. *Er wordt aangegeven dat wij worden gezien als gezonde groep deelnemers. Hoe weet je dat ik gezond ben en wat verstaat je onder gezond?*

In dit onderzoek bent u 'gezond' als er geen (hersen)ziekte of hersenbeschadiging bij u is vastgesteld die invloed kan hebben op de resultaten.
Om in kaart te brengen hoe uw huidige gezondheid is, zal ik voor aanvang van de tests een korte vragenlijst afnemen. Hierin staan vragen zoals: 'Is de ziekte van Alzheimer in uw familie aanwezig?' en 'Heeft u ooit een hersenbeschadiging opgelopen door een klap op het hoofd?' Hierna zal ik waarschijnlijk alsnog de tests afnemen. Het voorgaande hoeft namelijk helemaal niet te betekenen dat u slechter presteert op taken. Doordat u het aangeeft in de vragenlijst kan ik het echter wel altijd meenemen in de resultaten.

4. *Mocht er nu opeens uit dit onderzoek naar voren komen dat ik de tests slecht heb gemaakt, wordt ik hierover dan ingelicht?*

Aangezien ik nog student ben, mag ik geen conclusies trekken op basis van uw gegevens. Bij het stellen van diagnoses is de klinische blik van een gekwalificeerde neuropsycholoog ontzettend belangrijk. U kunt zich voorstellen dat een slechte prestatie op een geheugentest, niet hoeft te zeggen dat u een slecht geheugen heeft. Slechte prestaties kunnen bijvoorbeeld ook voortkomen uit een slechte concentratie, een stressvolle dag of verkeerde afname door mij. U heeft echter wel recht op inzage van uw eigen resultaten. Het kan natuurlijk zo zijn dat u zich los van mijn onderzoek al zorgen maakt over uw geheugen. U zou dan alsnog kunnen beslissen of u zich een keer wil laten testen door een echte neuropsycholoog. Dit doet u door een afspraak te maken met de huisarts. Die kan u daarna doorverwijzen.

5. *Er is al veel onderzoek gedaan naar Alzheimer. Wat is er nieuw aan dit onderzoek?*

Het klopt inderdaad dat er al een heleboel bekend is over de gevolgen van Alzheimer in de hersenen. Er is echter nog niet goed onderzocht welke atrofie (uitdunning in de hersenen) op welke plek samengaat met welke (geheugen)klachten bij Alzheimer. Hierdoor verschilt dit onderzoek van andere onderzoeken.

6. *Wat is precies de meerwaarde van dit onderzoek voor de samenleving?*

De meerwaarde van dit onderzoek zit hem vooral in dat het onderzoek bijdraagt aan de opbouw van kennis over de ziekte van Alzheimer. U moet zich bedenken dat elk onderzoek maar een klein onderdeeltje is van een groter geheel. Ook dit onderzoek is een klein onderdeel in een lijn van onderzoeken. Deze lijn van onderzoeken moet uiteindelijk tot gevolg hebben dat Alzheimer in vroegere stadia bij mensen kan worden vastgesteld en uiteindelijk behandeld kan worden.

7. *Mochten er bij u op basis van deze vraag-en-antwoordbrief nog andere vragen zijn opgekomen, neemt u dan contact met mij op. Ik sta u graag te woord!*

Toestemmingsformulier:

De link tussen verschillende vormen van Alzheimer en de verschillen op basis van structuur in de hersenen.

Bij het tekenen van deze brief ga ik akkoord met het volgende:

Ik heb de informatiebrief voor de proefpersoon gelezen. Ik kon aanvullende vragen stellen. Mijn vragen zijn genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.

Ik weet dat meedoen helemaal vrijwillig is. Ik weet dat ik op ieder moment kan beslissen om toch niet mee te doen. Daarvoor hoef ik geen reden te geven.

Ik weet dat sommige mensen mijn onderzoek mijn gegevens kunnen zien, maar dat deze gegevens niet gekoppeld zijn aan mijn naam en ik dus anoniem zal blijven.

Ik weet dat er op basis van dit onderzoek geen conclusies getrokken mogen worden, maar ik heb nog steeds recht op inzage van mijn resultaten.
☐ ja ☐ nee

Ik geef toestemming om mijn gegevens te gebruiken, voor de doelen die in de informatiebrief staan.

Ik wil een beknopte uitslag van het onderzoek op groepsniveau ontvangen als deze is afgerond.
☐ ja ☐ nee

Ik ga akkoord met deelname aan dit onderzoek.
Naam proefpersoon:
Handtekening: Datum : __ / __ / __

IN TE VULLEN DOOR DE ONDERZOEKER:
Ik verklaar hierbij dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.
Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.
Naam onderzoeker:
Handtekening: Datum: __ / __ / __

ADNI neuropsychological battery

Click on this page to open PDF-file.

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Cognitive Testing

Screening Visit
Order of Assessment

1. MMSE
2. Logical Memory IA
3. Logical Memory IIA