A cognitive perspective on clinical manifestations of Alzheimer s disease

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Trajectories of cognitive decline in different types of dementia

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Abstract

Objective: To investigate trajectories of cognitive decline in patients with different types of dementia compared to controls in a longitudinal study.

Methods: In 199 patients with Alzheimer's disease (AD), 10 vascular dementia (VaD), 26 dementia with Lewy bodies (DLB), 20 behavioural variant frontotemporal dementia (bvFTD), 15 language variant frontotemporal dementia (lvFTD) and 112 controls we assessed five cognitive domains: memory, language, attention, executive and visuo-spatial functioning and global cognition (Mini-Mental State Examination: MMSE). All subjects had at least two neuropsychological assessments (median 2, range 2-7). Neuropsychological data were standardized into z-scores using baseline performance of controls as reference. Linear mixed models were used to estimate baseline cognitive functioning and cognitive decline over time for each group, adjusted for age, gender and education.

Results: At baseline, patients with dementia performed worse than controls in all cognitive domains ($p<0.05$), except visuo-spatial functioning, which was only impaired in patients with AD and DLB ($p<0.001$). During follow-up, patients with AD declined in all cognitive domains ($p<0.001$). DLB showed decline in every cognitive domain except language and MMSE. bvFTD showed rapid decline in memory, language, attention and executive functioning (all $p<0.01$), while visuo-spatial functioning remained quite stable. lvFTD declined mostly in attention and executive functioning ($p<0.01$), while VaD showed decline in attention and executive functioning.

Conclusion: We show cognitive trajectories of different types of dementia. These estimations of natural disease course have important value for the design of clinical trials as neuropsychological measures are increasingly being used as outcome measures.

Introduction

The most common causes of dementia are characterised by specific profiles of cognitive impairment. Alzheimer's disease (AD) is characterized by prominent episodic memory impairment, while in other types, other domains are more primarily affected, i.e. executive functioning in vascular dementia (VaD) [1].

Trajectories of cognitive decline in different types of dementia in a single cohort have hardly been studied. Most studies were not longitudinal, which limits interpretation of results. Studies with a longitudinal set-up were frequently limited to the Mini-Mental State Examination (MMSE) as a cognitive measure [2,3]. Since the MMSE is a global screening test, no domain specific conclusions can be drawn. Furthermore, the single focus of most studies is AD instead of various types of dementia, making it hard to compare different types of dementia.

Two earlier longitudinal studies investigated decline on several neuropsychological tests in various types of dementia [4,5]. One study focussed on semantic memory tests and used patients with semantic dementia as a reference group [4]. They found that all types of dementia performed worse than controls and AD showed a similar, but milder pattern of impairment of semantic memory than as semantic dementia. The other study focused on three domains; executive functioning, language and visuo-construction in four subtypes of frontotemporal lobar degeneration (FTLD). They concluded that diverse neuropsychological patterns of FTLD-subtypes continue to exist [5].

We investigated decline in global cognition and five cognitive domains for five types of dementia compared to controls. We aimed to provide better insight in the trajectories of cognitive decline over time in different types of dementia. We expected that every type of dementia would particularly show decline in those cognitive domains that are associated with the brain areas most prominently involved in each type of dementia.

Methods

Subjects

We included 270 patients with a diagnosis of dementia and at least two visits including neuropsychological evaluations (baseline and follow up) from the Amsterdam Dementia Cohort at the Alzheimer Center of the VU University Medical Center Amsterdam, between January 2004 and December 2011 [6]. Patients with available follow-up were younger (65±8 versus 69±9), less often female (41% versus 51%), had higher education (5±1 versus 4.7±1), had higher MMSE-scores (22±4 versus 19±6) than 384 persons who presented during the same time period, but who received no follow-up (all $p<0.05$).

All patients underwent a standardized one-day assessment including medical history, informant-based history, physical and neurological exam including Clinical Dementia Rating, neuropsychological assessment and the Geriatric Depression Scale (GDS), laboratory tests, magnetic resonance imaging of the brain and electroencephalogram. The duration of the cognitive complaints as reported by the patient and / or caregiver was recorded to estimate the disease duration at time of diagnosis. Diagnoses were made in a multidisciplinary consensus meeting using international diagnostic consensus criteria. For a diagnosis of probable AD (N=199) patients had to fulfil the diagnostic criteria of McKhann [7,8], for vascular dementia (VaD), (N=10) the NINDS-AIREN criteria [9], for DLB (N=26) the criteria of McKeith [10], for behavioural variant frontotemporal dementia (bvFTD) (N=20) the criteria of Neary or Rascovsky [11,12] and for language variant frontotemporal dementia (lvFTD; N=15, including nonfluent progressive aphasia (N=7) and semantic dementia (N=8)) the criteria of Neary or Gorno-Tempini [11,13].

In addition, we included 112 patients with subjective complaints who served as controls. Patients were considered to have subjective cognitive complaints when they had normal laboratory investigations and did not have other known causes of cognitive complaints. Their performances on neuropsychological tests, corrected for age, education or sex, were normal. Furthermore, patients with subjective complaints were only included when they did not progress to MCI or dementia within the study period. Pharmalogical treatment for dementia was registered: 11 patients with AD used Galantamine and 16 patients were treated with Rivastigmine (12 AD, 3 DLB and one bvFTD). Level of education was classified according to the system of Verhage ranging from 1 to 7 (low to highly educated) [14]. The local Medical Ethics Committee approved the study and all patients gave written informed consent for their clinical data to be used for research purposes.

Neuropsychological assessment

Cognitive functions were assessed with a standardized test battery. We used the MMSE as a measure for global cognitive decline [15]. For memory, we used the Visual Association Test (VAT) and total immediate recall and delayed recall of the Dutch version of the Rey auditory verbal learning task (RAVLT) [16-18]. To examine language, we used VAT naming, category fluency (animals), the Dutch version of Controlled Oral Word Association Test (COWAT) (letter fluency), comparative questions and the naming condition of the Arizona Battery for Communication Disorders (ABCD) [18-21]. For attention we used Trail Making Test (TMT) A and the forward condition of Digit Span (extended version) [22,23]. We used TMT B, the backwards condition of Digit Span (extended version) and the Frontal Assessment Battery (FAB) to examine executive functioning [22-24]. We used three subtests of the Visual Object and Space Perception Battery (VOSP) to assess visuo-spatial functioning, namely (i) incomplete letters, (ii) dot counting and (iii) number location [25]. TMT A and B scores were log-transformed because they were not normally distributed. TMT A and B scores were inverted by computing the score by -1, because higher scores imply a worse performance. There was variability in the number of completed

neuropsychological tests. In total, the number of completed tests on baseline and follow up ranged from 931 (DS forward) to 602 (comparative questions).

Follow up

All subjects in this cohort (N=382) underwent follow-up, including physical and neurological exam, and a repeated neuropsychological evaluation. For the total sample, the median of the number of neuropsychological assessments was 2 (range 2-7) and the mean duration of follow-up was 1.5±0.8 years.

Statistical analysis

PASW Statistics 19.0 for Mac was used. For baseline demographics and raw neuropsychological data χ^2-tests, independent samples T-test and univariate analysis of variance (ANOVA) were performed when appropriate. ANOVA's were conducted with diagnosis as between-subjects factor and neuropsychological test as dependent variable. Sex, age and education were entered as covariates.

To obtain unbiased estimation of cognitive domain scores, we imputed missing neuropsychological test scores by multiple imputation of individual test scores in PASW. The method we used was predictive mean matching, because of the non-Gaussian distribution of some of the tests. Predictors for imputation were age (at time of neuropsychological assessment), gender, education, diagnosis, CDR-score, GDS-score and all available neuropsychological tests. Fifteen imputed data sets were created. Neuropsychological baseline data of controls were standardized into z-scores and based on these z-scores, we calculated compound z-scores for memory, language, attention, executive functioning and visuo-spatial functioning for each imputed dataset. Next, we computed z-scores relative to the baseline z-scores of controls for follow-up of controls and for baseline and follow-up for all dementia groups. We report pooled statistics over 15 imputed data sets.

Linear mixed models were used to assess associations between diagnosis and baseline cognition and cognitive performance over time. We used an unstructured covariance pattern because it has increased statistical power as it accounts for within-person correlation over time, allows inter-individual differences in number of assessments and differences in time between assessments. The model included terms for diagnosis, time and the interaction between diagnosis and time. Random effects were subject-ID and time. Beta±SE for diagnosis represents the association between the diagnosis and baseline cognitive performance, whereas the interaction between diagnosis and time represents the association between diagnosis and cognitive performance over time. Controls were used as a reference group. Outcome measures were compound z-scores and MMSE. All analyses were adjusted for age, gender and education. Data are presented as unadjusted beta±SE with p-values of the adjusted models. We repeated the analyses without the patients who were on pharmalogical treatment for dementia. For main effects, the significance level was set at $p<0.05$ and for interactions at $p<0.10$.

Results

Table 1 summarizes the baseline demographics of the diagnostic groups. In general, patients were older (65±8 years) and lower educated (5.0±1) than controls (61±8 and 5.5±1; both p<0.001). On the MMSE, patients with dementia scored lower than controls (all p<0.05). Patients with AD had the lowest MMSE-score (22±4). Table 2 lists the raw baseline neuropsychological test performance of controls and patients with different types of dementia. We conducted linear mixed models to compare the trajectories of cognitive decline as measured by a comprehensive neuropsychological test battery between patients with different types of dementia and controls. For the estimated effects, see table 3. In general, patients with a diagnosis of dementia performed worse than controls at baseline on all cognitive domains, except for visuo-spatial functioning, which was only impaired in AD and DLB.

Table 1. Baseline demographics of diagnostic groups.

	Controls	**AD**	**VaD**	**DLB**	**bvFTD**	**lvFTD**
N+	112	199	10	26	20	15
Age	61±8[bcd]	65±8	67±5	66±9	63±8	63±8
Sex, female	63 (56%)	98 (49%)	4 (40%)	0(0%)[acbef]	6 (30%)[ab]	3 (20%)[ab]
Education#	5.5±1.1	4.9±1.2[a]	4.5±2.1[a]	5.2±1	5±1.3	4.8±1[a]
Complaints, y	3.9±4[b]	3.1±2	3.7±2	3.4±2	3.9±4	3.1±1
No. of NPE	2 (2-7)	2 (2-4)	2 (2-3)	3 (2-5)	3 (2-5)	3 (2-4)
FU duration, y	1.6±1	1.5±0.7	1.4±0.7	1.7±0.9	1.6±0.9	1.5±0.8
CDR	0±0	1±0.4[ad]	1±0.3[a]	1±0.3[a]	1±0.5[a]	1±0.5[a]
GDS	2±2	2±2	3±2	4±3[abe]	2±2	3±3

Values are presented as mean±standard deviation, number (percent) or median (range).

= according to the Verhage-system, Complaints = years of reported cognitive complaints; an estimation of disease duration, NPE = neuropsychological examination, FU duration = Follow-up duration in years, CDR = Clinical Dementia Rating, GDS = Geriatric Depression Scale, MMSE = Mini-Mental State Examination, AD = Alzheimer's disease, VaD = Vascular Dementia, DLB = Dementia with Lewy Bodies, bvFTD = behavioural variant frontotemporal dementia, lvTD = language variant frontotemporal dementia.

a = significant difference p<0.05 compared to controls, b = significant difference p<0.05 compared to AD, c = significant difference p<0.05 compared to VaD, d = significant difference p<0.05 compared to DLB, e = significant difference p<0.05 compared to bvFTD, f = significant difference p<0.05 compared to lvFTD.

Table 2. Baseline raw neuropsychological test performance of diagnostic groups.

	Controls	AD	VaD	DLB	bvFTD	lvFTD
N+	112	199	10	26	20	15
MMSE	28±1	22±4[acdef]	25±4[a]	23±3[ae]	26±3[a]	24±3[a]
Memory						
VAT	12±0.5	6±4[acdef]	11±1	10±2[a]	11±2	10±3[a]
RAVLT total immediate recall	40±9	23±8[ae]	23±10[ae]	24±8[ae]	34±11[a]	25±6[ae]
RAVLT delayed	8±3	2±3[ade]	4±4[a]	4±3[a]	5±4[a]	3±2[ae]
Language						
VAT naming	12±0.2	11±2[a]	12±0.9	12±0.6	11±2[ad]	8±3[abcde]
ABCD naming	19±1	16±3[a]	18±1	17±2[a]	13±6[abcd]	10±5[abcde]
Comparative questions	6±0.4	5±1[a]	5±1	5±1[a]	5±1[a]	6±0.4
Animal fluency	23±6	13±5[a]	10±6[a]	13±5[a]	12±5[a]	11±7[a]
Letter fluency	38±11	26±12[a]	17±8[ab]	23±11[ab]	21±10[a]	18±11[ab]
Attention						
Digit span forward	13±3	11±3[a]	10±2[a]	11±3	12±2	12±3
TMT a §	38±14	90±68[aef]	87±64[a]	87±41[aef]	53±22	48±24
Executive functioning						
Digit span backwards	9±2	7±3[aef]	6±3[ae]	6±2[aef]	8±3	8±2
TMT b §	87±28	205±112[aef]	216±77[aef]	213±90[aef]	120±39	138±63
FAB	17±2	12±4[a]	14±3[a]	12±4[a]	14±2[a]	14±2[a]
Visuo-spatial functioning						
Frag. Letters	19±0.8	16±5[af]	18±1	15±4[aef]	18±3	19±1
Dot Counting	10±0.4	9±2[af]	9±1	9±1	10±0.5	10±0
Number location	9±1	8±2[acef]	9±1	8±1[acef]	9±1	10±0.6

Values are presented as mean±standard deviation, number (percent) or median (range). Cognitive profiles are divided into neuropsychological tests. + = N differs for every neuropsychological test since raw data are presented, § = higher scores means worse performance, MMSE = Mini-Mental State Examination, VAT = Visual Association Test, RAVLT = Rey auditory verbal learning task, ABCD = Arizona Battery for Communication Disorders, TMT = Trail Making Test, FAB = Frontal Assessment Battery, AD = Alzheimer's disease, VaD = Vascular Dementia, DLB = Dementia with Lewy Bodies, bvFTD = behavioural variant frontotemporal dementia, lvTD = language variant frontotemporal dementia.

a = significant difference $p<0.05$ compared to controls, b = significant difference $p<0.05$ compared to AD, c = significant difference $p<0.05$ compared to VaD, d = significant difference $p<0.05$ compared to DLB, e = significant difference $p<0.05$ compared to bvFTD, f = significant difference $p<0.05$ compared to lvFTD.

Table 3. Estimated effect of diagnosis on baseline- and annual change in MMSE score and compound scores for different cognitive domains.

	MMSE	Memory	Language	Attention	Executive functioning	Visuo-spatial functioning
Baseline cognitive score						
Controls°	0.02±0.2	-0.02±0.2	0.0±0.2	-0.01±0.1	0.01±0.1	-0.01±0.2
AD	-4.9±0.2***	-5.0±0.5***	-1.9±0.2***	-1.4±0.1***	-2.4±0.1***	-1.8±0.3***
VaD	-2.9±0.8**	-1.5±0.7*	-1.9±0.7**	-1.5±0.3***	-2.4±0.4***	-1±0.7
DLB	-3.5±0.5***	-2.4±0.5***	-1.3±0.4**	-1.3±0.2***	-2.6±0.3***	-1.5±0.5**
bvFTD	-1.6±0.6**	-1.2±0.5*	-2.6±0.5***	-0.7±0.2**	-1.2±0.3***	-0.4±0.4
lvFTD	-2.9±0.6***	-2.1±0.6***	-5.7±0.7***	-0.3±0.3	-1.2±0.3**	-0.2±0.5
Annual cognitive change						
Controls°	0.1±0.2	0.1±0.1	-0.1±0.1	0.1±0.1	0.04±0.1	0.004±0.1
AD	-1.4±0.1***	-0.9±0.1***	-0.8±0.1***	-0.4±0.04***	-0.5±0.1***	-0.8±0.2***
VaD	0.4±0.6	-0.6±0.4	0.03±0.5	-0.2±0.2*	-0.4±0.2*	-0.2±0.4
DLB	-0.1±0.4	-0.8±0.3**	-0.3±0.3	-0.3±0.1**	-0.3±0.1*	-0.6±0.2*
bvFTD	-1.8±0.4***	-1.8±0.3***	-2±0.4***	-0.3±0.1**	-0.7±0.1***	-0.4±0.3
lvFTD	-0.6±0.5	-0.4±0.3	-1±0.5*	-0.4±0.1**	-0.6±0.2**	-0.4±0.4

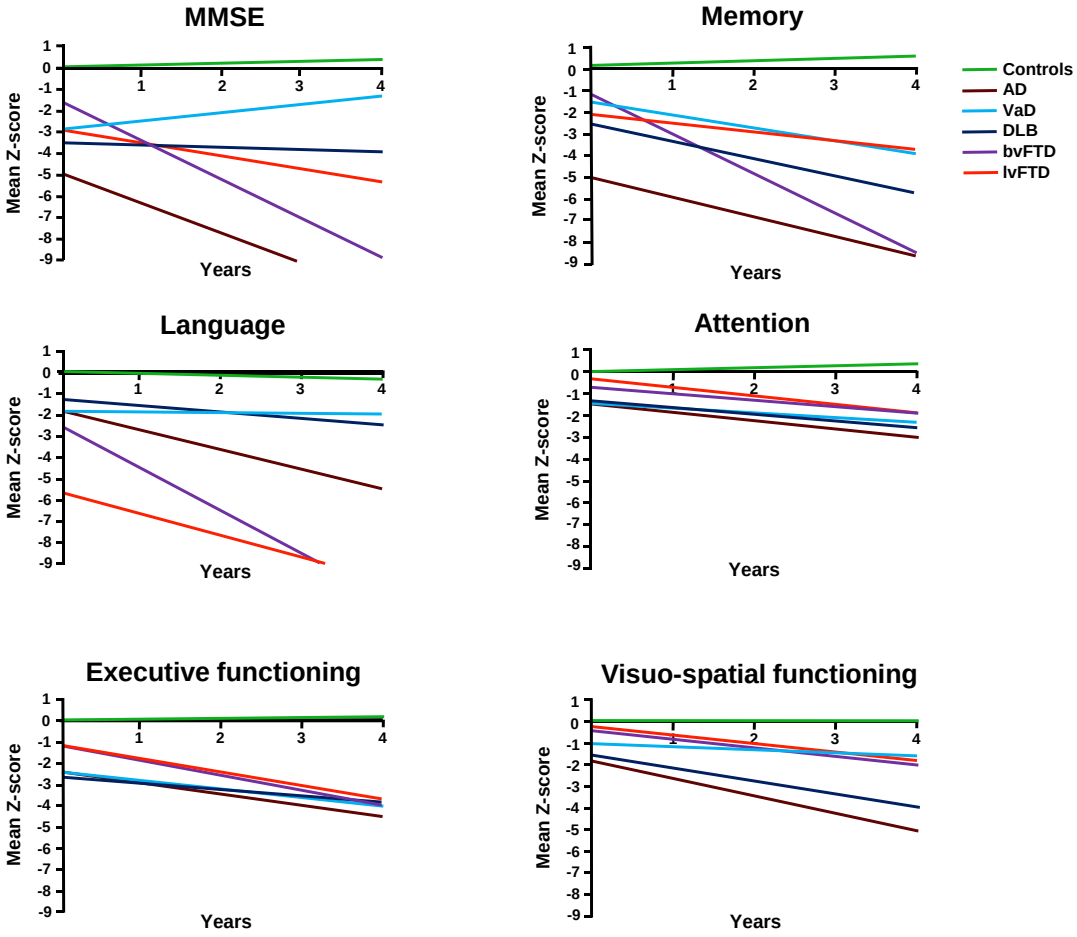
Data are presented as Beta(standard error). Beta's represent uncorrected estimated baseline performance or estimated change over time for the diagnoses compared with performance of controls at baseline. P-values for differences with controls are given for the models corrected for age, gender and education.

° Reference group, AD = Alzheimer's disease, VaD = Vascular Dementia, DLB = Dementia with Lewy Bodies, bvFTD = behavioural variant frontotemporal dementia, lvFTD = language variant frontotemporal dementia.

*p<0.05 for main effect; p<0.10 for interaction, **p<0.01, ***p<0.001.

Figure 1 visualizes the trajectories of decline for each of the cognitive domains. Regarding global cognition we found that over time, patients with AD and bvFTD declined faster than controls, while patients with VaD, DLB and lvFTD did not. On memory, patients with AD, DLB and bvFTD declined faster over time than controls, while patients with VaD and lvFTD did not. For language, patients with AD, bvFTD and lvFTD declined faster over time than controls, while patients with DLB and VaD did not. We found a significant decline over time for attention in all patients with dementia. Regarding executive functioning, patients with dementia declined over time compared to controls. On visuo-spatial functioning only patients with AD and DLB declined over time. When we repeated the analyses without the patients using pharmalogical treatment for dementia, results remained essentially unchanged. Table 4 summarizes the estimated annual cognitive decline for the different dementia groups, compared to controls in schematic overview.

Figure 1. Estimated cognitive performance over time compared with baseline z-scores of controls.



Lines represent beta's as presented in table 3.
AD = Alzheimer's disease, VaD = Vascular Dementia, DLB = Dementia with Lewy Bodies, bvFTD = behavioural variant frontotemporal dementia, lvFTD = language variant frontotemporal dementia.

Table 4. Schematic overview of estimated trajectories of cognitive decline for patients with dementia, compared to controls.

	AD	VaD	DLB	bvFTD	lvFTD
MMSE	↓	-	-	↓↓	-
Memory	↓	-	↓	↓↓	-
Language	↓	-	-	↓↓	↓
Attention	↓	↓	↓	↓	↓
Executive functioning	↓	↓	↓	↓	↓
Visuo-spatial functioning	↓	-	↓	-	-

MMSE = Mini-Mental State Examination, AD = Alzheimer's disease, VaD = Vascular Dementia, DLB = Dementia with Lewy Bodies, bvFTD = behavioural variant frontotemporal dementia, lvFTD = language variant frontotemporal dementia

↓ = significant annual decline $p<0.10$

↓↓ = significant annual decline $p<0.05$ and > 1.5 z-score annual decline

This table is based on the estimated annual cognitive change in table 3. Patients with AD showed decline on all cognitive domains with fastest decline on global cognition. Patients with VaD showed slight decline in attention and executive functioning. For DLB, we found decline over time in memory, visuo-spatial functioning, attention and executive functioning. bvFTD showed fast decline in global cognition and all cognitive domains, with the exception of visuo-spatial functioning. For lvFTD, we found decline in language, executive functioning and attention.

Discussion

In this prospective longitudinal study in a large sample of patients with different types of dementia, we found that during an average follow-up time of 1.5 years, patterns of cognitive decline differed between patient groups according to type of dementia. Patients with AD declined in all cognitive domains, while patients with bvFTD showed fastest decline over time. Patients with VaD showed decline in attention and executive functioning. Patients with lvFTD showed most decline in attention and executive functioning, while patients with DLB showed decline over time in several cognitive domains.

bvFTD is neuropsychologically characterized by executive dysfunction with relative sparing of memory and visuo-spatial functions [26]. The presence of this cognitive profile however is not required according to the revised diagnostic criteria for bvFTD [12]. Although it has often been reported that memory is relatively spared in bvFTD, prominent amnestic symptoms are present in a subgroup of elderly bvFTD patients [12]. In our study, executive dysfunction was not the only hallmark of bvFTD; we showed that baseline performance on almost every cognitive domain in bvFTD was worse compared to controls, with most pronounced language impairment. This striking language impairment might be due to fluency tasks that were included in the language domain [26]. Fluency tasks appeal both language and executive functioning and therefore one can debate how to interpret fluency tasks. As expected, lvFTD was at baseline most impaired in language [1,27], which declined further over time. In bvFTD and lvFTD visuo-spatial functioning was relatively preserved and showed limited decline over time [1,27]. This might be due to the sparing of anatomical regions associated with visuo-spatial abilities, i.e. the parieto-occipital lobes [28]. bvFTD showed the fastest decline of all investigated types of dementia, in all cognitive domains except visuo-spatial functioning. A former study showed a faster rate of cognitive decline and shorter survival in FTD compared to AD [29]. In our study bvFTD patients also showed faster cognitive decline than AD patients. However, the duration of illness seems to be wide in FTD; ranging from 2-20 years [26].

DLB is characterized by visuo-spatial and executive impairment, which is present early in the disease course [1]. We found that, at baseline, patients with DLB showed most severe impairment on memory and executive functioning. Over time, visuo-spatial functioning declined fastest after memory. We did not find pronounced impairment in attention in DLB, compared to the other types of dementia. Literature suggests that differences only can be found on more complex attentional tasks [1]. Perhaps the tasks we used were not sensitive enough. It is often thought that DLB is one of the fastest declining types of dementia, but our findings do not support this idea and earlier results seem conflicting [30,31]. We observed decline in most cognitive domains, but the rate of decline is not strikingly faster than in other types of dementia. An explanation could be that patients who declined too fast were lost to follow-up, and as a result we saw only the milder subgroup.

Memory impairment and executive dysfunction are well-known early features of AD [1]. In addition, we found more frank visuo-spatial impairment in AD. This could be due to the relatively young age of our patients with AD. Patients with AD and an earlier age of onset have more often posterior brain damage, including atrophy and functional brain changes [32,33]. We found that patients with VaD showed decline in attention and executive functioning. As far as we know, one study investigated rate of decline in VaD and AD. This was done in the preclinical stage however, and they found that persons with preclinical VaD show faster rate of cognitive decline than preclinical AD in episodic memory, visuo-spatial functioning and category fluency [34]. This former study did not incorporate tests for executive functioning and attention, the domains in which we found decline in VaD. Another relevant shortcoming of this former study is that no brain imaging was available and about 70% of

patients had a diagnosis of VaD, which was primarily a diagnosis of post-stroke dementia. In contrast, the diagnosis of all of our VaD patients was supported by brain imaging, mostly small vessel disease.

The diverse patterns of cognitive decline could not be explained by differences in disease duration at baseline or on the Clinical Dementia Rating, although we found differences on MMSE. At baseline, patients with AD performed worse on the MMSE and one might interpret that these patients are cognitively more impaired. However, the MMSE is known to rely heavily on memory, the domain on which AD most was impaired [35]. Besides memory it relies on language, patients with bvFTD declined fastest on language and memory and this might be reflected in their fast decline on MMSE. As a consequence, the MMSE might have some restrictions when it is used to compare global cognition in different types of dementia.

A possible limitation of this study is that, except for AD and controls, sample sizes are relatively small. On the other hand, longitudinal studies on non-AD dementias are scarce, and for these more rare types of dementia, our group sizes are in fact not so small. We feel that even when reported significance levels are limited by suboptimal power, reporting effect sizes of these groups is very valuable. Our results need to be replicated in larger studies. The sample described in our study is relatively young, which might limit generalizability to dementia in general. Nonetheless, we feel that the relative young age has also advantages, as non-AD types of dementia often develop at a younger age and as such we were able to include diverse types of dementia. In addition, dementia at a younger age is often thought to be more pure, and less mixed pathology, hence the patterns of decline may be more specific. Amongst the strengths of our study is the longitudinal set-up and the comprehensive neuropsychological assessment covering five cognitive domains.

Our findings have large impact, as they provide estimates of natural disease course in different types of dementia. Clinical trials have thus far most frequently used global outcome measures including the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) [36], Clinical Dementia Rating, questionnaires about activities of daily living and behaviour. Shortcomings of the ADAS-Cog includes its primary focus on memory and language, while tasks assessing attention, executive or visuo-spatial functioning are not incorporated in the test [37]. More extensive neuropsychological assessments covering several cognitive domains, like the Neuropsychological Test Battery, are increasingly being preferred over the ADAS-Cog. These neuropsychological batteries are better in detecting subtle cognitive changes and therefore seem more suitable for cognitive assessments in trials in preclinical/early disease stages. Recently, the Food and Drug Administration proposed to revise the criteria for drug approval since persons in very early disease stages have no obvious deterioration in daily functioning. They suggested that in trials (in very early stages of disease) cognitive tests should be used as end-points [38]. In addition, clinical trials are currently designed for other types of dementia than AD. Therefore, estimates of cognitive trajectories of different types of dementia are essential for trial design and power calculations.

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