

Supplementary Data

Neuropsychological Signs of Alzheimer's Disease 8 Years Prior to Diagnosis

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Supplementary Table 1

Comparison of longitudinal studies with long observation periods, at least three testing visits, and which administered comprehensive neuropsychological test batteries. All tests administered are noted. Tests showing significant group differences are noted in bold face. Obs, observation period; TRI, test-retest interval, Age at baseline and timepoints noted in years preceding diagnosis

Study	N		Obs. (y)	TRI (y)	Age (y)	Timepoint of emergence of neuropsychological impairment in years preceding diagnosis													
	NC	AD				-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1		
Baltimore Longitudinal Study of Aging Grober et al., 2008 [1]	822	92	15	2	79.8 ± 6.9** (AD patients at baseline)							VEM EF SFlu PFlu eVIQ	VEM EF SFlu PFlu eVIQ	VEM EF SFlu PFlu eVIQ	VEM EF SFlu PFlu eVIQ	VEM EF SFlu PFlu eVIQ	VEM EF SFlu PFlu eVIQ	VEM EF SFlu PFlu eVIQ	
Bronx Aging Study Masur et al., 1994 [2]	253	64	>4	1	78.9 ± 3.0**												VEM NVEM WM AbReas SFlu VisS- pat V- MS Lang	VEM NVEM WM AbReas SFlu VisS- pat V- MS Lang	VEM NVEM WM AbReas SFlu VisS- pat V- MS Lang
Hall et al., 2001 [3]	0	75	19	1	range: 75-85	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	VEM PIQ	
Tierny et al., 2005 [4]	10y: 216 5y: 474	10y: 47 5y: 77	10	5	75.2 ± 5.7** 5y: 80.0 ± 6.2**	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM WM AbReas SFlu PFlu Info VisS- pat Attn V- MS Lang		

Supplementary Table 1
(Continued)

Saxton et al., 2004 [5]	621	72	8	1	73.7 ± 4.3**		VEM NVEM EF SFlu PFlu Info VisS- pat Attn V- MS Lang		VEM NVEM EF SFlu PFlu Info VisS- pat Attn V- MS Lang	VEM NVEM EF SFlu PFlu Info VisS- pat Attn V- MS Lang
Elias et al., 2000 [6]	937	109	22	2	72.5 ± 5.7**	VEM NVEM WM AbReas PFlu		VEM NVEM WM AbReas PFlu		
Small et al., 1997a [7]	179	26	3	3	83.5 ± 4.7**				VEM NVEM WM SFlu PFlu VisS- pat MMSE	
Bäckman et al., 2001 [8]	105	15	6	3	82.2 ± 4.71**		VEM WM		VEM WM	
Chen et al., 2000 [9]	483	120	10	2	75.6 ± 4.6**					VEM EF SFlu PFlu Lang Prax MMSE
Chen et al., 2001 [10]	483	68	10	2	73.1 ± 4.5**			VEM EF SFlu PFlu Lang Prax MMSE	VEM EF SFlu PFlu Lang Prax MMSE	

Supplementary Table 1
(Continued)

Study	N		Obs. (y)	TRI (y)	Age (y)	Timepoint of emergence of neuropsychological impairment in years preceding diagnosis											
	NC	AD				-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
Jacobs et al., 1995 [11]	402	41	4	1	73.3 ± 6.8**												VEM NVEM AbReas SFlu PFlu VisS- pat Lang MMSE
Fabrigoule et al., 1998 [12]	1134	16	5	2	not reported (ca. 73 y)												VEM NVEM AbReas SFlu V-MS MMSE
Amieva et al., 2005 [13]	1050	215	10	2	not reported (ca. 73 y)			NVEM									AbReas SFlu MMSE
Amieva et al., 2008 [14]	350	350	15	2.3	not reported (ca. 73 y)	NVEM		NVEM	NVEM	NVEM	NVEM						NVEM AbReas SFlu MMSE IADL Dep Cog-Com

**mean ± SD not reported, calculated from text; VEM, verbal episodic memory; NVEM, nonverbal episodic memory; WM, working memory; EF, executive functioning (Trail Making Test B); AbReas, abstract reasoning; SFlu, semantic fluency; PFlu, phonemic fluency; VisSpat, visuo-spatial ability; V-MS = Visuo-motor speed; Attn = Attention; Info = Information subtest of the WAIS; Lang = Language; eVIQ = Estimated verbal intelligence; Prax, praxis; PIQ, performance IQ; MMSE, Mini-Mental State Examination; ADL/IADL, activities of daily living/instrumental activities of daily living; A/M/Dep, Affect/Mood/Depression; CogCom, cognitive complaints.

Supplementary Table 2

Comparison of Alzheimer's disease progressors' (AD-P) and cognitively healthy (NC) individuals' baseline performance an average of eight years prior to diagnosis

Test	NC <i>n</i> = 29	AD-P <i>n</i> = 29	<i>p</i> *'##+
Medical Background			
Do/did you suffer from vertigo/weakness/falls? (<i>n</i> of yes)	0	3	0.237*
Do/did you suffer from memory complaints? (<i>n</i> of yes)	0	5	0.052*
Are you currently suffering from heart problems? (<i>n</i> of yes)	0	5	0.052*
Do/did you suffer from stroke(s)? (<i>n</i> of yes)	0	1	1.000*
Do/did you suffer from diabetes? (<i>n</i> of yes)	0	1	1.000*
Do/did you smoke? (<i>n</i> of yes)	5	6	1.000*
Do/did you drink alcohol? (<i>n</i> of yes)	25	25	1.000*
Do you have a family history of memory problems? (<i>n</i>)	4	3	1.000*
Composite score for cardiac risk factors (<i>n</i> of >0)	13	16	0.460*
Mood: Questionnaire for the Diagnosis of Depression according to DSM-IV (FDD) [15]			
FDD Item 1 (<i>n</i> of >0)	1	7	0.052*
FDD Item 2 (<i>n</i> of >0)	11	14	0.408*
FDD Item 3 (<i>n</i> of >0)	2	6	0.253*
FDD Item 4 (<i>n</i> of >0)	2	1	1.000*
FDD Item 5 (<i>n</i> of >0)	1	7	0.052*
FDD Item 6 (<i>n</i> of >0)	1	9	0.012*
FDD Item 7 (<i>n</i> of >0)	5	7	0.747*
FDD Item 8 (<i>n</i> of >0)	3	6	0.470*
FDD Item 9 (<i>n</i> of >0)	1	6	0.102*
FDD Item 10 (<i>n</i> of >0)	13	17	0.268*
FDD Item 11 (<i>n</i> of >0)	2	6	0.203*
FDD Item 12 (<i>n</i> of >0)	2	1	1.000*
FDD Item 13 (<i>n</i> of >0)	1	3	0.487*
FDD Item 14 (<i>n</i> of >0)	1	1	1.000*
FDD Item 15 (<i>n</i> of >0)	7	5	0.574*
FDD Item 16 (<i>n</i> of >0)	7	13	0.143*
FDD Item 17 (<i>n</i> of >0)	5	7	0.746*
FDD Item 18 (<i>n</i> of >0)	1	7	0.046*
FDD total (median, min-max)	2, 0–15	4, 0–21	0.033#
General abilities: Mini Mental State Examination (MMSE) [16]			
Total points (median, min-max)	29, 27–30	29, 25–30	0.187#
General abilities: WAIS-R Similarities [17]			
Total points (median, min-max)	26, 10–31	25, 6–32	0.548#
Psychomotor speed: Trail Making Test (TMT) [18]			
TMT, part A (z-score)	0.10 ± 1.13	−0.28 ± 0.94	0.165+
Attention: Computerized Test of Attention (TAP/TAS) [19]			
TAP: Divided attention: reaction time (z-score)	−0.06 ± 0.84	−0.26 ± 0.95	0.395+
TAP: Divided attention: standard deviation (z-score)	−0.00 ± 1.03	0.01 ± 1.03	0.951+
TAP: Divided attention: errors (z-score)	0.21 ± 1.11	0.11 ± 1.03	0.721+
TAP: Divided attention: missings (z-score)	−0.14 ± 1.06	0.12 ± 1.13	0.368+
TAS: Reaction time (z-score)	0.15 ± 1.15	0.04 ± 1.05	0.704+
TAS: Standard deviation (z-score)	0.21 ± 1.28	−0.16 ± 0.89	0.207+
TAS: Total errors (median, min-max)	1, 0–4	0, 0–23	0.556#
TAS: Missings (z-score)	0.10 ± 1.05	−0.11 ± 1.05	0.458+
Verbal memory: German version of the California Verbal Learning Test (CVLT) [20]			
Encoding: Total correct trial 1–5 (z-score)	−0.02 ± 0.92	−0.51 ± 1.12	0.077+
Encoding: Total repetitions trial 1–5 (median, min-max)	2, 0–19	2, 0–9	0.598#
Encoding: Total intrusions trial 1–5 (median, min-max)	0, 0–5	1, 0–6	0.273#
Trial 1: Primacy ^a (median, min-max)	2, 0–4	2, 0–4	1.000#
Trial 1: Recency ^b (median, min-max)	2, 0–4	2, 0–4	0.623#
Trial 1: Index Primacy-Recency ^c (median, min-max)	0, −1 –1	0, −1 –1	0.941#
Regional primacy score across trials 1–5 ^d (median, min-max)	80, 20–100	70, 35–100	0.065#

Supplementary Table 2
(Continued)

Test	NC <i>n</i> = 29	AD-P <i>n</i> = 29	<i>p</i> *'##+
Regional middle score across trials 1-5 ^e (median, min-max)	60, 30–92.5	52.5, 10–82.5	0.087 [#]
Regional recency score across trials 1-5 ^f (median, min-max)	75, 30–95	70, 30–100	0.849 [#]
distractor list: total correct (z-score)	-0.10 ± 1.04	-0.24 ± 1.05	0.617 ⁺
Short Delayed Free Recall (SDRF: Total correct (z-score)	-0.05 ± 1.14	-0.53 ± 1.26	0.132 ⁺
Regional SDRF Primacy (%) ^g (median, min-max)	75, 50–100	75, 0–100	0.170 [#]
Regional SDRF Middle (%) ^h (median, min-max)	62.5, 25–100	62.5, 0–100	0.489 [#]
Regional SDRF Recency (%) ⁱ (median, min-max)	75, 0–100	50, 0–100	0.144 [#]
Short Delayed Cued Recall: total correct (z-score)	0.07 ± 1.11	-0.59 ± 1.20	0.035 ⁺
Long Delayed Free Recall: total correct (z-score)	0.12 ± 1.20	-0.52 ± 1.07	0.037 ⁺
Long Delayed Cued Recall: total correct (z-score)	-0.00 ± 1.14	-0.35 ± 1.08	0.235 ⁺
Recognition: Response bias (z-score)	-0.19 ± 1.00	-0.88 ± 1.46	0.040 ⁺
Recognition: Discrimination (z-score)	-0.15 ± 1.19	-0.38 ± 1.36	0.510 ⁺
Sum of all intrusions (median, min-max)	1, 0–19	3, 0–21	0.087 [#]
Sum of all repetitions (median, min-max)	3, 0–23	2, 0–11	0.244 [#]
Semantic cluster ratio (z-score)	-0.30 ± 1.12	-0.12 ± 0.93	0.490 ⁺
Recall: recall consistency index (z-score)	0.26 ± 1.02	-0.31 ± 1.14	0.049 ⁺
Verbal memory: CERAD-NAB-word list [21]			
Encoding: total correct trial 1–3 (z-score)	-0.06 ± 0.96	-0.42 ± 1.23	0.230 ⁺
Recall: total correct (z-score)	-0.05 ± 0.98	-0.64 ± 1.32	0.056 ⁺
Recall: total savings (z-score)	-0.10 ± 1.2	-0.74 ± 1.55	0.084 ⁺
Recall: total intrusions (z-score)	0.12 ± 0.90	-0.53 ± 1.24	0.028 ⁺
Recognition: total correct (z-score)	0.09 ± 1.06	-0.41 ± 1.26	0.112 ⁺
Visual memory: CERAD-NAB Figures [22]			
Figures – Delayed Recall: total (z-score)	0.15 ± 1.03	-0.52 ± 1.28	0.032 ⁺
Language: Boston Naming Test (BNT) [23]			
CERAD-NAB, 15 items: Total correct (z-score)	-0.09 ± 1.11	-0.31 ± 1.03	0.444 ⁺
CERAD-NAB, 15 items: Total Error (<i>n</i> of >0)	6	13	0.068 [*]
CERAD-NAB, 15 items: Semantic cue (<i>n</i> of >0)	3	2	0.547 [*]
CERAD-NAB, 15 items: Phonemic cue (<i>n</i> of >0)	16	15	0.639 [*]
BNT, 45 items: Total correct (z-score)	-0.01 ± 1.19	-0.55 ± 0.87	0.053 ⁺
BNT, 45 items: Semantic cue (<i>n</i> of >0)	11	12	0.754 [*]
BNT, 45 items: Phonemic cue (<i>n</i> of >0)	23	27	0.060 [*]
BNT 45 items: Total correct + semantic cue (z-score)	-0.06 ± 1.13	-0.57 ± 0.88	0.062 ⁺
Language: German version of AMNART (MWT-B) [24]			
Total points (z-scores)	-0.11 ± 1.14	-0.20 ± 1.04	0.740 ⁺
Language: WAIS-R, Vocabulary Test [17]			
Total points (median, min-max)	21, 4–32	21, 5–31	0.662 [#]
CERAD-NAB, Figures [22]			
Figures Copy: total points (z-score)	-0.06 ± 0.99	-0.20 ± 1.05	0.597 ⁺
Executive Functioning: Phonemic fluency [25]			
G-Words: Total correct (z-score)	0.12 ± 0.96	-0.07 ± 1.05	0.456 ⁺
G-Words: Total repetitions (<i>n</i> of >0)	8	5	0.428 [*]
G-Words: Total errors (z-score)	0.05 ± 0.67	-0.07 ± 0.81	0.549 ⁺
O-Words: Total correct (z-score)	-0.20 ± 1.38	-0.09 ± 0.98	0.724 ⁺
O-Words: Total repetitions (<i>n</i> of >0)	5	10	0.230 [*]
O-Words: Total errors (z-score)	0.11 ± 0.86	-0.01 ± 0.94	0.637 ⁺
S-Words: Total correct (z-score)	-0.10 ± 0.99	-0.19 ± 0.98	0.743 ⁺
S-Words: Total errors (<i>n</i> of >0)	5	10	0.112 [*]
S-Words: Total repetitions (<i>n</i> of >0)	4	8	0.251 [*]

Supplementary Table 2
(Continued)

Test	NC <i>n</i> = 29	AD-P <i>n</i> = 29	<i>p</i> *'##+
Executive functioning: Semantic fluency [25]			
Food: Total correct (z-score)	0.07 ± 0.86	-0.16 ± 0.95	0.347+
Food: Total repetitions (z-score)	-0.03 ± 1.01	0.03 ± 0.97	0.811+
Food: Total errors (z-scores)	0.29 ± 0.97	0.34 ± 0.86	0.848+
Tools: Total correct (z-scores)	-0.18 ± 1.02	-0.31 ± 0.86	0.597+
Tools: Total repetitions	12	10	0.759*
Tools: Total errors	3	1	0.611*
Animals: Total correct (z-scores)	0.23 ± 1.08	-0.25 ± 1.21	0.120+
Animals: Total repetitions	9	8	0.647*
Animals: Total errors	1	0	1.000*
Fluency Index semantic + phonemic (median, min-max)	0.33, -0.5-0.74	0.27, 0.06-0.62	0.437#
Fluency-Index animals + S-Words (median, min-max)	0.35, -0.02-0.76	0.29, -0.07-0.84	0.437#
Letter Fluency, mean of G + O + S (z-scores)	-0.06 ± 0.94	-0.12 ± 0.86	0.810+
Semantic mean of animals + tools + food (z-scores)	0.04 ± 0.83	-0.24 ± 0.77	0.192+
Sum of phonemic fluency (median, min-max)	29, 8-51	29, 10-44	0.808#
Sum of semantic fluency (median, min-max)	51, 33-90	48, 32-75	0.247#
Executive functioning: Clock Drawing Test (CDT) [26]			
Total points (median, min-max)	9, 5-9	8, 5-9	0.038#
Executive functioning: WAIS-R Block Design [17]			
Test 3, total points	29	29	0.873*
Test 4, total points	29	26	0.012*
Test 5, total points	28	21	0.011*
Test 6, total points	27	22	0.123*
Test 7, total points	14	10	0.190*
Test 8, total points	13	8	0.158*
Test 9, total points	3	0	0.237*
Block Design, Total points (median, min-max)	26, 16-45	21, 7-36	0.004#
Executive functioning: Trail Making Test (TMT) [18]			
TMT, part B (z-score)	0.20 ± 1.07	-0.10 ± 2.33	0.015+
TMT, B/A ratio (z-score)	0.12 ± 1.12	-0.87 ± 2.37	0.045+

* = Kendall's tau-c/Fisher's Exact Test; # = U-Test (Mann-Whitney) + = *t*-Test; ^aCVLT Primacy: Number of correctly recalled items from the first four items trial 1; ^bCVLT: Recency: Number of correctly recalled last from the last four items trial 1; ^cCVLT Index = trial 1: Primacy + Recency/Primacy - Recency; ^dCVLT Regional primacy score across trials 1-5: Sum of number of first 4 items across trial 1-5/20 * 100; ^eCVLT: Regional middle score across trials 1-5: Sum of number of middle 8 items across trial 1-5/40 * 100; ^fCVLT: Regional recency score across trials 1-5: Sum of number of last 4 items across trial 1-5/20 * 100; ^gCVLT: Regional SDFR Primacy: Number of first 4 items/4 * 100; ^hCVLT: Regional SDFR Middle (%) Number of middle 8 items/8 * 100; ⁱCVLT: Regional SDFR Recency (%) Number of last 4 items/4 * 100.

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