Supplementary Material

Identification of a Cascade of Changes in Activities of Daily Living Preceding Short-Term Clinical Deterioration in Mild Alzheimer's Disease Dementia via Lead-Lag Analysis

**Supplementary Table 1. Demographic and clinical characteristics at baseline.**

	Slow AD progressors	Moderate AD progressors	*p*	AD patients from the DAP study	*p*
	n = 78	n = 86		N = 351	
Age	69 (7.76)	72.3 (8.26)	*<0.05*	72.8 (8.30)	*0.59*
Female %	57.69%	47.67%	*0.27*	45.46 %	*0.99*
Education (y)	9.06 (1.96)	9.45 (1.92)	*0.27*	9.23 (1.98)	*1*
MMSE	24.6 (2.49)	23.3 (3.09)	*<0.01*	22.7 (3.25)	*<0.05*
CDR (SOB)	4.53 (1.35)	4.32 (1.37)	*0.39*	4.87 (1.57)	*0.14*
CDT	2.53 (1.12)	2.76 (1.15)	*0.27*	3.03 (1.18)	*0.09*
WLM (IR)	10.1 (5.6)	7.72 (5.04)	*<0.05*	7 (4.83)	*<0.05*
WLM (DR)	3.22 (4.16)	2.01 (3.34)	*0.08*	2.07 (3.38)	*1*
C.BNT	13.2 (1.64)	12.1 (2.24)	*<0.01*	12.07 (2.75)	*0.90*
C.SemF	13.6 (4.74)	12.3 (5.07)	*0.14*	11.53 (4.96)	*0.45*
C.Fig (C)	9.19 (1.89)	9.08 (1.83)	*0.74*	8.72 (2.01)	*1*
C.Fig (DR)	2.64 (2.34)	2.35 (2.52)	*0.52*	2.47 (2.51)	*1*
C.Word (IR)	12.6 (3.66)	11.6 (3.78)	*0.16*	11.4 (4.21)	*1*
C.Word (IR-I)	2.23 (2.63)	0.77 (1.35)	*<0.001*	0.94 (1.58)	*0.45*
C.Word (DR)	2.17 (1.95)	1.85 (2.03)	*0.38*	1.83 (1.81)	*1*
C.Word(DR-I)	1.12 (1.45)	0.51 (0.86)	*<0.01*	0.66 (1.20)	*1*
C.Word (Rej)	8.5 (1.85)	8.35 (2.06)	*0.67*	8.07 (2.51)	*1*
C.Word (Inc)	7.78 (2.02)	7.37 (2.66)	*0.34*	7.75 (2.29)	*1*
TMT-A (sec)	90.1 (51.2)	104 (59)	*0.16*	111.40 (65.26)	*1*
B-ADL (TS)	3.76 (1.69)	3.96 (2.09)	*0.57*	4.64 (2.10)	*<0.05*

B-ADL (HIGH)	4.76 (2.03)	4.78 (2.24)	*0.96*
B-ADL (LOW)	2.95 (1.6)	3.28 (2.24)	*0.34*
B-ADL (LEAD)	4.67 (2.05)	4.7 (2.27)	*0.95*
B-ADL (LAG)	3.18 (1.59)	3.50 (2.08)	*0.27*

AD, Alzheimer's disease dementia; DAP, Diagnostic and prognostic study. The AD collective was subdivided by a change in CDR-SOB within two years. As a threshold, a median change of two points in the CDR-SOB was used. This subdivision resulted in two groups: slow (change in CDR-SOB<2) and moderate (change in CDR-SOB≥2) AD progressors. The column on the far right reflects comparisons between AD patients selected from the DAP study for our analysis (n = 164) and the complete AD sample from the DAP study (N = 351).

B-ADL (HIGH), Bayer-activities of daily living (HIGH cognitive demand factor); B-ADL (LOW), Bayer-activities of daily living (LOW cognitive demand factor); B-ADL (LAG), Bayer- activities of daily living (i.e., B-ADL items with median lead-lag coefficients < 0); B-ADL (LEAD), Bayer-activities of daily living (i.e., B-ADL items with median lead-lag coefficients > 0); B-ADL (TS), Bayer- activities of daily living (total score); C.BNT, CERAD. 15-Item Version of the Boston Naming Test; C.Fig (C), CERAD. Figure constructional praxia (copy); C.Fig (DR), CERAD. Figure constructional praxia (delayed recall); C.SemF, CERAD. Semantic fluency (animals); C.Word (DR), CERAD. Word list (delayed recall); C.Word (DR-I), CERAD. Word list (delayed recall, intrusions); C.Word (Inc), CERAD. Word list (recognition task, correct inclusions); C.Word (IR), CERAD. Word list (immediate recall).; C.Word (IR-I), CERAD. Word list (immediate recall, intrusions); C.Word (Rej), CERAD. Word list (recognition task, correct rejections); CDR (SOB), Clinical Dementia Rating Scale (sum of boxes); CDT, Clock Drawing Test; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test A; WLM (DR), Wechsler Memory Scale–Revised (delayed recall, logical memory); WLM (IR), Wechsler Memory Scale–Revised (immediate recall, logical memory).
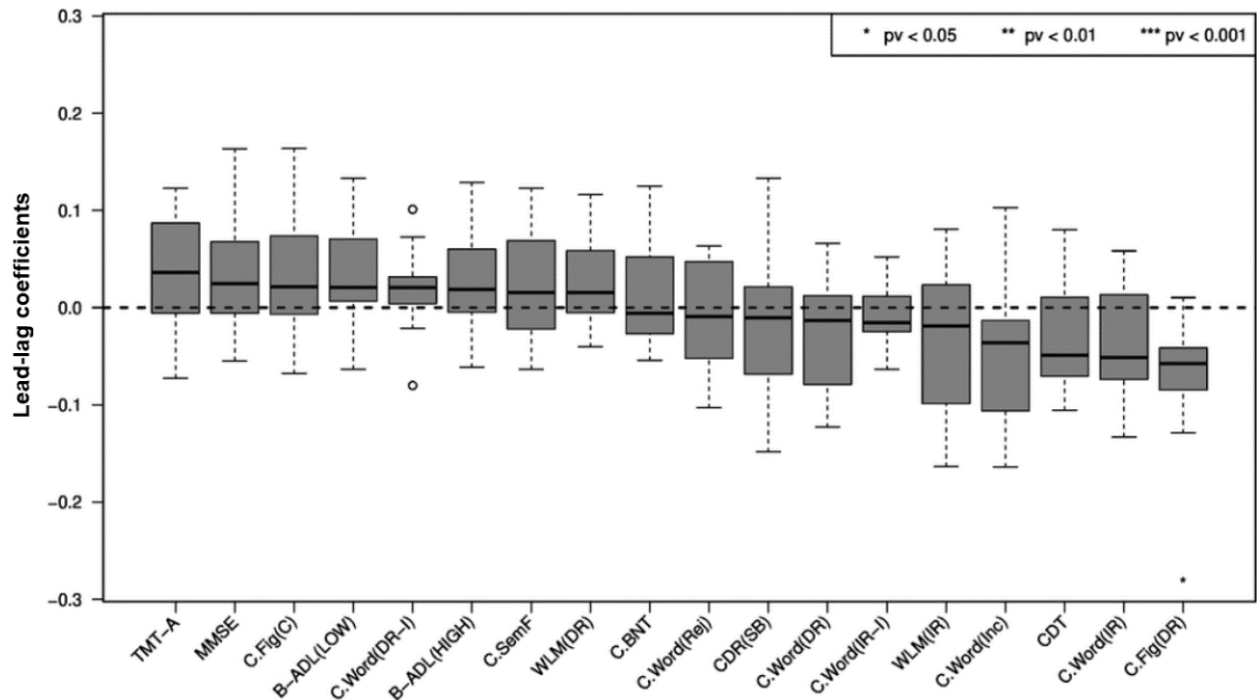
Supplementary Figure 1. Lead-lag results comprising the B-ADL total score (TS) and all cognitive variables: moderate AD progressors.
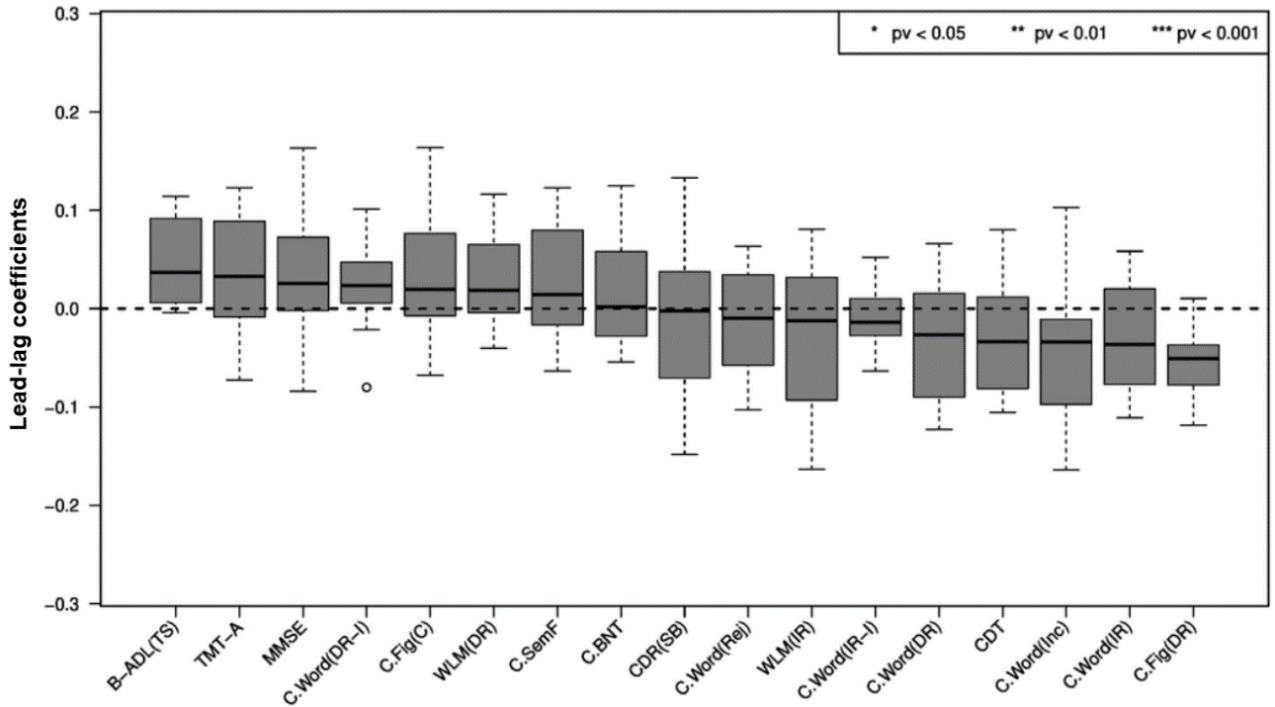
Boxplots of average lead-lag coefficients comprising the B-ADL total score and all cognitive variables. Each box is composed of 16 values. Variables are ordered by median lead-lag coefficients. A change in variables with positive and high lead-lag coefficients occurs earlier in moderate AD progressors. *p* values were calculated with resampling. Using a bootstrapping estimate, the *p* value for complete lead-lag analysis was 0.0388.

AD, Alzheimer's disease dementia; B-ADL (TS), Bayer-activities of daily living (total score); C.BNT, CERAD. 15-Item Version of the Boston Naming Test; C.Fig (C), CERAD. Figure constructional praxia (copy); C.Fig (DR), CERAD. Figure constructional praxia (delayed recall); C.SemF, CERAD. Semantic fluency (animals); C.Word (DR), CERAD. Word list (delayed recall); C.Word (DR-I), CERAD. Word list (delayed recall, intrusions); C.Word (Inc), CERAD. Word list (recognition task, correct inclusions); C.Word(IR), CERAD. Word list (immediate recall).; C.Word (IR-I), CERAD. Word list (immediate recall, intrusions); C.Word (Rej), CERAD. Word list (recognition task, correct rejections); CDR (SB), Clinical Dementia Rating Scale (sum of boxes); CDT, Clock Drawing Test; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test A; WLM (DR), Wechsler Memory Scale–Revised (delayed recall, logical memory); WLM (IR), Wechsler Memory Scale–Revised (immediate recall, logical memory).

Supplementary Figure 2. Lead-lag results comprising the B-ADL (HIGH) and B-ADL (LOW) composite scores, as well as all cognitive variables: moderate AD progressors.

Boxplots of average lead-lag coefficients comprising the B-ADL (HIGH) and B-ADL (LOW) composite scores, as well as all cognitive variables. Each box is composed of 17 values. Variables are ordered by median lead-lag coefficients. A change in variables with positive and high lead-lag coefficients occurs earlier in moderate AD progressors. *p* values were calculated with resampling. Using a bootstrapping estimate, the *p* value for complete lead-lag analysis was 0.0159.

AD, Alzheimer's disease dementia; B-ADL (HIGH), Bayer-activities of daily living (HIGH cognitive demand factor); B-ADL (LOW), Bayer-activities of daily living (LOW cognitive demand factor); C.BNT, CERAD. 15-Item Version of the Boston Naming Test; C.Fig (C), CERAD. Figure constructional praxia (copy); C.Fig (DR), CERAD. Figure constructional praxia (delayed recall); C.SemF, CERAD. Semantic fluency (animals); C.Word (DR), CERAD. Word list (delayed recall); C.Word (DR-I), CERAD. Word list (delayed recall, intrusions); C.Word (Inc), CERAD. Word list (recognition task, correct inclusions); C.Word (IR), CERAD. Word list (immediate recall).; C.Word (IR-I), CERAD. Word list (immediate recall, intrusions); C.Word (Rej), CERAD. Word list (recognition task, correct rejections); CDR (SB), Clinical Dementia Rating Scale (sum of boxes); CDT, Clock Drawing Test; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test A; WLM (DR), Wechsler Memory Scale–Revised (delayed recall, logical memory); WLM (IR), Wechsler Memory Scale–Revised (immediate recall, logical memory).

Supplementary Figure 3. Lead-Lag results comprising the B-ADL (LEAD) and B-ADL (LAG) composite scores, as well as all cognitive variables: slow and moderate AD progressors.
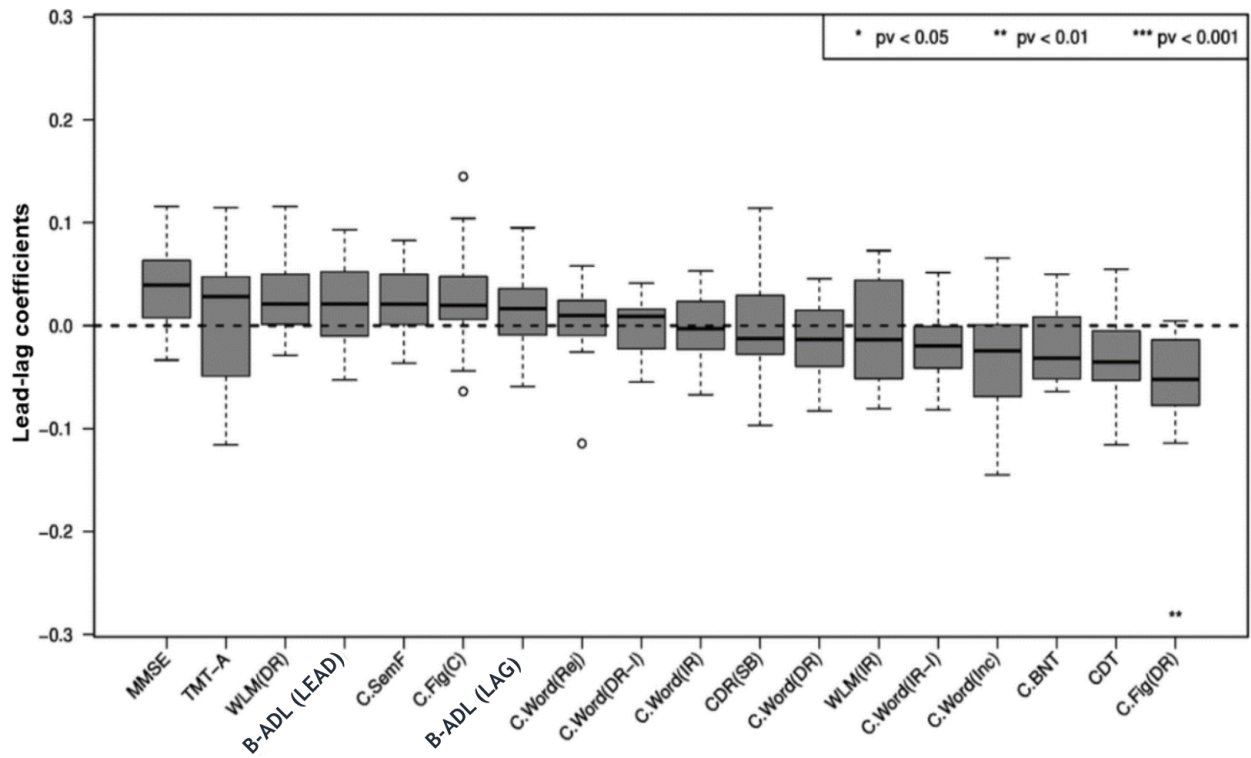
Boxplots of average lead-lag coefficients comprising the B-ADL (LEAD) and (LAG) composite scores, as well as cognitive variables. Each box is composed of 17 values. Variables are ordered by median lead-lag coefficients. A change in variables with positive and high lead-lag coefficients occurs earlier in slow and moderate AD progressors. *p* values were calculated with resampling. Using a bootstrapping estimate, the *p* value for complete lead-lag analysis was 1.5e-05.

AD, Alzheimer's disease dementia; B-ADL (LEAD), Bayer-activities of daily living (i.e., B-ADL items with median lead-lag coefficients > 0); B-ADL (LAG), Bayer-activities of daily living (i.e., B-ADL items with median lead-lag coefficients < 0); C.BNT, CERAD. 15-Item Version of the Boston Naming Test; C.Fig (C), CERAD. Figure constructional praxia (copy); C.Fig (DR), CERAD. Figure constructional praxia (delayed recall); C.SemF, CERAD. Semantic fluency (animals); C.Word (DR), CERAD. Word list (delayed recall); C.Word (DR-I), CERAD. Word list (delayed recall, intrusions); C.Word (Inc), CERAD. Word list (recognition task, correct inclusions); C.Word (IR), CERAD. Word list (immediate recall).; C.Word (IR-I), CERAD. Word list (immediate recall, intrusions); C.Word (Rej), CERAD. Word list (recognition task, correct rejections); CDR (SB), Clinical Dementia Rating Scale (sum of boxes); CDT, Clock Drawing Test; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test A; WLM (DR), Wechsler Memory Scale–Revised (delayed recall, logical memory); WLM (IR), Wechsler Memory Scale–Revised (immediate recall, logical memory).

Supplementary Figure 4. Lead-Lag results comprising the B-ADL (LEAD) and B-ADL (LAG) composite scores, as well as all cognitive variables: slow AD progressors.
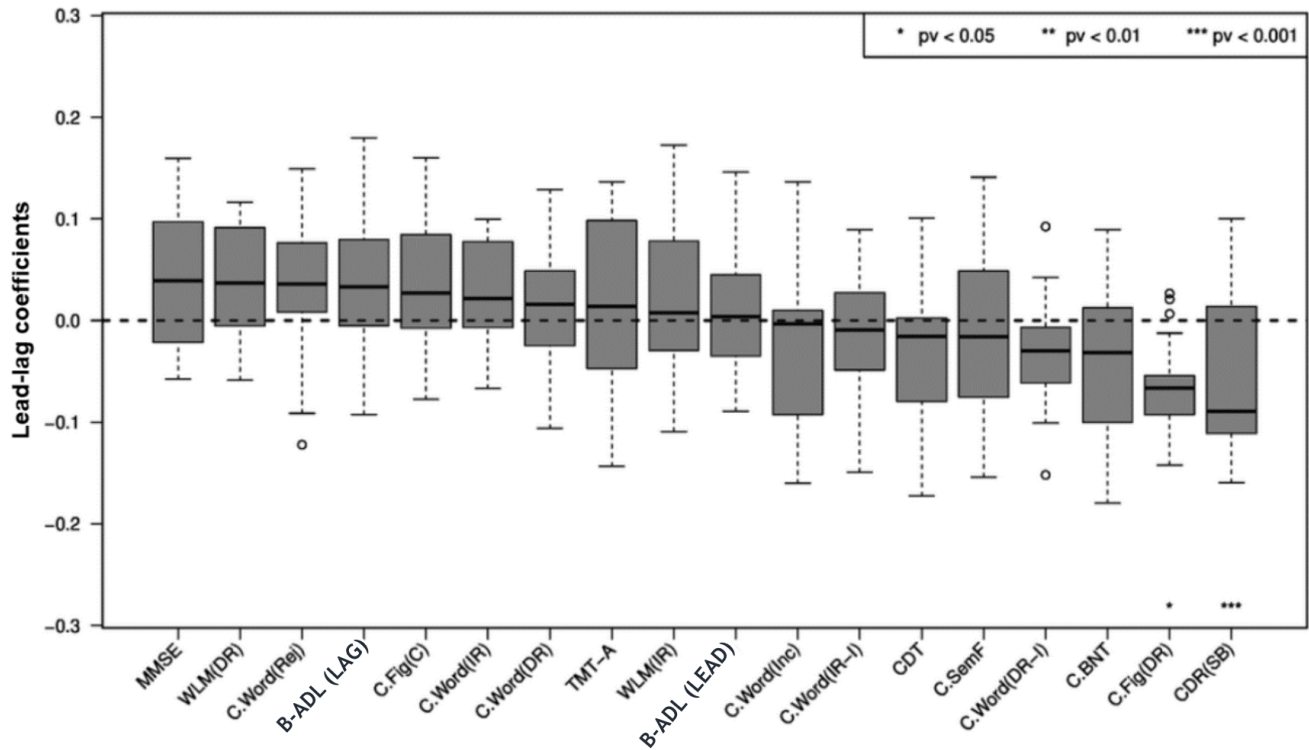
Boxplots of average lead-lag coefficients comprising the B-ADL (LEAD) and (LAG) composite scores, as well as cognitive variables. Each box is composed of 17 values. Variables are ordered by median lead-lag coefficients. A change in variables with positive and high lead-lag coefficients occurs earlier in slow AD progressors. *p* values were calculated with resampling. Using a bootstrapping estimate, the *p* value for complete lead-lag analysis was 0.000158.

AD, Alzheimer's disease dementia; B-ADL (LEAD), Bayer-activities of daily living (i.e., B-ADL items with median lead-lag coefficients > 0); B-ADL (LAG), Bayer-activities of daily living (i.e., B-ADL items with median lead-lag coefficients < 0); C.BNT, CERAD. 15-Item Version of the Boston Naming Test; C.Fig (C), CERAD. Figure constructional praxia (copy); C.Fig (DR), CERAD. Figure constructional praxia (delayed recall); C.SemF, CERAD. Semantic fluency (animals); C.Word (DR), CERAD. Word list (delayed recall); C.Word (DR-I), CERAD. Word list (delayed recall, intrusions); C.Word (Inc), CERAD. Word list (recognition task, correct inclusions); C.Word (IR), CERAD. Word list (immediate recall).; C.Word (IR-I), CERAD. Word list (immediate recall, intrusions); C.Word (Rej), CERAD. Word list (recognition task, correct rejections); CDR (SB), Clinical Dementia Rating Scale (sum of boxes); CDT, Clock Drawing Test; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test A; WLM (DR), Wechsler Memory Scale–Revised (delayed recall, logical memory); WLM (IR), Wechsler Memory Scale–Revised (immediate recall, logical memory).

METHODS

Cross-correlation analyses

For two variables of a given sample, the cross-correlation of the profiles $p1$ and $p2$ (each comprised of the three discretized values) were calculated as follows:

$$\frac{p_1 - mean(p_1)}{sd(p_1)}[V1..V2] \cdot \frac{p_2 - mean(p_2)}{sd(p_2)}[V2..V3] \cdot \frac{1}{(n-1)} -$$

$$\frac{p_1 - mean(p_1)}{sd(p_1)}[V2..V3] \cdot \frac{p_2 - mean(p_2)}{sd(p_2)}[V1..V2] \cdot \frac{1}{(n-1)}$$

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Please see the attached document for your information.