

Executive function markers of transition to amyloid-positive MCI and progression to amyloid-positive dementia

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BACKGROUND & OBJECTIVES

- Amyloid- β (A β) accumulation marks the biological onset of Alzheimer's disease (AD), preceding overt cognitive decline.
- Beyond episodic memory, executive function (EF) decline is increasingly recognized across the AD continuum and may track staging.
- EF is multidimensional — processing speed, inhibition, set-shifting, verbal fluency, motor programming — with components impaired at different stages.
- Objectives of this study**
 - Quantify the incremental discriminative value (Δ AUC) of 15 EF measures beyond age, sex, and education at two transitions:
 - Cognitively unimpaired $\rightarrow$ Amyloid- β -positive MCI
 - Amyloid- β -positive MCI $\rightarrow$ Amyloid- β -positive dementia
 - Rank markers and characterize how their contribution shifts across the continuum

METHODS

Participants

- All participants underwent amyloid PET imaging & comprehensive neuropsychological assessment.
- Participants were classified into 3 groups:
 - Cognitively unimpaired individuals (CU; $n = 555$)
 - Amyloid- β -positive mild cognitive impairment (AD-MCI; $n = 1,144$)
 - Amyloid- β -positive Alzheimer's disease dementia (ADD; $n = 992$)

Measures

- Executive functions were assessed using 15 neuropsychological measures.
 - Motor impersistence, Fist-Edge-Palm, Alternating hand movement, Alternating square & triangle, Copy of Luria loop, Contrasting program, Go/No-go, Semantic fluency: animal, Semantic fluency: supermarket, Phonemic fluency, Stroop word reading, Stroop color reading, Digit Symbol Coding, Korean TMT-Elderly's version-Part A, Korean TMT-Elderly's version-Part B

RESULTS

Table 1. Demographic and clinical characteristics

Characteristic	CU (1) (n=555)	AD-MCI (2) (n=1,144)	ADD (3) (n=992)	F or χ^2	p	Post-hoc
Age	69.68 $\pm$ 7.87	72.33 $\pm$ 7.72	69.85 $\pm$ 9.35	30.35	<.001	(1)>(3)<(2)
Education (yr)	12.11 $\pm$ 4.62	12.07 $\pm$ 4.72	11.44 $\pm$ 4.62	5.91	.003	(1)>(2)>(3)
Sex (M / F)	204 / 351	453 / 691	365 / 627	2.22	.330	—
APOE ϵ 4 (carriers/non-carriers)	89/443	453 / 679	392 / 573	313.69	<.001	—
K-MMSE	28.41 $\pm$ 1.72	25.17 $\pm$ 3.26	19.07 $\pm$ 5.06	1285.68	<.001	(3)<(2)<(1)
CDR-SB	0.64 $\pm$ 0.46	1.84 $\pm$ 1.24	6.15 $\pm$ 3.02	1756.63	<.001	(1)<(2)<(3)

Table 3. Incremental utility: CU vs. AD-MCI (Top 10 only)

Rank	Test	Univariate logistic regression				Incremental validity				
		β (SE)	Wald χ^2	OR	p	Basic AUC	Ext. AUC	Δ AUC	DeLong z	DeLong p
1	Stroop color reading	-0.065 (0.004)	302.74	0.937	<.001	0.601	0.822	0.221	-14.783	<.001
2	Semantic fluency: animal	-0.245 (0.016)	243.70	0.783	<.001	0.602	0.774	0.173	-11.145	<.001
3	Digit Symbol Coding	-0.080 (0.005)	227.12	0.924	<.001	0.600	0.772	0.171	-11.255	<.001
4	Semantic fluency: supermarket	-0.184 (0.012)	238.41	0.832	<.001	0.603	0.771	0.168	-10.932	<.001
5	K-TMT-E: Part B	0.017 (0.002)	98.63	1.017	<.001	0.598	0.738	0.140	-10.300	<.001
6	Go/No-go	-0.326 (0.037)	76.40	0.722	<.001	0.591	0.708	0.117	-10.018	<.001
7	Phonemic fluency	-0.060 (0.006)	112.48	0.942	<.001	0.601	0.704	0.103	-7.112	<.001
8	K-TMT-E: Part A	0.077 (0.007)	107.86	1.080	<.001	0.601	0.700	0.100	-7.151	<.001
9	Fist-Edge-Palm	1.648 (0.183)	80.85	5.195	<.001	0.592	0.666	0.074	-7.348	<.001
10	Alternating hand movement	1.339 (0.159)	71.25	3.814	<.001	0.590	0.656	0.066	-5.476	<.001

Table 4. Incremental utility: AD-MCI vs. ADD (Top 10 only)

Rank	Test	Univariate logistic regression				Incremental validity				
		β (SE)	Wald χ^2	OR	p	Basic AUC	Ext. AUC	Δ AUC	DeLong z	DeLong p
1	Semantic fluency: supermarket	-0.219 (0.012)	351.89	0.804	<.001	0.599	0.788	0.190	-13.964	<.001
2	Stroop color reading	-0.038 (0.002)	367.76	0.963	<.001	0.595	0.781	0.186	-13.344	<.001
3	K-TMT-E: Part B	0.010 (0.001)	359.14	1.010	<.001	0.592	0.775	0.183	-12.500	<.001
4	Semantic fluency: animal	-0.237 (0.013)	319.16	0.789	<.001	0.593	0.764	0.171	-12.581	<.001
5	Digit Symbol Coding	-0.057 (0.004)	247.55	0.945	<.001	0.585	0.739	0.154	-10.256	<.001
6	Go/No-go	-0.146 (0.009)	261.69	0.864	<.001	0.595	0.730	0.136	-10.456	<.001
7	K-TMT-E: Part A	0.027 (0.003)	114.73	1.028	<.001	0.594	0.712	0.118	-9.456	<.001
8	Phonemic fluency	-0.073 (0.005)	194.47	0.930	<.001	0.598	0.714	0.116	-8.879	<.001
9	Contrasting program	-0.163 (0.013)	152.75	0.850	<.001	0.594	0.682	0.088	-8.948	<.001
10	Stroop word reading	-0.032 (0.003)	127.95	0.968	<.001	0.594	0.676	0.081	-8.746	<.001

Statistical analysis

- Group comparisons: ANOVA, χ^2 tests, or ANCOVA
- Univariate logistic regression analysis
- ROC curve analyses & AUC for each test
- Incremental validity
 - Basic model (age, sex, and education) vs.
 - Extended model including each test individually
 - Changes in AUC and DeLong test results were used to assess added predictive value.

Table 2. Executive function performance across groups

Measure	CU (1) (n=555)	AD-MCI (2) (n=1,144)	ADD (3) (n=992)	F or χ^2	p	Post-hoc
Categorical variables (Normal / Abnormal)						
Motor impersistence	509 / 1	1071 / 12	919 / 27	17.76	<.001	—
Fist-Edge-Palm	471 / 38	752 / 328	407 / 524	363.56	<.001	—
Alternating hand movement	435 / 57	695 / 349	431 / 474	235.47	<.001	—
Alternating square & triangle	450 / 44	837 / 223	506 / 401	236.67	<.001	—
Copy of Luria loop	482 / 29	939 / 159	572 / 377	288.47	<.001	—
Continuous variables (Mean $\pm$ SD)						
Contrasting program	19.87 $\pm$ 0.77	19.17 $\pm$ 2.83	15.29 $\pm$ 7.06	216.32	<.001	(1)>(2)>(3)
Go/No-go	19.52 $\pm$ 1.66	17.15 $\pm$ 4.57	11.99 $\pm$ 6.88	403.94	<.001	(1)>(2)>(3)
Semantic fluency: animal	16.78 $\pm$ 4.77	12.35 $\pm$ 4.24	8.46 $\pm$ 4.22	691.95	<.001	(1)>(2)>(3)
Semantic fluency: supermarket	18.81 $\pm$ 5.73	13.31 $\pm$ 5.45	8.08 $\pm$ 4.79	750.22	<.001	(1)>(2)>(3)
Phonemic fluency	29.83 $\pm$ 11.93	22.94 $\pm$ 11.84	15.19 $\pm$ 10.46	329.30	<.001	(1)>(2)>(3)
Stroop word reading	110.94 $\pm$ 7.76	107.74 $\pm$ 14.29	92.67 $\pm$ 30.29	101.34	<.001	(1)>(2)>(3)
Stroop color reading	93.21 $\pm$ 18.03	64.72 $\pm$ 27.08	36.17 $\pm$ 27.21	930.24	<.001	(1)>(2)>(3)
Digit Symbol Coding	56.60 $\pm$ 18.76	41.48 $\pm$ 16.97	26.97 $\pm$ 17.62	565.08	<.001	(1)>(2)>(3)
K-TMT-E: Part A	21.96 $\pm$ 8.74	31.47 $\pm$ 21.72	67.15 $\pm$ 74.32	193.67	<.001	(1)<(2)<(3)
K-TMT-E: Part B	46.61 $\pm$ 46.78	97.70 $\pm$ 89.63	206.34 $\pm$ 109.74	616.38	<.001	(1)<(2)<(3)

DISCUSSION & CONCLUSIONS

- Executive function measures showed significant impairment across the AD clinical continuum.
- The discriminative utility of individual EF markers varied by disease stage.
 - Early-stage discrimination was mainly driven by inhibitory control and processing speed, whereas dementia-stage progression involved broader deficits in semantic retrieval and set-shifting.
- CU $\rightarrow$ AD-MCI:
 - Stroop color reading + Semantic fluency + Digit Symbol Coding
- AD-MCI $\rightarrow$ ADD:
 - Semantic fluency + Stroop color reading + K-TMT-E Part B
- These findings highlight the clinical value of multidimensional EF assessment in the AD continuum.
- Stage-sensitive EF markers may help characterize cognitive transition from preclinical/early symptomatic AD to dementia.

CONTACT

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