

Supplementary Material

Automated Early Detection of Alzheimer's Disease by Capturing Impairments in Multiple Cognitive Domains with Multiple Drawing Tasks

Supplementary Table 1. Descriptions of the 22 drawing features

Feature	Description
Motion-related (speed/acceleration)	
Drawing speed, mm/s	Mean drawing speed
Drawing speed variability (CV)	Coefficient of variation of the drawing speed
Drawing speed non-smoothness, /mm	Number of local extrema in the drawing speed, per unit stroke length
Drawing acceleration, mm/s/s	Mean drawing acceleration
Drawing acceleration variability (SD), mm/s/s	Standard deviation of the drawing acceleration
Drawing acceleration non-smoothness, /mm	Number of local extrema in the drawing acceleration, per unit stroke length
Motion-related (pen pressure)	
Pressure	Mean pen pressure
Pressure variability (CV)	Coefficient of variation of the pen pressure
Pressure non-smoothness, /mm	Number of local extrema in the pen pressure, per unit stroke length
Pressure change speed, /s	Median speed of pen pressure changes
Pressure change speed variability (SD), /s	Standard deviation of the speed of pen pressure changes
Motion-related (pen posture)	
Tilt-x variability (SD), deg	Standard deviation of the pen's horizontal inclination (tilt-x)
Tilt-x change speed, deg/s	Median speed of tilt-x changes
Tilt-x change speed variability, deg/s	Standard deviation of the speed of tilt-x changes

Tilt-y variability (SD), deg	Standard deviation of the pen's vertical inclination (tilt-y)
Tilt-y change speed, deg/s	Median speed of tilt-y changes
Tilt-y change speed variability, deg/s	Standard deviation of the speed of tilt-y changes

Pause-related

Mean pause duration, s	Mean duration of pauses between drawing motions (i.e., between strokes and within a stroke)
Adjusted total pause duration, s/mm	Sum of pause durations, per unit stroke length
Pause/drawing duration ratio	Ratio of the pause and drawing durations
Adjusted total duration, s/mm	Sum of the pause and drawing durations, per unit stroke length
Number of drawing motions	Number of drawing motions separated by pauses

Supplementary Table 2. Factor loadings of the 22 drawing features on the first two principal components for each task. A positive loading indicates that the feature value was larger in the Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients, while a negative loading indicates that the feature value was smaller.

	Sentence		Pentagon		TMT-A		TMT-B		CDT	
	PC1	PC2	PC1	PC2	PC1	PC2	PC1	PC2	PC1	PC2
Motion-related (speed/acceleration)										
Drawing speed	-0.797	-0.368	-0.837	-0.295	-0.635	-0.594	-0.854	-0.100	-0.873	0.012
Drawing speed variability (CV)	0.061	0.502	-0.098	0.577	-0.009	0.468	0.345	0.283	0.040	0.272
Drawing speed non-smoothness	0.794	0.396	0.786	0.380	0.626	0.641	0.871	0.122	0.855	0.140
Drawing acceleration	-0.779	-0.424	-0.851	-0.117	-0.786	-0.372	-0.834	0.172	-0.870	-0.084
Drawing acceleration variability (SD)	-0.849	-0.308	-0.845	-0.170	-0.802	-0.429	-0.882	0.150	-0.860	-0.111
Drawing acceleration non-smoothness	0.801	0.379	0.841	0.340	0.679	0.607	0.873	0.093	0.894	0.104
Motion-related (pen pressure)										
Pressure	-0.227	-0.374	-0.051	-0.380	0.178	-0.355	-0.138	-0.402	-0.224	-0.104
Pressure variability (CV)	0.177	0.696	-0.011	0.639	-0.142	0.726	0.263	0.765	0.374	0.141
Pressure non-smoothness	0.752	0.398	0.876	0.199	0.690	0.500	0.838	-0.052	0.896	0.102
Pressure change speed	-0.346	-0.419	-0.734	0.256	-0.624	0.162	-0.335	0.532	-0.658	-0.061
Pressure change speed variability (SD)	-0.296	-0.647	-0.700	0.203	-0.532	0.324	-0.147	0.587	-0.750	-0.191
Motion-related (pen posture)										
Tilt-x variability (SD)	-0.662	0.006	-0.306	-0.185	-0.533	-0.010	-0.446	-0.036	-0.486	0.464
Tilt-x change speed	-0.792	-0.085	-0.648	0.103	-0.782	0.240	-0.351	0.466	-0.570	0.087
Tilt-x change speed variability (SD)	-0.725	-0.082	-0.508	-0.155	-0.732	0.061	-0.656	0.133	-0.650	-0.056
Tilt-y variability (SD)	-0.680	-0.202	-0.294	-0.205	-0.448	0.152	-0.310	0.527	-0.424	0.617
Tilt-y change speed	-0.838	-0.264	-0.712	0.051	-0.720	0.383	-0.246	0.769	-0.615	0.274
Tilt-y change speed variability (SD)	-0.794	-0.315	-0.582	-0.220	-0.739	0.188	-0.416	0.552	-0.803	0.104
Pause-related										
Mean pause duration	-0.109	0.837	0.315	0.588	-0.121	0.776	0.331	0.709	-0.049	0.891
Adjusted total pause duration	0.520	0.722	0.447	0.809	-0.035	0.885	0.472	0.786	0.415	0.794
Pause/drawing duration ratio	0.086	0.822	-0.244	0.793	-0.369	0.684	0.150	0.820	0.034	0.948
Adjusted total duration	0.648	0.659	0.596	0.736	0.098	0.930	0.522	0.770	0.504	0.748
Number of drawing motions	0.196	-0.017	0.326	0.656	0.052	0.775	0.374	0.194	0.463	-0.206

Absolute factor loadings greater than 0.7 are shown in bold.

Sentence, sentence-writing item of the Mini-Mental State Examination (MMSE); Pentagon, pentagon-copying item of the MMSE; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; CDT, Clock Drawing Test; CV, coefficient of variation; SD, standard deviation; PC, principal component.

Supplementary Table 3. Associations of the cognitive measures with the principal components of the drawing features for each task. The values are displayed as beta coefficients (standard errors), which were calculated by using multiple linear regression analyses before adjusting for covariates with a stepwise variable selection procedure.

Task	MMSE		FAB		LM-immediate		LM-delayed		TMT-A		TMT-B		CDT	
	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>
Sentence														
PC1					-0.021 (0.013)	0.124			-0.006 (0.004)	0.086	-0.025 (0.014)	0.071		
PC2			-0.030 (0.015)	0.043			-0.023 (0.014)	0.109			-0.039 (0.014)	0.007		
Pentagon														
PC1	-0.020 (0.010)	0.044												
PC2														
TMT-A														
PC1			0.065 (0.016)	<0.001					0.012 (0.004)	0.004				
PC2									-0.067 (0.005)	<0.001	0.036 (0.021)	0.090		
TMT-B														
PC1	0.031 (0.010)	0.002			0.053 (0.013)	<0.001	0.053 (0.015)	0.001			0.146 (0.015)	<0.001	0.038 (0.015)	0.010
PC2	-0.050 (0.009)	<0.001	-0.086 (0.015)	<0.001	-0.064 (0.013)	<0.001	-0.051 (0.013)	<0.001	0.008 (0.005)	0.094	-0.193 (0.017)	<0.001	-0.049 (0.013)	<0.001
CDT														
PC1			-0.031 (0.016)	0.051			-0.022 (0.015)	0.144					-0.034 (0.014)	0.022
PC2	-0.024 (0.009)	0.008	-0.038 (0.014)	0.009	-0.029 (0.013)	0.031			-0.025 (0.004)	<0.001	-0.044 (0.016)	0.006	-0.086 (0.013)	<0.001

The bold values highlight statistically significant associations (multiple linear regression, $p < 0.05$). The possible score ranges of the cognitive measures were rescaled from 0 to 1. In addition, the TMT scores were inverted by multiplying them by -1 to enable comparison with the other variable coefficients, because higher scores on the TMT indicate lower functioning. Sentence, sentence-writing item of the Mini-Mental State Examination (MMSE); Pentagon, pentagon-copying item of the MMSE; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; CDT, Clock Drawing Test; PC, principal component; SE, standard error.

Supplementary Table 4. Associations of the cognitive measures with the principal components of the drawing features for each task after adjusting for the age, sex, and years of education as covariates. The values are displayed as beta coefficients (standard errors), which were calculated by using multiple linear regression analyses with the above adjustment and a stepwise variable selection procedure.

Task	MMSE		FAB		LM-immediate		LM-delayed		TMT-A		TMT-B		CDT	
	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>
Sentence														
PC1					-0.023 (0.013)	0.077	-0.021 (0.013)	0.110	-0.006 (0.004)	0.086	-0.030 (0.014)	0.026		
PC2			-0.025 (0.014)	0.077							-0.035 (0.014)	0.015		
Pentagon														
PC1	-0.019 (0.010)	0.060												
PC2														
TMT-A														
PC1			0.051 (0.016)	0.002					0.012 (0.004)	0.004				
PC2									-0.067 (0.005)	<0.001	0.041 (0.022)	0.058		
TMT-B														
PC1	0.026 (0.010)	0.008			0.045 (0.013)	0.001	0.048 (0.013)	<0.001			0.141 (0.015)	<0.001	0.043 (0.015)	0.004
PC2	-0.048 (0.009)	<0.001	-0.071 (0.015)	<0.001	-0.059 (0.013)	<0.001	-0.052 (0.013)	<0.001	0.008 (0.005)	0.094	-0.189 (0.017)	<0.001	-0.051 (0.013)	<0.001
CDT														
PC1			-0.032 (0.015)	0.036									-0.035 (0.014)	0.015
PC2	-0.023 (0.009)	0.010	-0.034 (0.014)	0.013	-0.028 (0.013)	0.035			-0.025 (0.004)	<0.001	-0.045 (0.016)	0.005	-0.087 (0.013)	<0.001

The bold values highlight statistically significant associations (multiple linear regression, $p < 0.05$). The possible score ranges of the cognitive measures were rescaled from 0 to 1. In addition, the TMT scores were inverted by multiplying them by -1 to enable comparison with the other variable coefficients, because higher scores on the TMT indicate lower functioning. Sentence, sentence-writing item of the Mini-Mental State Examination (MMSE); Pentagon, pentagon-copying item of the MMSE; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; CDT, Clock Drawing Test; PC, principal component; SE, standard error.

Supplementary Table 5. Top 12 features used in the classification model for Alzheimer's disease (AD) versus cognitively normal (CN). Each feature's average impact on the model output is represented by the mean absolute SHapley Additive exPlanations (SHAP) value.

Feature category	Feature	Mean absolute SHAP value	Cumulative impact on model output, %
Motion	Pressure non-smoothness (TMT-B)	0.0743	14.7
Pause	Pause/drawing duration ratio (TMT-B)	0.0733	29.2
Pause	Adjusted total duration (TMT-B)	0.0715	43.3
Pause	Adjusted total pause duration (TMT-B)	0.0708	57.3
Motion	Pressure variability, CV (CDT)	0.0385	65.0
Motion	Pressure variability, CV (Pentagon)	0.0369	72.2
Motion	Drawing speed variability, CV (Pentagon)	0.0345	79.1
Motion	Drawing speed, mm/s (TMT-B)	0.0279	84.6
Motion	Pressure change speed variability, SD (TMT-B)	0.0264	89.8
Pause	Pause/drawing duration ratio (CDT)	0.0214	94.0
Motion	Tilt-x variability, SD (CDT)	0.0195	97.9
Pause	Adjusted total pause duration (Pentagon)	0.0065	99.2

Pentagon, pentagon-copying item of the Mini-Mental State Examination; TMT-B, Trail Making Test part B; CDT, Clock Drawing Test; CV, coefficient of variation; SD, standard deviation.

Supplementary Table 6. Top 12 features used in the classification model for mild cognitive impairment (MCI) versus cognitively normal (CN). Each feature's average impact on the model output is represented by the mean absolute SHapley Additive exPlanations (SHAP) value.

Feature category	Feature	Mean absolute SHAP value	Cumulative impact on model output, %
Motion	Tilt-x variability, SD (CDT)	0.0735	11.7
Pause	Mean pause duration (TMT-B)	0.0607	21.4
Motion	Tilt-y change speed (TMT-B)	0.0562	30.3
Motion	Drawing speed (TMT-B)	0.0556	39.2
Motion	Drawing speed (Sentence)	0.0468	46.7
Motion	Pressure variability, CV (CDT)	0.0400	53.0
Motion	Drawing speed non-smoothness (TMT-B)	0.0386	59.2
Motion	Pressure non-smoothness (TMT-B)	0.0386	65.3
Motion	Drawing speed variability, CV (CDT)	0.0360	71.1
Motion	Drawing acceleration non-smoothness (TMT-B)	0.0323	76.2
Motion	Pressure variability, CV (TMT-A)	0.0319	81.3
Pause	Adjusted total duration (Pentagon)	0.0244	85.2

Sentence, sentence-writing item of the Mini-Mental State Examination (MMSE); Pentagon, pentagon-copying item of the MMSE; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; CDT, Clock Drawing Test; CV, coefficient of variation; SD, standard deviation.