Supplementary Material

Characteristics of Drawing Process Differentiate Alzheimer's Disease and Dementia with Lewy Bodies

Supplementary Method 1. Structural magnetic resonance imaging

The severity of medial temporal lobe atrophy was evaluated from structural magnetic resonance imaging scans at 1.5 T, T1-weighted images, and a 3D gradient-echo sequence with the following parameters: sagittal orientation with 1.2-mm-thick sections; time repetition/time echo 2400/3.52 ms; flip angle 8°; field of view 240×240. The severity was expressed as a Z-score relative to cognitively healthy adults by using a stand-alone, voxel-based specific regional analysis system for Alzheimer's disease [1].

Supplementary Method 2. Classification model parameters

The random forest hyperparameters that we used were as follows: search range of 2 and 3 for the maximum tree depth; 2, 3, and 4 for the maximum number of features; 1.0, 0.75, 0.5, and 0.25 for the proportion of the maximum number of samples to train each base regressor; and 2, 3, and 4 for the minimum number of samples required at a leaf node. The parameter for class weights was set to the "balanced" mode to adjust the weights in inverse proportion to the class frequencies in the input data. All other parameters were kept at their default values.

Supplementary Result 1. Missing drawing data

Three patients (2 AD, 1 LBD) could not perform the TMT-B task, and one LBD patient could not perform the TMT-A and TMT-B tasks. In addition, drawing data from a total of nine task

trials by six participants were missing because of technical issues with the data recording. As a result, all 40 features (five tasks) were extracted for 114 of the 123 participants, while 32, 24, and 16 features (four, three, and two tasks) were used for six, one, and two participants, respectively.

Supplementary Table 1. Additional clinical information for the LBD group

	MCI-LB (*n*=19)	DLB (*n*=8)
DLB core features, *n* (%)		
Cognitive fluctuations	3 (15.8%)	6 (75.0%)
Visual hallucinations	5 (26.3%)	4 (50.0%)
REM sleep behavior disorder	12 (63.2%)	5 (62.5%)
Parkinsonism	5 (26.3%)	4 (50.0%)
Five-item Unified Parkinson's Disease Rating Scale[1] [2,3], mean±SD	1.7 ± 1.5	3.3 ± 2.8

LBD, Lewy body disease; MCI-LB, mild cognitive impairment with Lewy bodies;

DLB, dementia with Lewy bodies; REM, rapid eye movement; SD, standard deviation.

[1] The total score range: 0 to 20.

Supplementary Table 2. Drawing features for the AD, LBD, and CN groups

	Mean (SD)				Adjusted p
	CN (*n*=49)	**AD (*n*=47)**	**LBD (*n*=27)**	η^2	
Sentence					
Drawing speed, mm/s	53.5 (18.9) [L]	50.8 (13.9) [L]	39.2 (13.0) [A,C]	0.101	**0.002**
Drawing speed variability (CV)	0.484 (0.110)	0.520 (0.137)	0.523 (0.147)	0.010	0.521
Drawing speed non-smoothness, /mm	0.261 (0.093) [L]	0.268 (0.086) [L]	0.386 (0.187) [A,C]	0.149	**<0.001**
Pressure variability (CV)	0.295 (0.034) [L]	0.307 (0.036)	0.325 (0.049) [C]	0.082	**0.008**
Pressure non-smoothness, /mm	0.218 (0.069) [L]	0.219 (0.078) [L]	0.280 (0.108) [A,C]	0.080	**0.008**
Mean pause duration, s	0.239 (0.079) [A]	0.326 (0.151) [C]	0.321 (0.141)	0.082	**0.008**
Pause/drawing duration ratio	1.01 (0.52) [L]	1.27 (0.51)	1.54 (0.70) [C]	0.099	**0.004**
Adjusted total duration, s/mm	0.036 (0.022) [L]	0.038 (0.014) [L]	0.060 (0.032) [A,C]	0.140	**<0.001**
Pentagon					
Drawing speed, mm/s	55.0 (23.3) [L]	50.0 (20.3) [L]	33.8 (16.1) [A,C]	0.140	**<0.001**
Drawing speed variability (CV)	0.422 (0.149)	0.480 (0.137)	0.472 (0.149)	0.023	0.256
Drawing speed non-smoothness, /mm	0.490 (0.313) [L]	0.554 (0.400) [L]	1.029 (0.687) [A,C]	0.189	**<0.001**
Pressure variability (CV)	0.189 (0.051)	0.212 (0.070)	0.237 (0.099)	0.042	0.081
Pressure non-smoothness, /mm	0.377 (0.204) [L]	0.408 (0.212) [L]	0.598 (0.357) [A,C]	0.113	**0.002**
Mean pause duration, s	0.567 (0.259) [L]	0.610 (0.218) [L]	0.848 (0.340) [A,C]	0.150	**<0.001**
Pause/drawing duration ratio	1.44 (0.66)	1.69 (0.73)	1.88 (0.74)	0.046	0.056
Adjusted total duration, s/mm	0.049 (0.023) [L]	0.057 (0.025) [L]	0.089 (0.046) [A,C]	0.202	**<0.001**
TMT-A					
Drawing speed, mm/s	103.1 (24.6) [L]	95.5 (37.6)	75.8 (27.9) [C]	0.064	**0.021**
Drawing speed variability (CV)	0.508 (0.104)	0.552 (0.113)	0.548 (0.093)	0.021	0.279

Drawing speed non-smoothness, /mm	0.185 (0.061) [L]	0.239 (0.166)	0.333 (0.206) [C]	0.082	**0.007**
Pressure variability (CV)	0.130 (0.040) [A,L]	0.173 (0.071) [C]	0.179 (0.063) [C]	0.116	**0.002**
Pressure non-smoothness, /mm	0.201 (0.052) [L]	0.238 (0.126)	0.311 (0.129) [C]	0.093	**0.004**
Mean pause duration, s	0.609 (0.269) [A,L]	0.888 (0.621) [C]	0.898 (0.327) [C]	0.085	**0.008**
Pause/drawing duration ratio	1.16 (0.59) [A]	1.91 (1.66) [C]	1.53 (0.63)	0.084	**0.008**
Adjusted total duration, s/mm	0.021 (0.007) [A]	0.035 (0.036) [C]	0.036 (0.017)	0.073	**0.013**
TMT-B					
Drawing speed, mm/s	95.4 (23.3) [L]	84.8 (33.4)	67.5 (27.4) [C]	0.093	**0.005**
Drawing speed variability (CV)	0.634 (0.136)	0.672 (0.156)	0.712 (0.138)	0.038	0.123
Drawing speed non-smoothness, /mm	0.213 (0.061) [L]	0.271 (0.128) [L]	0.406 (0.246) [A,C]	0.171	**<0.001**
Pressure variability (CV)	0.163 (0.051) [L]	0.187 (0.086)	0.232 (0.086) [C]	0.084	**0.008**
Pressure non-smoothness, /mm	0.218 (0.054) [L]	0.257 (0.103) [L]	0.354 (0.161) [A,C]	0.172	**<0.001**
Mean pause duration, s	1.459 (0.506) [A,L]	2.210 (1.014) [C]	2.473 (1.182) [C]	0.167	**<0.001**
Pause/drawing duration ratio	2.98 (1.12) [A,L]	5.60 (3.77) [C]	4.71 (2.07) [C]	0.155	**<0.001**
Adjusted total duration, s/mm	0.040 (0.013) [A,L]	0.081 (0.059) [C]	0.092 (0.057) [C]	0.169	**<0.001**
CDT					
Drawing speed, mm/s	66.7 (20.2) [L]	60.4 (17.8) [L]	42.9 (15.2) [A,C]	0.186	**<0.001**
Drawing speed variability (CV)	0.565 (0.108) [L]	0.618 (0.127)	0.696 (0.158) [C]	0.104	**0.003**
Drawing speed non-smoothness, /mm	0.283 (0.086) [L]	0.330 (0.133) [L]	0.514 (0.279) [A,C]	0.206	**<0.001**
Pressure variability (CV)	0.250 (0.043) [A,L]	0.278 (0.065) [C]	0.303 (0.073) [C]	0.130	**<0.001**
Pressure non-smoothness, /mm	0.232 (0.057) [L]	0.262 (0.087) [L]	0.352 (0.151) [A,C]	0.168	**<0.001**
Mean pause duration, s	0.680 (0.197) [A,L]	0.934 (0.461) [C]	1.012 (0.519) [C]	0.107	**0.002**
Pause/drawing duration ratio	1.69 (0.53) [A,L]	2.51 (1.49) [C]	2.60 (0.98) [C]	0.123	**0.001**
Adjusted total duration, s/mm	0.035 (0.010) [A,L]	0.054 (0.038) [C]	0.073 (0.041) [C]	0.156	**<0.001**

Data were compared by using one-way analyses of covariance (ANCOVAs) with the age, sex, and years of education as covariates, with Benjamini-Hochberg correction for multiple testing. Bold values highlight statistically significant differences among the three groups. Significant differences between individual diagnostic groups (Tukey-Kramer test, $p < 0.05$) are marked with A, L, or C (A: different from AD; L: different from LBD; C: different from CN). AD, Alzheimer's disease; LBD, Lewy body disease; CN, cognitively normal; 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; SD, standard deviation; CV, coefficient of variation.

Supplementary Table 3. Number of drawing features with significant differences between the diagnostic groups for each feature type

	Number of tasks with significant difference between AD versus CN	Number of tasks with significant difference between LBD versus CN
Speed-related		
Drawing speed	0	5 (Sentence, Pentagon, TMT-A, TMT-B, CDT)
Drawing speed variability	0	1 (CDT)
Drawing speed non-smoothness	0	5 (Sentence, Pentagon, TMT-A, TMT-B, CDT)
Pressure-related		
Pressure variability	2 (TMT-A, CDT)	4 (Sentence, TMT-A, TMT-B, CDT)
Pressure non-smoothness	0	5 (Sentence, Pentagon, TMT-A, TMT-B, CDT)
Pause-related		
Mean pause duration	4 (Sentence, TMT-A, TMT-B, CDT)	4 (Pentagon, TMT-A, TMT-B, CDT)
Pause/drawing duration ratio	3 (TMT-A, TMT-B, CDT)	3 (Sentence, TMT-B, CDT)
Adjusted total duration	3 (TMT-A, TMT-B, CDT)	4 (Sentence, Pentagon, TMT-B, CDT)
Total		
	12	31

AD, Alzheimer's disease; LBD, Lewy body disease; CN, cognitively normal; 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.

Supplementary Table 4. Number of drawing features with significant differences between the diagnostic groups for each drawing task

	AD versus CN	LBD versus CN	AD versus LBD
Sentence	1	6	4
Pentagon	0	5	5
TMT-A	4	5	0
TMT-B	3	7	2
CDT	4	8	3

AD, Alzheimer's disease; LBD, Lewy body disease; CN, cognitively normal; 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.

Supplementary Table 5. Drawing features for the AD, LBD, and CN groups when only MCI patients were included in the AD and LBD groups

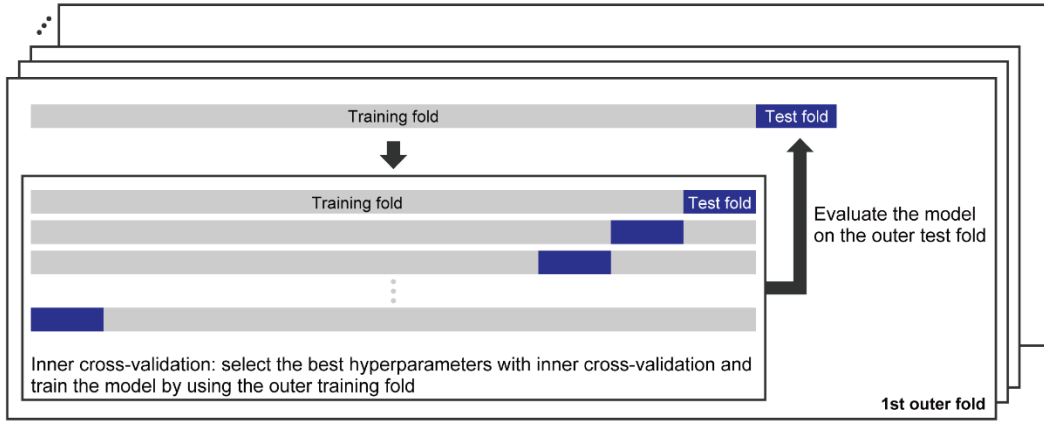|	Mean (SD)			Adjusted	
	CN (_n_=49)	**MCI-AD (_n_=25)**	**MCI-LB (_n_=19)**	η^2	_p_
Sentence					
Drawing speed, mm/s	53.5 (18.9) [L]	56.1 (13.9) [L]	40.6 (14.3) [A,C]	0.094	**0.013**
Drawing speed variability (CV)	0.484 (0.110)	0.525 (0.140)	0.502 (0.112)	0.015	0.519
Drawing speed non-smoothness, /mm	0.261 (0.093) [L]	0.235 (0.063) [L]	0.376 (0.192) [A,C]	0.160	**0.001**
Pressure variability (CV)	0.295 (0.034) [L]	0.306 (0.023)	0.325 (0.053) [C]	0.082	**0.028**
Pressure non-smoothness, /mm	0.218 (0.069) [L]	0.189 (0.047) [L]	0.276 (0.109) [A,C]	0.126	**0.005**
Mean pause duration, s	0.239 (0.079)	0.280 (0.128)	0.293 (0.114)	0.028	0.293
Pause/drawing duration ratio	1.01 (0.52)	1.13 (0.52)	1.38 (0.57)	0.049	0.129
Adjusted total duration, s/mm	0.036 (0.022) [L]	0.032 (0.009) [L]	0.055 (0.026) [A,C]	0.128	**0.005**
Pentagon					
Drawing speed, mm/s	55.0 (23.3) [L]	54.2 (23.0) [L]	35.4 (17.8) [A,C]	0.113	**0.009**
Drawing speed variability (CV)	0.422 (0.149)	0.443 (0.145)	0.440 (0.122)	0.003	0.884
Drawing speed non-smoothness, /mm	0.490 (0.313) [L]	0.529 (0.402) [L]	1.031 (0.742) [A,C]	0.191	**<0.001**
Pressure variability (CV)	0.189 (0.051)	0.208 (0.069)	0.206 (0.082)	0.015	0.519
Pressure non-smoothness, /mm	0.377 (0.204) [L]	0.390 (0.203) [L]	0.622 (0.379) [A,C]	0.133	**0.005**
Mean pause duration, s	0.567 (0.259) [L]	0.582 (0.172) [L]	0.822 (0.382) [A,C]	0.123	**0.006**
Pause/drawing duration ratio	1.44 (0.66)	1.51 (0.65)	1.73 (0.70)	0.025	0.345
Adjusted total duration, s/mm	0.049 (0.023) [L]	0.050 (0.022) [L]	0.084 (0.045) [A,C]	0.188	**<0.001**
TMT-A					
Drawing speed, mm/s	103.1 (24.6)	108.3 (37.9) [L]	82.8 (27.5) [A]	0.066	0.071
Drawing speed variability (CV)	0.508 (0.104)	0.500 (0.099)	0.532 (0.098)	0.007	0.731

Drawing speed non-smoothness, /mm	0.185 (0.061) [L]	0.189 (0.107) [L]	0.280 (0.137) [A,C]	0.101	**0.013**
Pressure variability (CV)	0.130 (0.040)	0.144 (0.063)	0.157 (0.047)	0.038	0.223
Pressure non-smoothness, /mm	0.201 (0.052) [L]	0.204 (0.103) [L]	0.285 (0.111) [A,C]	0.107	**0.012**
Mean pause duration, s	0.609 (0.269)	0.640 (0.235)	0.825 (0.336)	0.058	0.094
Pause/drawing duration ratio	1.16 (0.59)	1.34 (0.80)	1.38 (0.57)	0.016	0.519
Adjusted total duration, s/mm	0.021 (0.007) [L]	0.022 (0.009)	0.030 (0.012) [C]	0.090	**0.018**
TMT-B					
Drawing speed, mm/s	95.4 (23.3)	99.6 (36.5) [L]	74.8 (27.5) [A]	0.068	0.068
Drawing speed variability (CV)	0.634 (0.136)	0.625 (0.135)	0.707 (0.115)	0.041	0.176
Drawing speed non-smoothness, /mm	0.213 (0.061) [L]	0.224 (0.106) [L]	0.338 (0.159) [A,C]	0.158	**0.002**
Pressure variability (CV)	0.163 (0.051) [L]	0.154 (0.061) [L]	0.213 (0.089) [A,C]	0.085	**0.034**
Pressure non-smoothness, /mm	0.218 (0.054) [L]	0.217 (0.092) [L]	0.320 (0.143) [A,C]	0.148	**0.003**
Mean pause duration, s	1.459 (0.506) [A,L]	1.840 (0.640) [C]	2.046 (0.829) [C]	0.109	**0.012**
Pause/drawing duration ratio	2.98 (1.12) [A]	4.02 (1.76) [C]	3.93 (1.50)	0.111	**0.012**
Adjusted total duration, s/mm	0.040 (0.013) [A,L]	0.051 (0.023) [C]	0.067 (0.029) [C]	0.176	**<0.001**
CDT					
Drawing speed, mm/s	66.7 (20.2) [L]	64.9 (16.5) [L]	44.5 (16.2) [A,C]	0.176	**<0.001**
Drawing speed variability (CV)	0.565 (0.108)	0.598 (0.099)	0.644 (0.100)	0.054	0.115
Drawing speed non-smoothness, /mm	0.283 (0.086) [L]	0.291 (0.090) [L]	0.479 (0.273) [A,C]	0.215	**<0.001**
Pressure variability (CV)	0.250 (0.043) [L]	0.265 (0.042) [L]	0.303 (0.074) [A,C]	0.153	**0.002**
Pressure non-smoothness, /mm	0.232 (0.057) [L]	0.236 (0.070) [L]	0.334 (0.155) [A,C]	0.161	**0.002**
Mean pause duration, s	0.680 (0.197)	0.780 (0.270)	0.857 (0.332)	0.060	0.089
Pause/drawing duration ratio	1.69 (0.53) [L]	1.97 (0.71)	2.27 (0.73) [C]	0.092	**0.026**
Adjusted total duration, s/mm	0.035 (0.010) [L]	0.039 (0.011) [L]	0.063 (0.036) [A,C]	0.232	**<0.001**

Data were compared by using one-way analyses of covariance (ANCOVAs) with the age, sex, and years of education as covariates, with Benjamini-Hochberg correction for multiple testing. Bold values highlight statistically significant differences among the three groups. Significant differences between individual diagnostic groups (Tukey-Kramer test, $p < 0.05$) are marked with A, L, or C (A: different from MCI-AD; L: different from MCI-LB; C: different from CN). AD, Alzheimer's disease; LBD, Lewy body disease; CN, cognitively normal; MCI-AD, mild cognitive impairment (MCI) due to AD; MCI-LB, MCI with Lewy bodies; 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; SD, standard deviation; CV, coefficient of variation.

Supplementary Table 6. Number of drawing features retaining significant differences between the diagnostic groups for each feature type when only MCI patients were included in the AD and LBD groups

	Number of tasks with significant difference between MCI-AD versus CN	Number of tasks with significant difference between MCI-LB versus CN
Speed-related		
Drawing speed	0	3 (Sentence, Pentagon, CDT)
Drawing speed variability	0	0
Drawing speed non-smoothness	0	5 (Sentence, Pentagon, TMT-A, TMT-B, CDT)
Pressure-related		
Pressure variability	0	3 (Sentence, TMT-B, CDT)
Pressure non-smoothness	0	5 (Sentence, Pentagon, TMT-A, TMT-B, CDT)
Pause-related		
Mean pause duration	1 (TMT-B)	2 (Pentagon, TMT-B)
Pause/drawing duration ratio	1 (TMT-B)	1 (CDT)
Adjusted total duration	1 (TMT-B)	4 (Sentence, Pentagon, TMT-B, CDT)
Total		
	3	23

AD, Alzheimer's disease; LBD, Lewy body disease; CN, cognitively normal; MCI-AD, mild cognitive impairment (MCI) due to AD; MCI-LB, MCI with Lewy bodies; 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.

Supplementary Figure 1. Schematic overview of the nested cross-validation procedure.

REFERENCES

[1]   Matsuda H, Mizumura S, Nemoto K, Yamashita F, Imabayashi E, Sato N, Asada T (2012) Automatic voxel-based morphometry of structural MRI by SPM8 plus diffeomorphic anatomic registration through exponentiated lie algebra improves the diagnosis of probable Alzheimer disease. *AJNR Am J Neuroradiol* **33**, 1109-1114.

[2]   Thomas AJ, Taylor JP, McKeith I, Bamford C, Burn D, Allan L, O'Brien J (2018) Revision of assessment toolkits for improving the diagnosis of Lewy body dementia: The DIAMOND Lewy study. *Int J Geriatr Psychiatry* **33**, 1293–304.

[3]   Thomas A (2022) Corrigendum: Revision of assessment toolkits for improving the diagnosis of Lewy body dementia: The DIAMOND Lewy study. *Int J Geriatr Psychiatry* **37**, doi: 10.1002/gps.5663.