

# Supplementary material

Table S1. Demographic and clinical characteristics of the overall study population based on a priori NMSS subtyping

	Overall (n= 168) (100%)	Cortical (n= 38) (22.6%)	Limbic (n=48) (28.6%)	Brainstem (n=82) (48.8%)	P-value	Adj. P-value (Benjamini- Hochberg)	Post hoc test (significant pairs)
<b>Gender</b> <b>(male)</b>	100 (59.9%)	24 (63.2%)	20 (41.7%)	56 (68.3%)	0.010 $\chi^2$	0.020	Limbic-M/F
<b>Age (years)</b>	71.70 $\pm$ 9.57	77.08 $\pm$ 8.42	68.81 $\pm$ 8.88	70.89 $\pm$ 9.57	<0.001 <sup>KW</sup>	0.055 (sig.)	Cortical- Limbic Cortical- Brainstem
<b>Age at onset</b> <b>(years)</b>	65.45 $\pm$ 10.18	72.21 $\pm$ 8.06	61.90 $\pm$ 9.55	64.40 $\pm$ 10.06	<0.001 <sup>KW</sup>	0.014	Cortical- Limbic Cortical- Brainstem
<b>Age at onset</b> <b>50-70 years</b> <b>(%)</b>	103 (61.3%)	12 (31.6%)	33 (68.8%)	58 (70.7%)	<0.001 <sup>KW</sup>	0.014	Cortical- Limbic Cortical- Brainstem
<b>Education <math>\geq</math></b> <b>3. stage</b> <b>based on</b> <b>ISCED (%)</b>	123 (73.2%)	18 (47.3%)	39 (81.2%)	66 (80.4%)	<0.001 <sup>KW</sup>	0.028	Cortical- Limbic Cortical- Brainstem
<b>Right-</b> <b>handed (%)</b>	144 (85.7%)	23 (60.5%)	45 (93.8%)	76 (92.7%)	0.001 $\chi^2$	0.018	Cortical- Left/Right
<b>Disease</b> <b>duration &gt; 10</b> <b>years (%)</b>	34 (20.2%)	3 (7.9%)	12 (25.0%)	19 (23.2%)	0.045 <sup>KW</sup>	0.077	Cortical- Limbic
<b>+ family</b> <b>history</b>	27 (16.1%)	11 (28.9%)	6 (12.5%)	10 (12.2%)	0.235 $\chi^2$	0.294	
<b>Side of onset</b> <b>- right (%)</b>	92 (54.8%)	25 (65.8%)	23 (47.9%)	44 (53.7%)	0.245 $\chi^2$	0.299	
<b>Motor subtype:</b>							
<b>TD (%)</b>	87 (51.8%)	2 (5.3%)	36 (75.0%)	49 (59.8%)	<0.001 $\chi^2$	0.004	Cortical- TD/PIGD, Limbic- TD/PIGD Brainstem- PIGD
<b>PIGD (%)</b>	61 (36.3%)	33 (86.8%)	7 (14.6%)	21 (25.6%)			
<b>Intermediate</b> <b>(%)</b>	20 (11.9%)	3 (7.9%)	5 (10.4%)	12 (14.6%)			
<b>Risk factors</b>							
<b>Pesticides</b> <b>(%)</b>	53 (31.5%)	11 (28.9%)	11 (22.9%)	31 (37.8%)	0.196 $\chi^2$	0.251	
<b>Solvents (%)</b>	28 (16.7%)	5 (13.2%)	7 (14.6%)	16 (19.5%)	0.617 $\chi^2$	0.640	
<b>Rural</b> <b>environment</b> <b>(%)</b>	111 (66.1%)	20 (52.6%)	31 (64.6%)	60 (73.2%)	0.084 $\chi^2$	0.136	
<b>Head injury</b> <b>(%)</b>	26 (15.5%)	10 (26.3%)	6 (12.5%)	10 (12.2%)	0.110 $\chi^2$	0.168	

<b>Non-caffeine (%)</b>	56 (33.3%)	16 (42.1%)	7 (14.6%)	33 (40.2%)	0.005 $\chi^2$	0.012	Limbic-Y/N
<b>Alcohol (%)</b>	53 (31.5%)	6 (15.8%)	10 (20.8%)	37 (45.1%)	0.002 $KW$	0.006	Cortical-Brainstem Limbic-Brainstem
<b>Non-smoking (%)</b>	104 (61.9%)	14 (36.8%)	31 (64.6%)	59 (72.0%)	0.003 $KW$	0.008	Cortical-Limbic Cortical-Brainstem
<b>Prodromal NMS</b>							
<b>RBD (%)</b>	49 (29.2%)	14 (36.8%)	9 (18.8%)	26 (31.7%)	0.145 $\chi^2$	0.199	
<b>Smell disorder (%)</b>	46 (27.4%)	14 (36.8%)	6 (12.5%)	26 (31.7%)	0.020 $\chi^2$	0.039	Limbic-Y/N
<b>Constipation (%)</b>	51 (30.4%)	8 (21.1%)	9 (18.8%)	34 (41.5%)	0.009 $\chi^2$	0.019	Brainstem-Y/N
<b>EDS (%)</b>	15 (8.9%)	3 (7.9%)	2 (4.2%)	10 (12.2%)	0.292 $\chi^2$	0.349	
<b>Hypotension (%)</b>	23 (13.7%)	9 (23.7%)	4 (8.3%)	10 (12.2%)	0.104 $\chi^2$	0.163	
<b>Sexual dysfunction (%)</b>	29 (17.3%)	5 (13.2%)	11 (22.9%)	13 (15.9%)	0.441 $\chi^2$	0.505	
<b>Micturition dysfunction (%)</b>	17 (10.1%)	2 (5.3%)	5 (10.4%)	10 (12.2%)	0.502 $\chi^2$	0.552	
<b>Depression (%)</b>	39 (23.2%)	3 (7.9%)	24 (50%)	12 (14.6%)	<0.001 $\chi^2$	0.011	All pairs
<b>No. of prodromes</b>	2.2 $\pm$ 1.34	2.16 $\pm$ 1.26	2.17 $\pm$ 1.04	2.24 $\pm$ 1.53	0.947 $KW$	0.947	
<b>No. of NMS</b>	6.88 $\pm$ 3.21	5.89 $\pm$ 2.15	7.25 $\pm$ 2.99	7.12 $\pm$ 3.66	0.154 $KW$	0.207	
<b>MoCA</b>	25.77 $\pm$ 2.55	23.97 $\pm$ 1.94	26.50 $\pm$ 2.54	26.18 $\pm$ 2.43	<0.001 $KW$	0.005	Cortical-Limbic Cortical-Brainstem
<b>HAM-A</b>	6.05 $\pm$ 5.32	2.58 $\pm$ 1.73	10.90 $\pm$ 5.07	4.83 $\pm$ 4.57	<0.001 $KW$	0.005	All pairs
<b>HAM-D</b>	6.95 $\pm$ 5.61	3.11 $\pm$ 1.69	12.54 $\pm$ 5.50	5.46 $\pm$ 4.28	<0.001 $KW$	0.004	All pairs
<b>UPDRS III</b>	37.37 $\pm$ 10.96	35.76 $\pm$ 9.11	39.85 $\pm$ 10.51	36.66 $\pm$ 11.85	0.130 $KW$	0.183	
<b>H&amp;Y</b>	2.45 $\pm$ 0.70	2.82 $\pm$ 0.51	2.33 $\pm$ 0.75	2.35 $\pm$ 0.69	<0.001 $KW$	0.004	Cortical-Limbic Cortical-Brainstem
<b>LED</b>	725.00 $\pm$ 285.76	733.68 $\pm$ 283.27	685.62 $\pm$ 276.14	744.02 $\pm$ 293.50	0.522 $KW$	0.563	
<b>ESS</b>	6.72 $\pm$ 4.24	6.79 $\pm$ 4.69	5.10 $\pm$ 2.68	7.63 $\pm$ 4.53	0.002 $KW$	0.006	Limbic-Brainstem
<b>FSS</b>	31.81 $\pm$ 13.18	29.76 $\pm$ 10.74	35.67 $\pm$ 11.65	30.50 $\pm$ 14.64	0.023 $KW$	0.044	Cortical-Limbic
<b>RBDSQ</b>	4.92 $\pm$ 2.65	4.39 $\pm$ 2.52	4.23 $\pm$ 2.15	5.57 $\pm$ 2.83	0.008 $KW$	0.018	Limbic-Brainstem

SAS	11.35 ± 6.39	14.63 ± 5.75	10.35 ± 5.29	10.40 ± 6.81	0.001 <sup>KW</sup>	0.003	Cortical- Limbic Cortical- Brainstem
NMSS	59.38 ± 36.94	48.92 ± 21.43	66.58 ± 34.87	60.00 ± 42.61	0.077 <sup>KW</sup>	0.128	

**Table S2. Frequencies of individual NMS in the overall study population and individual NMS subtype (a priori approach)**

NMS	Overall (n= 168) (100%)	Cortical (n= 38) (22.6%)	Limbic (n=48) (20.6%)	Brainstem (n=82) (48.8%)	P- value*	Adj. P- value (Benjamini- Hochberg)	Post hoc test (significant pairs)
Salivation (%)	38 (22.6%)	7 (18.4%)	9 (18.8%)	22 (26.8%)	0.444	0.498	
Smell disorder (%)	54 (32.1%)	16 (42.1%)	7 (14.6%)	31 (37.8%)	0.008	0.018	Limbic
Dysphagia (%)	36 (21.4%)	9 (23.7%)	8 (16.7%)	19 (23.2%)	0.635	0.647	
Nausea/vomiting (%)	40 (23.8%)	4 (10.5%)	10 (20.8%)	26 (31.7%)	0.034	0.060	
Constipation (%)	75 (44.6%)	10 (26.3%)	17 (35.4%)	48 (58.5%)	<0.001	0.009	Cortical, Brainstem
Micturition dysfunction (%)	81 (48.2%)	12 (31.6%)	19 (39.6%)	50 (61.0%)	0.004	0.010	Brainstem
Sexual dysfunction (%)	97 (57.7%)	19 (50.0%)	28 (58.3%)	50 (61.0%)	0.524	0.554	
Dizziness (%)	94 (56.0%)	20 (52.6%)	31 (64.6%)	43 (52.4%)	0.362	0.424	
Sleep dysfunction (%)	121 (72.0%)	24 (63.2%)	32 (66.7%)	65 (79.3%)	0.116	0.168	
Legs swelling (%)	40 (23.8%)	7 (18.4%)	16 (33.3%)	17 (20.7%)	0.179	0.234	
Excessive sweating (%)	48 (28.6%)	4 (10.5%)	12 (25.0%)	32 (39.0%)	0.005	0.012	Cortical, Brainstem
Diplopia (%)	21 (12.5%)	3 (7.9%)	2 (4.2%)	16 (19.5%)	0.024	0.044	Brainstem
Pain (%)	86 (51.2%)	15 (39.5%)	35 (72.9%)	36 (43.9%)	0.002	0.006	Limbic
Depression (%)	91 (54.2%)	14 (36.8%)	40 (83.3%)	37 (45.1%)	<0.001	0.008	Cortical, Limbic
Anxiety (%)	78 (46.4%)	7 (18.4%)	43 (89.6%)	28 (34.1%)	<0.001	0.007	Cortical, Limbic, Brainstem
Psychosis (%)	27 (16.1%)	2 (5.3%)	10 (20.8%)	15 (18.3%)	0.111	0.165	
Cognitive impairment (%)	102 (60.7%)	34 (89.5%)	26 (54.2%)	42 (51.2%)	<0.001	0.006	Cortical, Brainstem

<b>Apathy (%)</b>	53 (31.5%)	22 (57.9%)	11 (22.9%)	20 (24.4%)	<0.001	0.006	Cortical
-------------------	---------------	---------------	---------------	------------	--------	-------	----------

\*All hypotheses tested using  $\chi^2$  test of independence.

**Table S3. Frequencies of individual first NMS in the overall study population and individual NMS subtype (a priori approach)**

<b>First NMS</b>	<b>Overall (n= 168) (100%)</b>	<b>Cortical (n= 38) (22.6%)</b>	<b>Limbic (n=48) (20.6%)</b>	<b>Brainstem (n=82) (48.8%)</b>
<b>Smell disorder (%)</b>	32 (19.0%)	12 (31.6%)	3 (6.3%)	17 (20.7%)
<b>Constipation (%)</b>	33 (19.6%)	6 (15.8%)	5 (10.4%)	22 (26.8%)
<b>Micturition dysfunction (%)</b>	2 (1.2%)	0	1 (2.1%)	1 (1.2%)
<b>Sexual dysfunction (%)</b>	8 (4.8%)	2 (5.3%)	2 (4.2%)	4 (4.9%)
<b>Dizziness (%)</b>	9 (5.4%)	2 (5.3%)	4 (8.3%)	3 (3.7%)
<b>Sleep dysfunction (%)</b>	27 (16.1%)	8 (21.1%)	4 (8.3%)	15 (18.3%)
<b>Legs swelling (%)</b>	1 (0.6%)	0	0	1 (1.2%)
<b>Excessive sweating (%)</b>	10 (6.0%)	1 (2.6%)	2 (4.2%)	7 (8.5%)
<b>Pain (%)</b>	9 (5.4%)	2 (5.3%)	3 (6.3%)	4 (4.9%)
<b>Depression (%)</b>	19 (11.3%)	0	14 (29.2%)	5 (6.1%)
<b>Anxiety (%)</b>	13 (7.7%)	1 (2.6%)	10 (20.8%)	2 (2.4%)
<b>Cognitive impairment (%)</b>	4 (2.4%)	4 (10.5%)	0	0

**Table S4. Demographic and clinical characteristics of the overall study population based on cluster analysis**

	<b>Overall (n= 168) (100%)</b>	<b>Cluster 1 (n=31) (18.5%)</b>	<b>Cluster 2 (n=33) (19.6%)</b>	<b>Cluster 3 (n=34) (20.2%)</b>	<b>Cluster 4 (n=52) (31.0%)</b>	<b>Cluster 5 (n=18) (10.7%)</b>	<b>P-value</b>	<b>Adj. P-value (Benjamini-Hochberg)</b>
<b>Gender (male) (%)</b>	100 (59.9%)	21 (67.7%)	11 (33.3%)	21 (61.8%)	34 (65.3%)	13 (72.2%)	0.015 $\chi^2$	0.025
<b>Age (years)</b>	71.70 $\pm$ 9.57	78.29 $\pm$ 8.60	69.33 $\pm$ 8.67	71.85 $\pm$ 10.29	68.58 $\pm$ 8.87	73.39 $\pm$ 7.94	<0.001 KW	0.038
<b>Age at onset (years)</b>	65.45 $\pm$ 10.18	72.74 $\pm$ 8.71	62.42 $\pm$ 9.09	64.91 $\pm$ 10.05	64.10 $\pm$ 9.77	63.39 $\pm$ 11.03	<0.001 KW	0.019
<b>Age at onset 50-70 years (%)</b>	103 (61.3%)	8 (25.8%)	24 (72.7%)	24 (70.6%)	37 (71.2%)	10 (55.6%)	<0.001 KW	0.013

Education ≥ 3. stage based on ISCED (%)	123 (73.2%)	14 (45.2%)	28 (84.8%)	26 (76.5%)	42 (80.8%)	13 (72.2%)	0.004 <sup>KW</sup>	0.008
Right-handed (%)	144 (85.7%)	20 (64.5%)	31 (93.9%)	31 (91.2%)	34 (65.4%)	17 (94.4%)	0.002 <sup>χ²</sup>	0.004
Disease duration > 10 years (%)	34 (20.2%)	4 (12.9%)	7 (21.2%)	10 (29.4%)	5 (9.6%)	8 (44.4%)	0.003 <sup>KW</sup>	0.006
+ family history	27 (16.1%)	9 (29.0%)	4 (12.1%)	6 (17.6%)	6 (11.5%)	2 (11.1%)	0.449 <sup>χ²</sup>	0.461
Side of onset – right (%)	92 (54.8%)	20 (64.5%)	18 (54.5%)	18 (52.9%)	29 (55.8%)	7 (38.9%)	0.543 <sup>χ²</sup>	0.543
Motor subtype:								
TD (%)	87 (51.8%)	2 (6.5%)	28 (84.8%)	19 (55.9%)	29 (55.8%)	9 (50.0%)	<0.001 <sup>χ²</sup>	0.003
PIGD (%)	61 (36.3%)	28 (90.3%)	5 (15.2%)	9 (26.5%)	12 (23.1%)	7 (38.9%)		
Intermediate (%)	20 (11.9%)	1 (3.2%)	0 (0.0%)	6 (17.6%)	11 (21.2%)	2 (11.1%)		
Risk factors								
Pesticides (%)	53 (31.5%)	9 (29.0%)	7 (21.2%)	13 (38.2%)	14 (26.9%)	10 (55.6%)	0.101 <sup>χ²</sup>	0.132
Solvents (%)	28 (16.7%)	5 (16.1%)	1 (3.0%)	4 (11.8%)	13 (25.0%)	5 (27.8%)	0.056 <sup>χ²</sup>	0.082
Rural environment (%)	111 (66.1%)	15 (48.4%)	21 (63.6%)	24 (70.6%)	37 (71.2%)	14 (77.8%)	0.170 <sup>χ²</sup>	0.202
Head injury (%)	26 (15.5%)	10 (32.3%)	2 (6.1%)	4 (11.8%)	3 (5.8%)	7 (38.9%)	<0.001 <sup>χ²</sup>	0.010
Non-caffeine (%)	56 (33.3%)	15 (48.4%)	29 (87.9%)	20 (58.8%)	36 (69.2%)	12 (66.7%)	0.014 <sup>χ²</sup>	0.024
Alcohol (%)	53 (31.5%)	6 (19.4%)	8 (24.2%)	19 (55.9%)	13 (25.0%)	7 (38.9%)	0.019 <sup>χ²</sup>	0.030
Non-smoking (%)	104 (61.9%)	13 (41.9%)	20 (60.6%)	24 (70.6%)	36 (69.2%)	11 (61.1%)	0.286 <sup>χ²</sup>	0.320
Prodromal NMS								
RBD (%)	49 (29.2%)	11 (35.5%)	7 (21.2%)	9 (26.5%)	14 (26.9%)	8 (44.4%)	0.421 <sup>χ²</sup>	0.444
Smell disorder (%)	46 (27.4%)	14 (45.2%)	4 (12.1%)	10 (29.4%)	12 (23.1%)	6 (33.3%)	0.046 <sup>χ²</sup>	0.070
Constipation (%)	51 (30.4%)	5 (16.1%)	5 (15.2%)	20 (58.8%)	12 (23.1%)	9 (50.0%)	<0.001 <sup>χ²</sup>	0.008
EDS (%)	15 (8.9%)	3 (9.7%)	0 (0.0%)	6 (17.6%)	5 (9.6%)	1 (5.6%)	0.152 <sup>χ²</sup>	0.186

<b>Hypotension (%)</b>	23 (13.7%)	9 (29.0%)	4 (12.1%)	3 (8.8%)	6 (11.5%)	1 (5.6%)	0.087 $\chi^2$	0.118
<b>Sexual dysfunction (%)</b>	29 (17.3%)	6 (19.4%)	6 (18.2%)	6 (17.6%)	5 (9.6%)	6 (33.3%)	0.240 $\chi^2$	0.276
<b>Micturition dysfunction (%)</b>	17 (10.1%)	2 (6.5%)	1 (3.0%)	3 (8.8%)	8 (15.4%)	3 (16.7%)	0.311 $\chi^2$	0.338
<b>Depression (%)</b>	39 (23.2%)	2 (6.5%)	17 (51.5%)	5 (14.7%)	9 (17.3%)	6 (33.3%)	<0.001 $\chi^2$	0.006
<b>No. of prodromes</b>	2.2 $\pm$ 1.34	2.42 $\pm$ 1.23	2.06 $\pm$ 0.97	2.41 $\pm$ 1.74	1.85 $\pm$ 1.18	2.72 $\pm$ 1.49	0.106 $KW$	0.134
<b>No. of NMS</b>	6.88 $\pm$ 3.21	6.58 $\pm$ 1.65	7.58 $\pm$ 2.54	8.03 $\pm$ 2.67	4.35 $\pm$ 2.66	11.28 $\pm$ 2.35	<0.001 $KW$	0.005 (sig.)
<b>MoCA</b>	25.77 $\pm$ 2.55	23.45 $\pm$ 1.75	26.55 $\pm$ 2.21	25.94 $\pm$ 2.41	27.10 $\pm$ 2.12	24.22 $\pm$ 2.32	<0.001 $KW$	0.004
<b>HAM-A</b>	6.05 $\pm$ 5.32	2.87 $\pm$ 2.13	12.33 $\pm$ 4.76	4.15 $\pm$ 2.23	3.02 $\pm$ 2.43	12.39 $\pm$ 5.17	<0.001 $KW$	0.004
<b>HAM-D</b>	6.95 $\pm$ 5.61	3.06 $\pm$ 1.18	14.27 $\pm$ 4.89	4.88 $\pm$ 2.27	3.83 $\pm$ 1.92	163.17 $\pm$ 5.44	<0.001 $KW$	0.003
<b>UPDRS III</b>	37.37 $\pm$ 10.96	36.29 $\pm$ 7.26	39.21 $\pm$ 6.80	38.85 $\pm$ 9.56	32.63 $\pm$ 11.93	46.72 $\pm$ 14.90	<0.001 $KW$	0.003
<b>H&amp;Y</b>	2.45 $\pm$ 0.70	2.90 $\pm$ 0.40	2.27 $\pm$ 0.63	2.50 $\pm$ 0.66	2.04 $\pm$ 0.52	3.11 $\pm$ 0.83	<0.001 $KW$	0.003
<b>LED</b>	725.00 $\pm$ 285.76	748.39 $\pm$ 296.56	673.18 $\pm$ 270.57	751.47 $\pm$ 234.74	682.88 $\pm$ 308.40	851.39 $\pm$ 294.87	0.077 $KW$	0.108
<b>ESS</b>	6.72 $\pm$ 4.24	7.13 $\pm$ 4.77	5.18 $\pm$ 2.69	8.29 $\pm$ 5.24	5.52 $\pm$ 3.19	9.33 $\pm$ 4.23	<0.001 $KW$	0.003
<b>FSS</b>	31.81 $\pm$ 13.18	31.42 $\pm$ 9.91	35.12 $\pm$ 10.68	34.56 $\pm$ 14.14	24.77 $\pm$ 12.77	41.56 $\pm$ 12.35	<0.001 $KW$	0.002
<b>RBDSQ</b>	4.92 $\pm$ 2.65	4.90 $\pm$ 2.71	4.48 $\pm$ 2.32	5.85 $\pm$ 2.80	4.10 $\pm$ 2.07	6.39 $\pm$ 3.33	0.010 $KW$	0.018
<b>SAS</b>	11.35 $\pm$ 6.39	15.71 $\pm$ 5.62	10.85 $\pm$ 5.69	11.24 $\pm$ 5.56	7.77 $\pm$ 5.07	15.28 $\pm$ 7.51	<0.001 $KW$	0.002
<b>NMSS</b>	59.38 $\pm$ 36.94	56.90 $\pm$ 15.91	68.27 $\pm$ 21.48	64.47 $\pm$ 22.61	25.54 $\pm$ 13.04	135.44 $\pm$ 27.20	<0.001 $KW$	0.005