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Supplementary Materials for

Mass spectrometry imaging identifies abnormally elevated brain L-DOPA levels and extrastriatal monoaminergic dysregulation in L-DOPA–induced dyskinesia

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The PDF file includes:

Other Supplementary Material for this manuscript includes the following:

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Supplementary Material

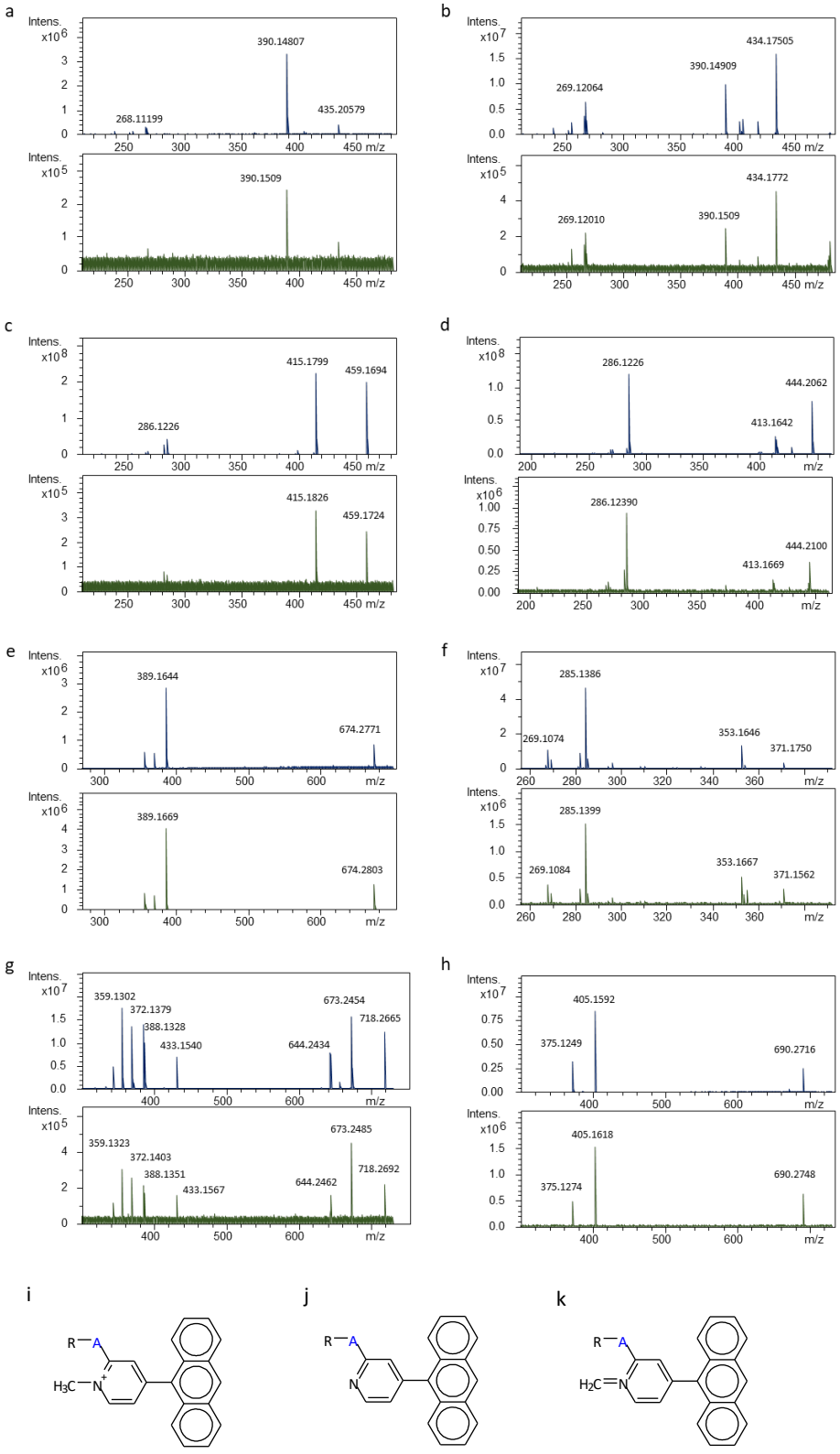


Fig. S1. Identification of neurotransmitter metabolites and structural formulas of the different forms of the reactive matrix, FMP-10, detected in MALDI-MSI experiments.

(a-h) MS/MS spectra collected from metabolite standards (blue) matched with MS/MS spectra obtained from tissue (green). **(a)** 3-MT, precursor ion *m/z* 435.20, **(b)** 3-OMD, precursor ion *m/z* 479.19, **(c)** 5-HIAA, precursor ion *m/z* 459.17, **(d)** 5-HT, precursor ion *m/z* 444.20, **(e)** DA, precursor ion *m/z* 674.28,**(f)** GABA, precursor ion *m/z* 371.00, **(g)** L-DOPA, precursor ion *m/z* 718.28, **(h)** NE, precursor ion *m/z* 690.28. The CID value was 30 eV and the precursor ion isolation window (Q1) was 1 Da for all analyses. **(i-k)** FMP-10 may be detected in three different molecular forms attached to primary amines or phenolic hydroxyl groups on target molecules. This creates a possibility of several *m/z* per target molecule. **(i)** Molecules that have only one reactive moiety (primary amine or phenolic hydroxyl group) are derivatized with FMP-10 (adding a positive charge, $z = +1$). **(j,k)** Molecules that have more than one reactive moiety have one FMP-10 in form **(i)** and another one in form **(j)** or **(k)** ($z = +1$). A, either an oxygen (O) or a nitrogen (N). R-A, the FMP-10 derivatized molecule.

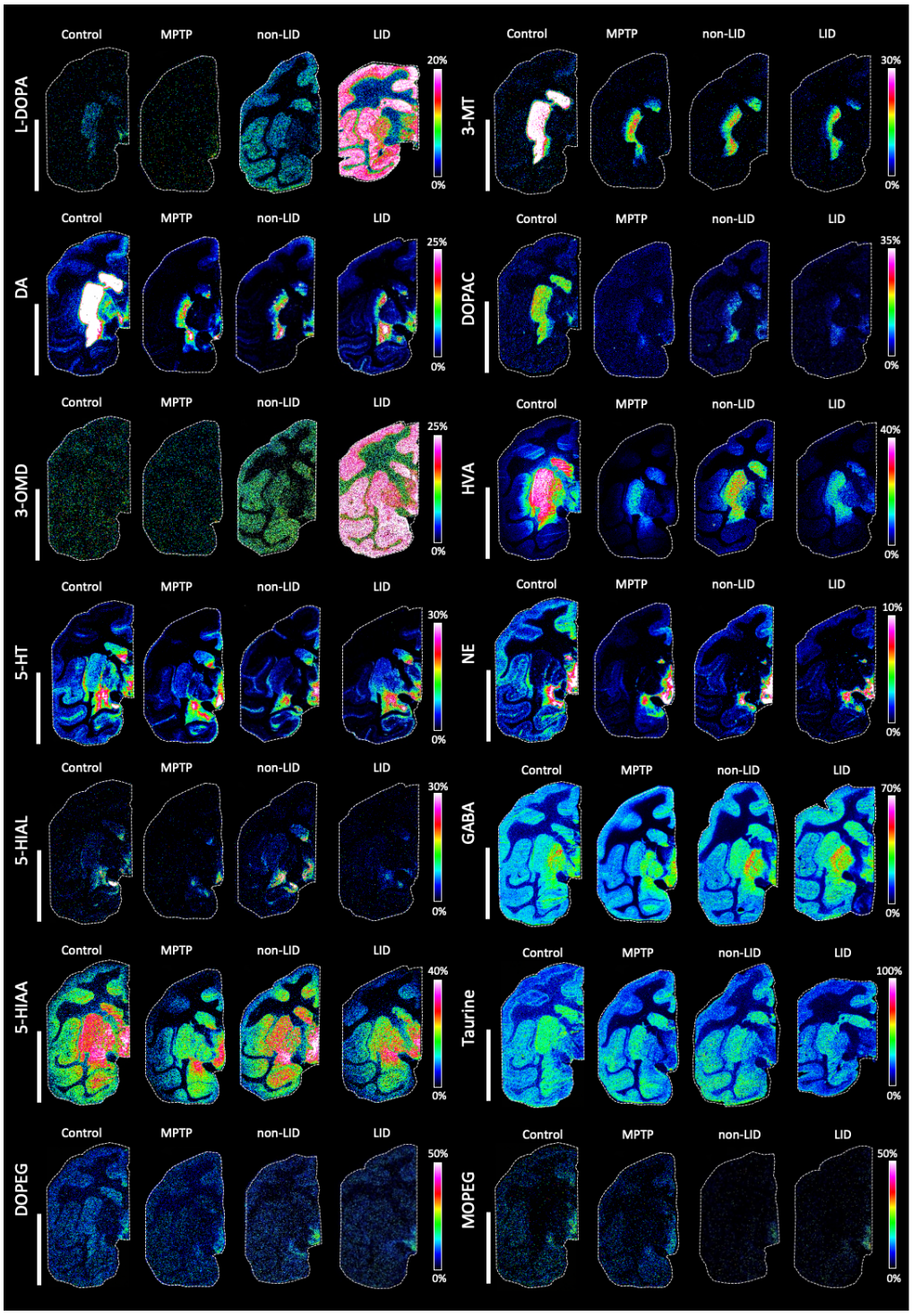


Fig. S2. MALDI-MS images of neurotransmitters and metabolites in control, MPTP, non-LID and LID tissue sections.

Ion intensity are indicated with a rainbow colour scale. All images are RMS normalized and log transformed. Lateral resolution 150 µm, scale bar 20 mm.

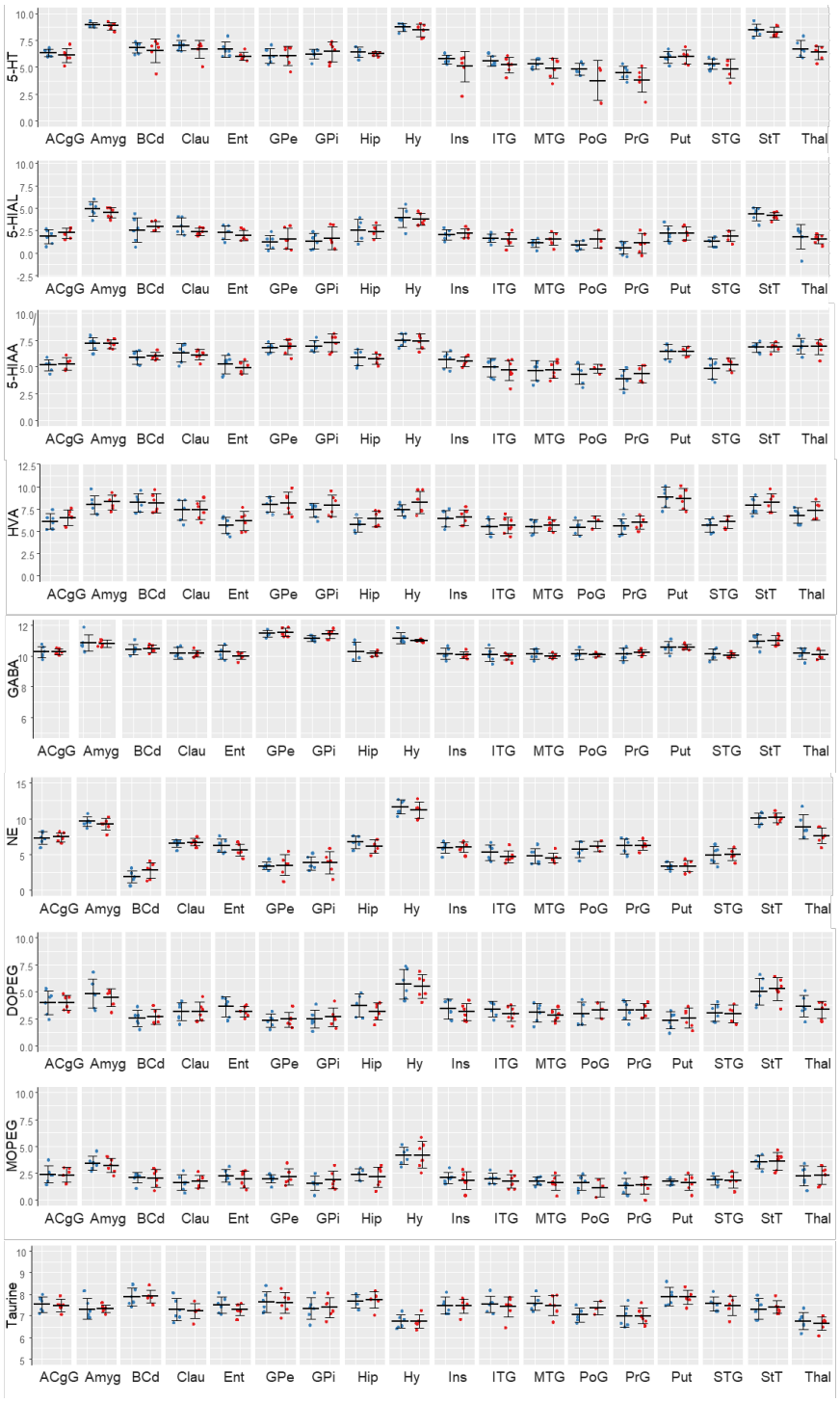
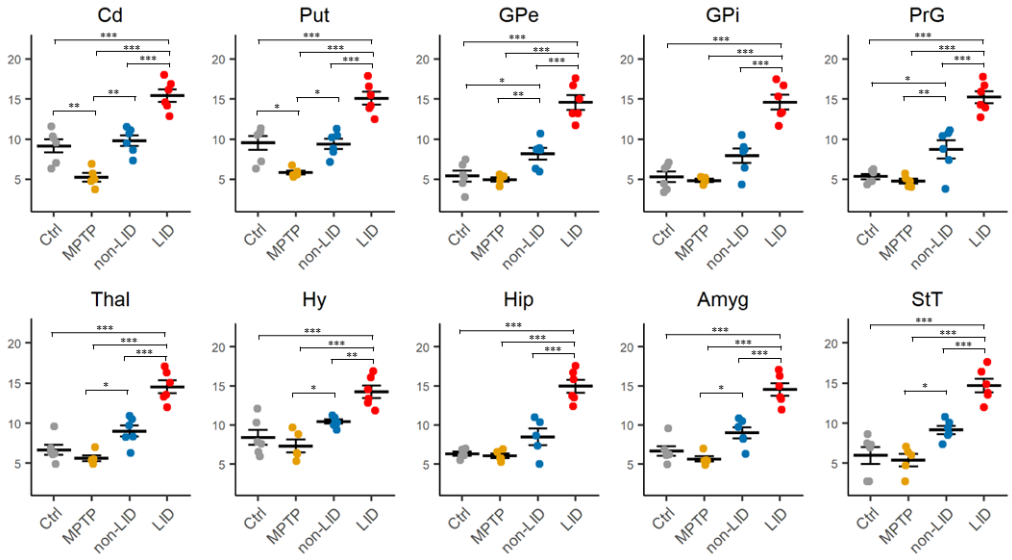


Fig. S3. Relative quantitation of neurotransmitters and metabolites in non-LID versus LID.

The relative levels are presented as $\log_2$AUC of each data point. Blue is non-LID, red is LID. Mean values and standard deviations are shown. A two-sample independent Mann-Whitney U test was performed, $*P < 0.05$.

a


Cd
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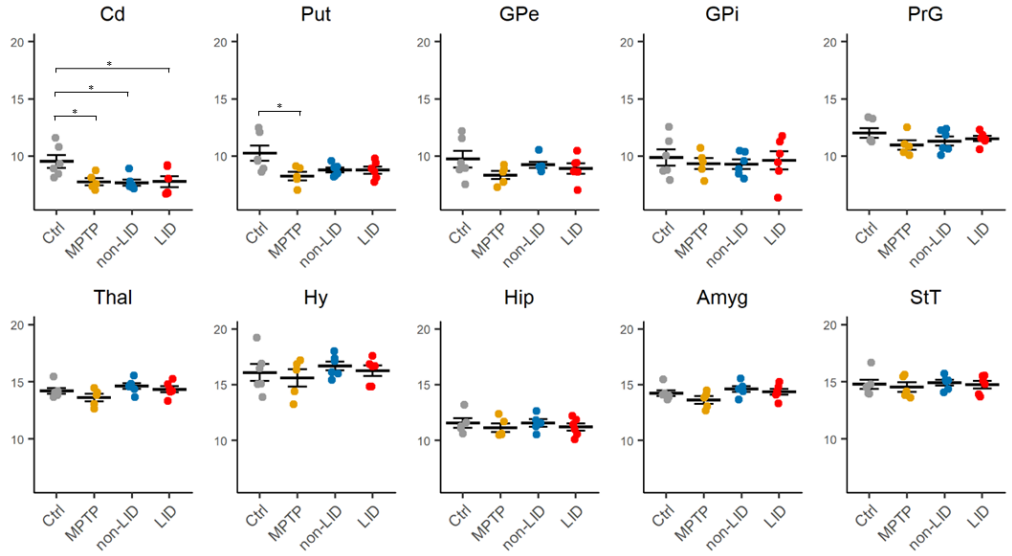
LID

b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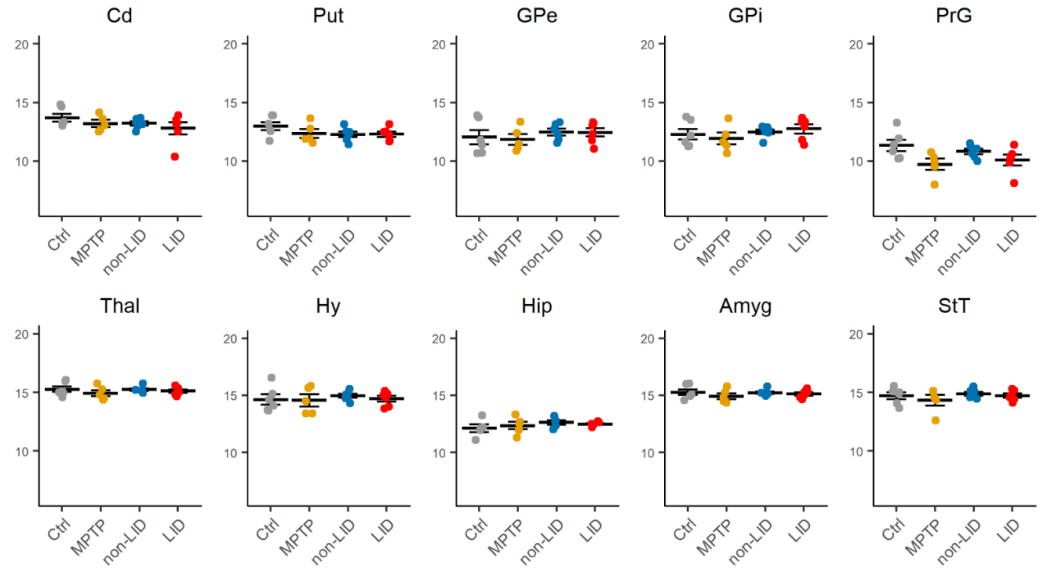
c



d

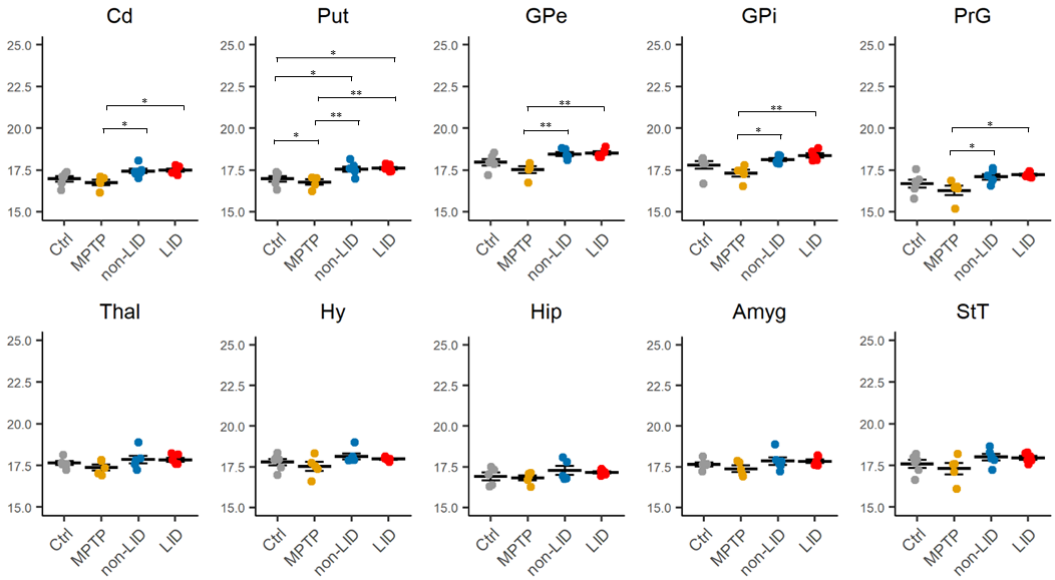
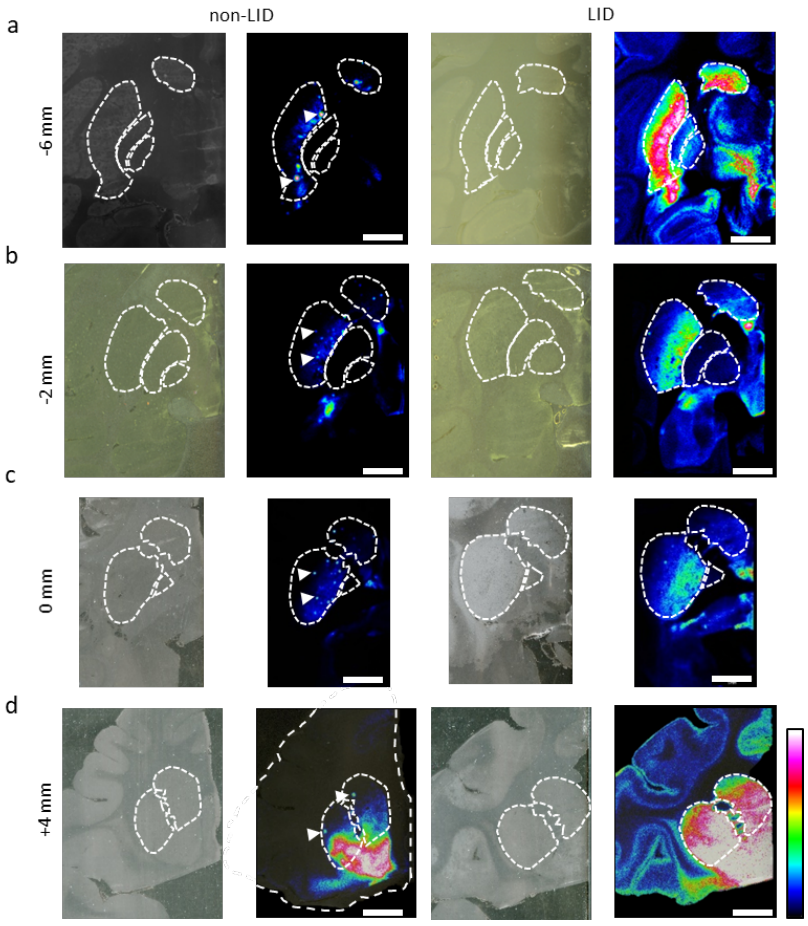
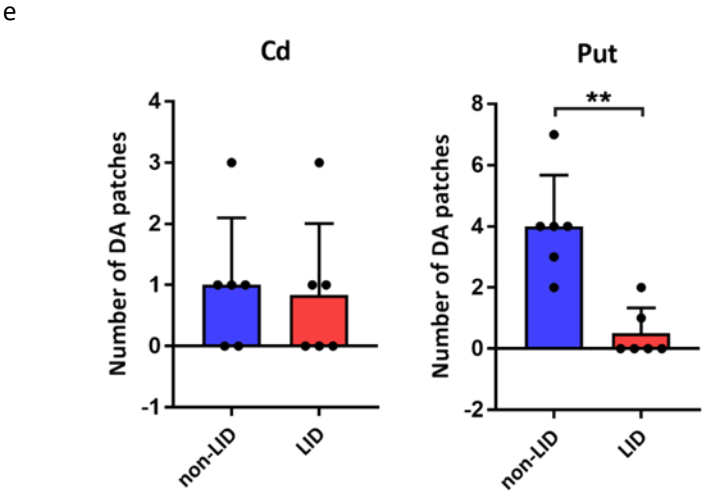


Fig. S4. Relative comparison of L-DOPA, NE, 5-HT and GABA abundance between control, MPTP, non-LID and LID.

The relative levels **(a)** L-DOPA, **(b)** NE, **(c)** 5-HT and **(d)** GABA are presented as log_2AUC of each data point. Mean values and standard errors are shown. Statistics were performed using one-way ANOVA followed by a Tukey's post hoc test. Abbreviation: Ctrl, control.
**P < 0.05, **P < 0.01 ***P < 0.001.*


a
non-LID
LID
-6 mm
b
-2 mm
c
0 mm
d
+4 mm


e
Cd
Put
Number of DA patches
Number of DA patches
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non-LID
LID
non-LID
LID

Fig. S5. Dopamine distribution at different rostro-caudal brain levels in non-LID and LID tissue sections displaying dopamine patches in non-LID striatum and quantitation of dopamine patches.

MALDI MS images of DA at (**a)** -6 mm ac (colour intensity scale 0-50%, lateral resolution 100 μm), **(b)** -2 mm ac (colour intensity scale 0-100%, lateral resolution 70 μm) **(c)** 0 mm ac (colour intensity scale 0-100%, lateral resolution 80 μm) and **(d)** +4 mm ac (colour intensity scale 0-50%, lateral resolution 80 μm). Scale bar is 5 mm. Images are log transformed and RMS normalised. Dopamine patches are pointed out by the arrows. **(e)** Number of dopamine patches observed in striatal structures in non-LID and LID animals at -4 mm ac (average number of DA patches and standard deviation). A Mann-Whitney U test was performed. $^{**}P < 0.01$.

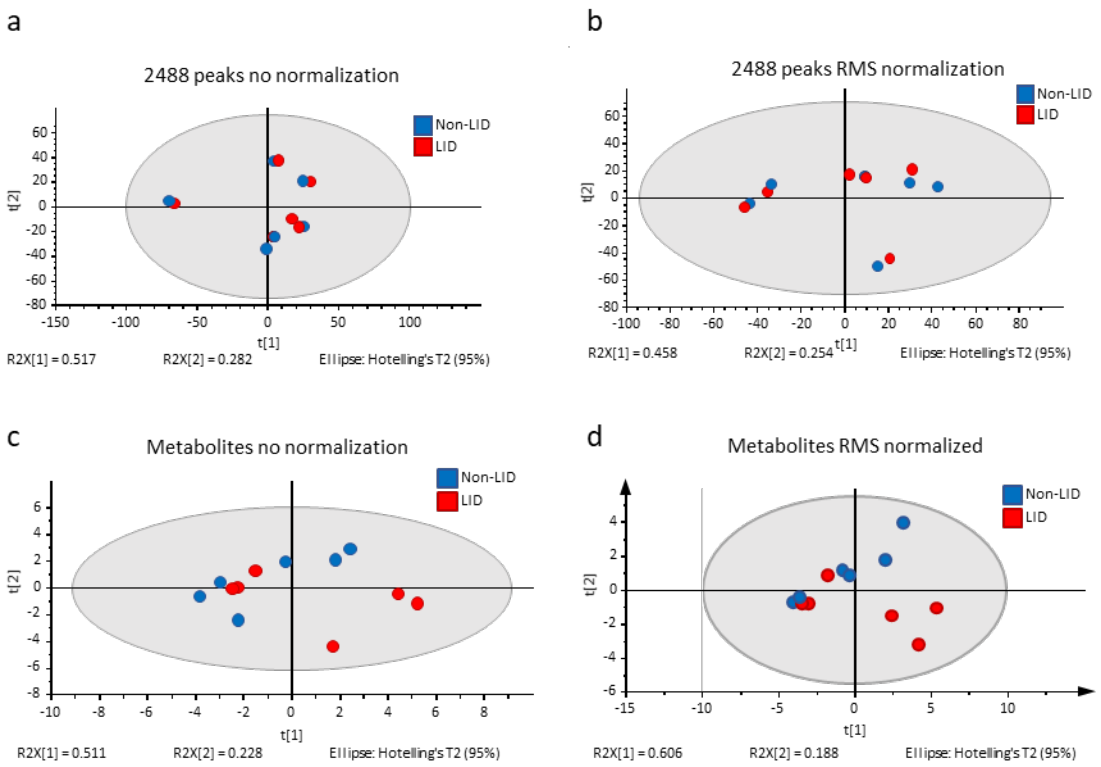
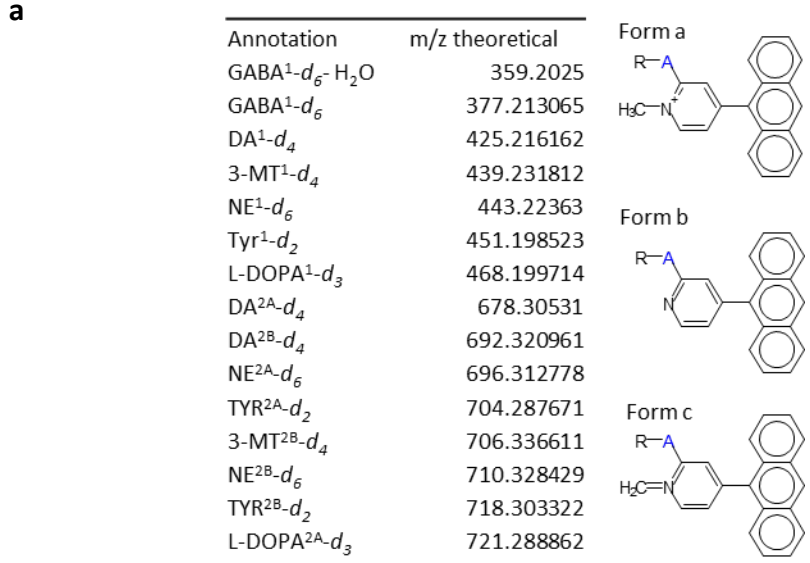


Fig. S6. PCA analysis using untargeted and targeted *m/z* values as input variables.

PCA results were computed using **(a)** non-normalised and **(b)** RMS normalised spectra from the 2488 most abundant ions in the average spectra from all experiments. The PCA showed pairing of samples prepared at the same time and acquired in the same experiment. RMS normalisation did not compensate for this pairing. PCA results were computed from the 14 identified metabolites as input variables using **(c)** non-normalised and **(d)** RMS normalised spectra. PCA from the identified metabolites did not result in pairing of samples and illustrated that although the overall intensity and major matrix clusters were affected by sample preparation and variation between experiments, the analysed metabolites were not affected to the same extent since they did not result in pairing of samples.

a

Annotation	m/z theoretical
GABA^{1}-d_6- H_2O	359.2025
GABA^{1}-d_6	377.213065
DA^{1}-d_4	425.216162
3-MT^{1}-d_4	439.231812
NE^{1}-d_6	443.22363
Tyr^{1}-d_2	451.198523
L-DOPA^{1}-d_3	468.199714
DA^{2A}-d_4	678.30531
DA^{2B}-d_4	692.320961
NE^{2A}-d_6	696.312778
TYR^{2A}-d_2	704.287671
3-MT^{2B}-d_4	706.336611
NE^{2B}-d_6	710.328429
TYR^{2B}-d_2	718.303322
L-DOPA^{2A}-d_3	721.288862
L-DOPA^{2B}-d_3	735.304513



b

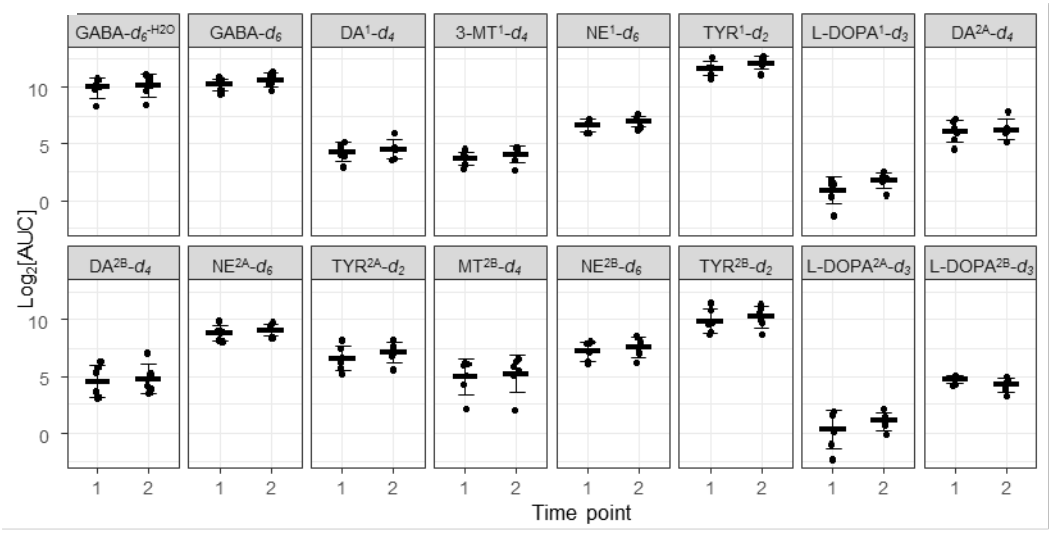


Fig. S7. Evaluation of ion intensity changes over time using quality control standards.

(a) *m/z* values used from quality control standards to evaluate intensity changes. All single derivatized standards have one FMP-10 molecule (form a [1]), the doubly derivatized molecules have one FMP-10 (form a) and a second FMP-10 molecule (either in form b [2A] or c [2B]). **(b)** Experimental intensity changes of quality control standards. The AUC values are collected before (time point 1) and after (time point 2) pairwise acquisition of macaque samples with an average of 30 hours between the two time-points. Mean values and standard deviations are shown. Significant changes were tested using a two sample Mann-Whitney U test showing that there were no significant changes between the two time points in any of the standards analysed, α=0.05.

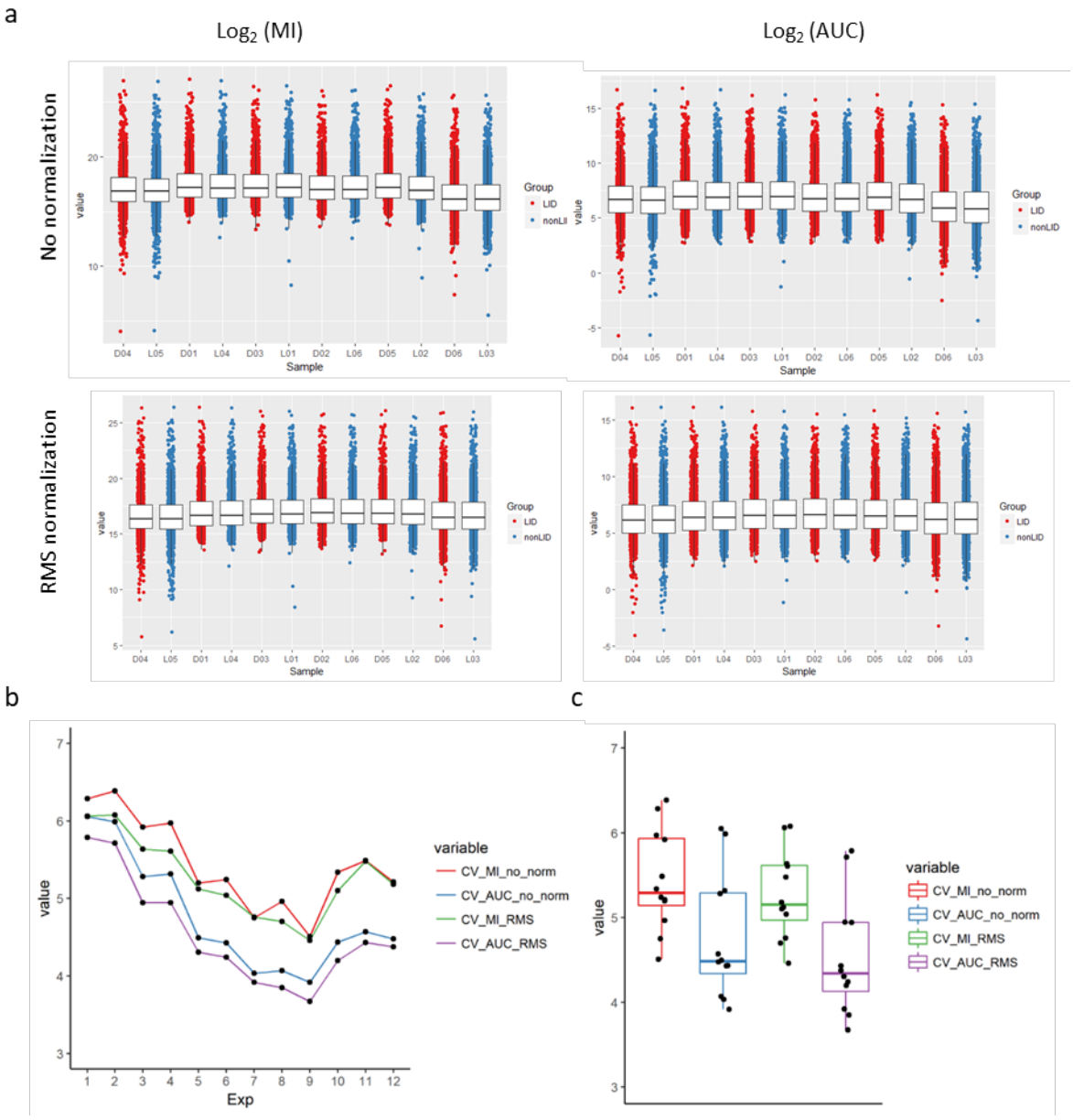


Fig. S8. Variability between the different experiments acquired from non-LID and LID samples.

(a) The variability between samples and ion intensity changes between experiments were investigated by plotting $\log_2$ of area under curve ($\log_2$AUC) and $\log_2$ of the maximum ion intensity ($\log_2$MI) for the 2488 most abundant peaks for each sample (tissue section). Samples are presented in chronological order of experiments (from left to right), red LID, blue non-LID. **(b)** Coefficient of variation (CV) throughout all experiments using MI or AUC and no normalization or RMS normalisation. **(c)** The most appropriate parameters for export of intensity values were determined by comparing CV between MI and AUC, with and without normalisation. RMS normalised AUC values had the lowest CV and were therefore used in the statistical analysis.

Table S1. Experimental and theoretical *m/z* values and mass error for analysed metabolites.

Metabolite	Experimental [m/z]	Theoretical [m/z]	Mass error [ppm]	Maximum intensity - RMS
GABA[1]-H2O	353.1652	353.16484	1.0194	2.15E+06
GABA[1]	371.1758	371.175405	1.0642	490836
Taurine[1]	393.1271	393.12674	0.9157	345309
DA[1]	421.1913	421.191055	0.5817	12980.5
3-MT[1]	435.2070	435.206705	0.6778	19275.9
DOPAC[1]	436.1544	436.154335	0.1490	19685.7
NE[1]	437.1862	437.185969	0.5284	4812.03
5-HIAL[1]	443.1754	443.175405	-0.0113	5186.97
5-HT[1]	444.2073	444.207039	0.5876	82117.1
HVA[1]	450.1702	450.169985	0.4776	178787
MOPEG	452.1854	452.185635	-0.5197	2295.54
5-HIAA[1]	459.1706	459.170319	0.6120	64435.5
L-DOPA[1]	465.1811	465.180884	0.4643	24007.9
3-OMD[1]	479.1968	479.196534	0.5551	237163
DA[2A]	674.2798	674.280203	-0.5977	241909
3-MT[2A] / DA[2B]	688.2955	688.295854	-0.5143	8458.67
DOPAC[2A]	689.2431	689.243483	-0.5557	30071.5
NE[2A]	690.2747	690.275117	-0.6041	115229
DOPEG[2A]	691.2586	691.259133	-0.7711	5948.52
5-HT[2A]	697.2963	697.296187	0.1621	1604.53
3-MT[2B]	702.3113	702.311504	-0.2905	13903.4
DOPAC[2B]	703.2585	703.259133	-0.9001	15355.6
NE[2B]	704.2906	704.290767	-0.2371	13360.8
5-HT[2B]	711.3118	711.311838	-0.0534	27754.3
L-DOPA[2A]	718.2697	718.270032	-0.4622	651388
3-OMD[2A] / L-DOPA[2B]	732.2855	732.285682	-0.2485	29951.3

Structural formulas of the different forms of the reactive matrix (FMP-10) derivatization is shown in superscript (see Fig. S1); [1] molecule + 1 FMP-10 with form i, [2A] molecule + 1 FMP-10 form i + 1 FMP-10 form j, [2B] molecule + 1 FMP-10 form i + 1 FMP-10 form k. Maximum intensity values are collected from average spectra of all the experiments combined. For each metabolite that produces multiple different FMP-10 derivatives, the derivative that produced the highest intensity, was used i.e. GABA[1]-H_2O, 3-MT[1], DA[2A], 5-HT[1] DOPAC[2A], NE[2A], DOPEG[2A], L-DOPA[2A], 3-OMD[1]. Overlapping peaks were not used. Values are RMS normalised.

Table S2. Summarised results from hypothesis tests comparing metabolite abundances between non-LID and LID.

Region: ACgG		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.43	0.35	0.923				
	LID	6	10.48	0.23	0.208	t-test	0.034	10	0.973
Taurine	non-LID	6	7.87	0.40	0.537				
	LID	6	7.90	0.30	0.483	t-test	0.183	10	0.858
3-MT	non-LID	6	4.52	1.68	0.494				
	LID	6	5.25	1.58	0.219	t-test	3.040	10	0.012
5-HIAL	non-LID	6	2.59	1.39	0.559				
	LID	6	2.93	0.54	0.477	t-test	0.979	10	0.351
5-HT	non-LID	6	6.80	0.50	0.270				
	LID	6	6.56	1.11	0.857	t-test	0.838	10	0.422
HVA	non-LID	6	8.23	1.00	0.611				
	LID	6	8.18	1.06	0.454	t-test	0.811	9.984	0.436
MOPEG	non-LID	6	2.09	0.49	0.622				
	LID	6	2.06	0.81	0.209	t-test	0.125	9.725	0.903
5-HIAA	non-LID	6	5.89	0.61	0.603				
	LID	6	5.98	0.33	0.291	t-test	0.285	10	0.782
3-OMD	non-LID	6	4.62	0.50	0.561				
	LID	6	8.38	1.22	0.239	t-test	7.112	10	< 0.001
DA	non-LID	6	7.12	1.98	0.852				
	LID	6	9.06	2.01	0.212	t-test	3.350	10	0.007
DOPAC	non-LID	6	5.49	1.15	0.054				
	LID	6	6.45	1.44	0.549	t-test	1.546	10	0.153
NE	non-LID	6	1.94	0.84	0.806				
	LID	6	2.79	1.14	0.740	t-test	0.296	10	0.773
DOPEG	non-LID	6	2.53	0.73	0.704				
	LID	6	2.69	0.68	0.420	t-test	0.066	10	0.948
L-DOPA	non-LID	6	4.72	1.70	0.239				
	LID	6	10.50	1.92	0.873	t-test	5.278	10	< 0.001

Region: Amyg		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.85	0.55	0.086				
	LID	6	10.81	0.22	0.285	t-test	0.148	10	0.885
Taurine	non-LID	6	7.32	0.48	0.181				
	LID	6	7.34	0.18	0.979	t-test	0.564	10	0.585
3-MT	non-LID	6	4.89	1.17	0.752				
	LID	6	5.26	1.09	0.054	t-test	0.109	10	0.916
5-HIAL	non-LID	6	4.88	0.83	0.947				
	LID	6	4.47	0.58	0.347	t-test	0.993	10	0.344
5-HT	non-LID	6	8.91	0.23	0.037				
	LID	6	8.82	0.33	0.940	Mann-Whitney U	16.000	NA	0.820
HVA	non-LID	6	7.99	1.08	0.527				
	LID	6	8.28	0.84	0.841	t-test	0.524	10	0.612
MOPEG	non-LID	6	3.43	0.65	0.622				
	LID	6	3.20	0.67	0.957	t-test	0.624	10	0.547
5-HIAA	non-LID	6	7.16	0.59	0.555				
	LID	6	7.12	0.40	0.562	t-test	0.115	10	0.911
3-OMD	non-LID	6	4.53	0.45	0.229				
	LID	6	8.21	1.23	0.475	t-test	6.881	10	< 0.001
DA	non-LID	6	10.22	0.45	0.493				
	LID	6	11.29	0.79	0.663	t-test	2.893	10	0.016
DOPAC	non-LID	6	6.51	1.10	0.899				
	LID	6	7.41	1.07	0.697	t-test	1.427	10	0.184
NE	non-LID	6	9.55	0.65	0.374				
	LID	6	9.22	0.82	0.625	t-test	0.772	10	0.458
DOPEG	non-LID	6	4.81	1.35	0.705				
	LID	6	4.47	0.82	0.057	t-test	0.540	10	0.601
L-DOPA	non-LID	6	3.84	1.88	0.635				
	LID	6	9.64	1.93	0.873	t-test	5.270	10	< 0.001

Region: Cd		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.43	0.35	0.396				
	LID	6	10.48	0.23	0.618	t-test	0.258	10	0.802
Taurine	non-LID	6	7.87	0.40	0.616				
	LID	6	7.90	0.30	0.188	t-test	0.165	10	0.872
3-MT	non-LID	6	4.52	1.68	0.406				
	LID	6	5.25	1.58	0.506	t-test	0.780	10	0.454
5-HIAL	non-LID	6	2.59	1.39	0.937				
	LID	6	2.93	0.54	0.059	t-test	0.561	10	0.587
5-HT	non-LID	6	6.80	0.50	0.313				
	LID	6	6.56	1.11	0.023	Mann-Whitney U	17.000	NA	0.937
HVA	non-LID	6	8.23	1.00	0.732				
	LID	6	8.18	1.06	0.418	t-test	0.083	10	0.936
MOPEG	non-LID	6	2.09	0.49	0.032				
	LID	6	2.06	0.81	0.676	Mann-Whitney U	12.000	NA	0.662
5-HIAA	non-LID	6	5.89	0.61	0.236				
	LID	6	5.98	0.33	0.523	t-test	0.317	7.739	0.760
3-OMD	non-LID	6	4.62	0.50	0.407				
	LID	6	8.38	1.22	0.226	t-test	6.994	6.648	< 0.001
DA	non-LID	6	7.12	1.98	0.201				
	LID	6	9.06	2.01	0.676	t-test	1.680	10	0.124
DOPAC	non-LID	6	5.49	1.15	0.686				
	LID	6	6.45	1.44	0.843	t-test	1.278	10	0.230
NE	non-LID	6	1.94	0.84	0.979				
	LID	6	2.79	1.14	0.385	t-test	1.480	10	0.170
DOPEG	non-LID	6	2.53	0.73	0.925				
	LID	6	2.69	0.68	0.281	t-test	0.380	10	0.712
L-DOPA	non-LID	6	4.72	1.70	0.542				
	LID	6	10.50	1.92	0.938	t-test	5.520	10	< 0.001

Region: Clau		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.17	0.37	0.115				
	LID	6	10.15	0.22	0.374	t-test	0.121	10	0.906
Taurine	non-LID	6	7.29	0.52	0.728				
	LID	6	7.22	0.33	0.179	t-test	0.278	10	0.787
3-MT	non-LID	6	-0.26	1.91	0.725				
	LID	6	2.63	1.64	0.834	t-test	2.814	10	0.018
5-HIAL	non-LID	6	2.97	0.91	0.286				
	LID	6	2.37	0.40	0.245	t-test	1.473	6.914	0.185
5-HT	non-LID	6	7.04	0.51	0.628				
	LID	6	6.66	0.80	0.004	Mann-Whitney U	15.000	NA	0.699
HVA	non-LID	6	7.39	1.14	0.356				
	LID	6	7.40	1.04	0.954	t-test	0.021	10	0.983
MOPEG	non-LID	6	1.64	0.75	0.962				
	LID	6	1.74	0.59	0.662	t-test	0.258	10	0.802
5-HIAA	non-LID	6	6.27	0.85	0.334				
	LID	6	6.11	0.47	0.548	t-test	0.417	10	0.686
3-OMD	non-LID	6	3.54	0.60	0.312				
	LID	6	7.66	1.30	0.321	t-test	7.042	7.058	< 0.001
DA	non-LID	6	4.67	1.13	0.416				
	LID	6	7.79	1.12	0.853	t-test	4.807	10	0.001
DOPAC	non-LID	6	4.27	0.64	0.059				
	LID	6	5.40	0.93	0.255	t-test	2.450	10	0.034
NE	non-LID	6	6.54	0.53	0.151				
	LID	6	6.71	0.54	0.993	t-test	0.549	10	0.595
DOPEG	non-LID	6	3.16	0.83	0.589				
	LID	6	3.18	0.86	0.622	t-test	0.034	10	0.973
L-DOPA	non-LID	6	2.84	2.57	0.252				
	LID	6	9.69	1.96	0.766	t-test	5.200	10	< 0.001

Region: Ent		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.26	0.44	0.393				
	LID	6	10.02	0.24	0.135	t-test	1.163	10	0.272
Taurine	non-LID	6	7.51	0.39	0.838				
	LID	6	7.28	0.27	0.508	t-test	1.209	10	0.254
3-MT	non-LID	6	-2.26	1.76	0.750				
	LID	6	2.67	2.74	0.340	t-test	3.706	10	0.004
5-HIAL	non-LID	6	2.26	0.75	0.521				
	LID	6	1.95	0.60	0.099	t-test	0.785	10	0.450
5-HT	non-LID	6	6.66	0.70	0.256				
	LID	6	6.01	0.40	0.400	t-test	1.999	10	0.074
HVA	non-LID	6	5.70	0.93	0.492				
	LID	6	6.18	1.10	0.631	t-test	0.819	10	0.432
MOPEG	non-LID	6	2.28	0.59	0.964				
	LID	6	1.96	0.77	0.336	t-test	0.802	10	0.441
5-HIAA	non-LID	6	5.21	0.86	0.203				
	LID	6	4.93	0.56	0.416	t-test	0.667	10	0.520
3-OMD	non-LID	6	4.50	0.47	0.868				
	LID	6	8.16	1.26	0.166	t-test	6.682	6.39	< 0.001
DA	non-LID	6	3.95	1.32	0.532				
	LID	6	7.73	1.40	0.493	t-test	4.812	10	0.001
DOPAC	non-LID	6	4.50	0.60	0.557				
	LID	6	5.38	1.20	0.726	t-test	1.602	10	0.140
NE	non-LID	6	6.23	0.96	0.392				
	LID	6	5.63	0.84	0.471	t-test	1.162	10	0.272
DOPEG	non-LID	6	3.63	0.90	0.138				
	LID	6	3.17	0.49	0.920	t-test	1.089	10	0.302
L-DOPA	non-LID	6	3.94	2.76	0.158				
	LID	6	10.23	1.85	0.769	t-test	4.631	10	0.001

Region: GPe		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	11.47	0.22	0.542				
	LID	6	11.54	0.28	0.227	t-test	0.518	10	0.616
Taurine	non-LID	6	7.65	0.50	0.615				
	LID	6	7.60	0.48	0.973	t-test	0.162	10	0.875
3-MT	non-LID	6	0.33	1.65	0.533				
	LID	6	2.83	2.17	0.489	t-test	2.240	10	0.049
5-HIAL	non-LID	6	1.21	0.77	0.745				
	LID	6	1.61	1.16	0.240	t-test	0.694	10	0.503
5-HT	non-LID	6	6.08	0.68	0.778				
	LID	6	6.07	0.91	0.305	t-test	0.014	10	0.989
HVA	non-LID	6	8.04	0.86	0.284				
	LID	6	8.18	1.23	0.716	t-test	0.238	10	0.817
MOPEG	non-LID	6	2.00	0.40	0.246				
	LID	6	2.15	0.76	0.235	t-test	0.443	10	0.667
5-HIAA	non-LID	6	6.76	0.41	0.705				
	LID	6	6.85	0.70	0.410	t-test	0.270	10	0.793
3-OMD	non-LID	6	3.71	0.78	0.442				
	LID	6	7.75	1.47	0.434	t-test	5.929	7.63	< 0.001
DA	non-LID	6	5.27	1.21	0.079				
	LID	6	7.91	1.91	0.649	t-test	2.860	10	0.017
DOPAC	non-LID	6	3.85	0.53	0.373				
	LID	6	5.09	1.63	0.292	t-test	1.764	6.054	0.128
NE	non-LID	6	3.45	0.52	0.418				
	LID	6	3.50	1.44	0.911	t-test	0.088	10	0.931
DOPEG	non-LID	6	2.34	0.59	0.989				
	LID	6	2.42	0.69	0.320	t-test	0.213	10	0.835
L-DOPA	non-LID	6	2.94	1.90	0.422				
	LID	6	9.67	2.24	0.724	t-test	5.625	10	< 0.001

Region: GPi		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	11.15	0.17	0.521				
	LID	6	11.41	0.29	0.463	t-test	1.853	10	0.094
Taurine	non-LID	6	7.33	0.50	0.945				
	LID	6	7.39	0.45	0.971	t-test	0.195	10	0.849
3-MT	non-LID	6	-1.95	1.77	0.150				
	LID	6	3.44	1.96	0.169	t-test	4.990	10	0.001
5-HIAL	non-LID	6	1.32	0.84	0.462				
	LID	6	1.67	1.23	0.141	t-test	0.570	10	0.581
5-HT	non-LID	6	6.24	0.48	0.120				
	LID	6	6.44	0.93	0.218	t-test	0.475	10	0.645
HVA	non-LID	6	7.38	0.79	0.090				
	LID	6	7.89	1.19	0.412	t-test	0.887	10	0.396
MOPEG	non-LID	6	1.56	0.66	0.302				
	LID	6	1.88	0.84	0.390	t-test	0.731	10	0.481
5-HIAA	non-LID	6	6.93	0.50	0.476				
	LID	6	7.22	0.80	0.320	t-test	0.760	10	0.465
3-OMD	non-LID	6	3.42	0.99	0.200				
	LID	6	7.74	1.53	0.379	t-test	5.797	10	< 0.001
DA	non-LID	6	5.17	1.33	0.101				
	LID	6	8.54	1.59	0.732	t-test	3.973	10	0.003
DOPAC	non-LID	6	3.86	0.76	0.959				
	LID	6	5.62	1.72	0.780	t-test	2.289	6.871	0.057
NE	non-LID	6	3.78	0.94	0.317				
	LID	6	3.87	1.49	0.870	t-test	0.119	10	0.908
DOPEG	non-LID	6	2.47	0.84	0.783				
	LID	6	2.64	0.87	0.748	t-test	0.348	10	0.735
L-DOPA	non-LID	6	2.19	3.34	0.169				
	LID	6	9.73	2.28	0.676	t-test	4.561	10	0.001

Region: Hip		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	5	10.25	0.62	0.097				
	LID	6	10.16	0.16	0.895	t-test	0.338	4.451	0.751
Taurine	non-LID	5	7.67	0.29	0.693				
	LID	6	7.74	0.38	0.188	t-test	0.367	9	0.722
3-MT	non-LID	5	-1.99	0.83	0.044				
	LID	6	2.65	1.86	0.929	Mann-Whitney U	0.000	NA	0.004
5-HIAL	non-LID	5	2.56	1.22	0.665				
	LID	6	2.36	0.74	0.443	t-test	0.334	9	0.746
5-HT	non-LID	5	6.37	0.49	0.922				
	LID	6	6.25	0.19	0.555	t-test	0.572	9	0.581
HVA	non-LID	5	5.76	0.81	0.933				
	LID	6	6.40	0.90	0.069	t-test	1.235	9	0.248
MOPEG	non-LID	5	2.39	0.56	0.392				
	LID	6	2.15	0.94	0.574	t-test	0.499	9	0.630
5-HIAA	non-LID	5	5.90	0.79	0.196				
	LID	6	5.74	0.46	0.885	t-test	0.414	9	0.689
3-OMD	non-LID	5	4.39	0.35	0.623				
	LID	6	8.18	1.32	0.248	t-test	6.735	5.811	0.001
DA	non-LID	5	3.85	1.12	0.137				
	LID	6	7.75	1.22	1.000	t-test	5.478	9	< 0.001
DOPAC	non-LID	5	3.85	0.76	0.120				
	LID	6	5.24	1.28	0.787	t-test	2.116	9	0.063
NE	non-LID	5	6.74	0.84	0.535				
	LID	6	6.14	0.90	0.606	t-test	1.118	9	0.293
DOPEG	non-LID	5	3.72	1.07	0.313				
	LID	6	3.15	0.79	0.549	t-test	1.001	9	0.343
L-DOPA	non-LID	5	3.37	2.33	0.798				
	LID	6	10.00	2.04	0.605	t-test	5.036	9	0.001

Region: Hy		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	11.15	0.36	0.010				
	LID	6	11.00	0.09	0.791	Mann-Whitney U	16.000		0.820
Taurine	non-LID	6	6.74	0.31	0.509				
	LID	6	6.73	0.29	0.446	t-test	0.049	10	0.962
3-MT	non-LID	6	0.63	1.58	0.135				
	LID	6	2.91	2.52	0.332	t-test	1.877	10	0.090
5-HIAL	non-LID	6	3.93	1.10	0.724				
	LID	6	3.74	0.65	0.323	t-test	0.363	10	0.725
5-HT	non-LID	6	8.71	0.37	0.537				
	LID	6	8.44	0.58	0.249	t-test	0.974	10	0.353
HVA	non-LID	6	7.38	0.66	0.761				
	LID	6	8.25	1.26	0.212	t-test	1.499	10	0.165
MOPEG	non-LID	6	4.11	0.81	0.851				
	LID	6	4.20	1.24	0.854	t-test	0.146	10	0.887
5-HIAA	non-LID	6	7.45	0.55	0.576				
	LID	6	7.35	0.65	0.492	t-test	0.304	10	0.768
3-OMD	non-LID	6	4.07	0.54	0.303				
	LID	6	7.82	1.40	0.353	t-test	6.146	10	< 0.001
DA	non-LID	6	8.68	0.42	0.430				
	LID	6	10.32	1.38	0.415	t-test	2.790	10	0.019
DOPAC	non-LID	6	6.10	0.83	0.668				
	LID	6	7.78	1.65	0.623	t-test	2.224	10	0.050
NE	non-LID	6	11.61	0.98	0.275				
	LID	6	11.16	1.12	0.347	t-test	0.738	10	0.478
DOPEG	non-LID	6	5.71	1.39	0.405				
	LID	6	5.49	1.09	0.609	t-test	0.311	10	0.762
L-DOPA	non-LID	6	5.34	0.73	0.991				
	LID	6	9.38	2.02	0.848	t-test	4.606	10	< 0.001

Region: Ins		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.13	0.36	0.551				
	LID	6	10.07	0.21	0.672	t-test	0.376	10	0.715
Taurine	non-LID	6	7.47	0.39	0.472				
	LID	6	7.46	0.33	0.283	t-test	0.085	10	0.934
3-MT	non-LID	6	-0.95	0.78	0.979				
	LID	6	1.71	2.02	0.324	t-test	3.004	6.469	0.022
5-HIAL	non-LID	6	2.06	0.57	0.990				
	LID	6	2.21	0.52	0.522	t-test	0.474	10	0.646
5-HT	non-LID	6	5.76	0.40	0.790				
	LID	6	5.04	1.38	0.005	Mann-Whitney U	18.000	NA	1.000
HVA	non-LID	6	6.44	0.92	0.623				
	LID	6	6.58	0.90	0.425	t-test	0.276	10	0.788
MOPEG	non-LID	6	2.10	0.51	0.181				
	LID	6	1.84	0.82	0.715	t-test	0.653	10	0.528
5-HIAA	non-LID	6	5.66	0.77	0.278				
	LID	6	5.49	0.45	0.578	t-test	0.444	10	0.667
3-OMD	non-LID	6	4.43	0.49	0.322				
	LID	6	8.07	1.20	0.296	t-test	6.879	6.591	< 0.001
DA	non-LID	6	4.46	1.21	0.826				
	LID	6	6.98	1.17	0.639	t-test	3.667	10	0.004
DOPAC	non-LID	6	4.23	0.59	0.076				
	LID	6	4.97	1.03	0.131	t-test	1.524	7.99	0.166
NE	non-LID	6	5.99	0.75	0.524				
	LID	6	6.05	0.76	0.691	t-test	0.157	10	0.878
DOPEG	non-LID	6	3.41	0.92	0.093				
	LID	6	3.13	0.78	0.591	t-test	0.572	10	0.580
L-DOPA	non-LID	6	3.68	3.16	0.131				
	LID	6	10.19	1.83	0.708	t-test	4.363	10	0.001

Region: ITG		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.06	0.43	0.995				
	LID	6	9.95	0.24	0.428	t-test	0.586	10	0.571
Taurine	non-LID	6	7.54	0.39	0.531				
	LID	6	7.40	0.50	0.192	t-test	0.541	10	0.600
3-MT	non-LID	6	-1.76	1.44	0.565				
	LID	6	1.51	2.61	0.053	t-test	2.684	10	0.023
5-HIAL	non-LID	6	1.65	0.47	0.970				
	LID	6	1.63	0.81	0.837	t-test	0.033	10	0.974
5-HT	non-LID	6	5.58	0.47	0.089				
	LID	6	5.21	0.74	0.830	t-test	1.038	10	0.324
HVA	non-LID	6	5.56	0.83	0.764				
	LID	6	5.75	1.00	0.749	t-test	0.354	10	0.731
MOPEG	non-LID	6	2.01	0.47	0.266				
	LID	6	1.78	0.67	0.498	t-test	0.689	10	0.506
5-HIAA	non-LID	6	4.93	0.83	0.094				
	LID	6	4.75	1.01	0.334	t-test	0.346	10	0.736
3-OMD	non-LID	6	4.26	0.45	0.404				
	LID	6	8.10	1.27	0.287	t-test	6.998	10	< 0.001
DA	non-LID	6	5.11	0.84	0.682				
	LID	6	7.37	1.43	0.224	t-test	3.333	10	0.008
DOPAC	non-LID	6	4.36	0.59	0.164				
	LID	6	4.89	1.32	0.210	t-test	0.901	10	0.389
NE	non-LID	6	5.28	1.07	0.397				
	LID	6	4.78	0.86	0.227	t-test	0.900	10	0.389
DOPEG	non-LID	6	3.39	0.68	0.303				
	LID	6	2.99	0.76	0.514	t-test	0.961	10	0.359
L-DOPA	non-LID	6	3.90	2.77	0.147				
	LID	6	10.24	1.88	0.660	t-test	4.639	10	< 0.001

Region: MTG		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.14	0.32	0.417				
	LID	6	10.00	0.15	0.543	t-test	0.912	10	0.383
Taurine	non-LID	6	7.59	0.34	0.629				
	LID	6	7.47	0.47	0.588	t-test	0.506	10	0.624
3-MT	non-LID	6	-0.39	0.84	0.668				
	LID	6	1.82	1.85	0.340	t-test	2.660	6.974	0.033
5-HIAL	non-LID	6	1.10	0.47	0.682				
	LID	6	1.55	0.72	0.782	t-test	1.282	10	0.229
5-HT	non-LID	6	5.27	0.43	0.213				
	LID	6	4.90	0.92	0.332	t-test	0.879	10	0.400
HVA	non-LID	6	5.57	0.75	0.201				
	LID	6	5.69	0.64	0.725	t-test	0.297	10	0.773
MOPEG	non-LID	6	1.78	0.41	0.332				
	LID	6	1.63	0.71	0.719	t-test	0.449	10	0.663
5-HIAA	non-LID	6	4.64	0.90	0.140				
	LID	6	4.75	0.78	0.530	t-test	0.210	10	0.838
3-OMD	non-LID	6	4.29	0.55	0.575				
	LID	6	8.11	1.22	0.173	t-test	6.993	6.956	< 0.001
DA	non-LID	6	5.10	0.62	0.697				
	LID	6	7.31	1.01	0.263	t-test	4.572	10	0.001
DOPAC	non-LID	6	4.34	0.68	0.069				
	LID	6	4.67	0.90	0.608	t-test	0.708	10	0.495
NE	non-LID	6	4.80	1.09	0.247				
	LID	6	4.51	0.73	0.099	t-test	0.541	10	0.600
DOPEG	non-LID	6	3.07	0.84	0.564				
	LID	6	2.80	0.56	0.939	t-test	0.644	10	0.534
L-DOPA	non-LID	6	3.88	3.03	0.197				
	LID	6	10.33	1.90	0.812	t-test	4.419	10	0.001

Region: PoG		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	5	10.11	0.30	0.607				
	LID	3	10.06	0.15	0.646	t-test	0.252	6	0.810
Taurine	non-LID	5	7.03	0.33	0.860				
	LID	3	7.37	0.31	0.813	t-test	1.405	6	0.210
3-MT	non-LID	5	-1.71	1.07	0.658				
	LID	3	1.88	1.48	0.164	t-test	4.030	6	0.007
5-HIAL	non-LID	5	0.86	0.49	0.432				
	LID	3	1.50	0.99	0.731	t-test	1.254	6	0.256
5-HT	non-LID	5	4.85	0.54	0.479				
	LID	3	3.76	1.83	0.091	t-test	1.003	2.21	0.413
HVA	non-LID	5	5.45	0.82	0.733				
	LID	3	6.05	0.67	0.377	t-test	1.064	6	0.328
MOPEG	non-LID	5	1.63	0.70	0.809				
	LID	3	1.20	0.85	0.704	t-test	0.795	6	0.457
5-HIAA	non-LID	5	4.29	0.95	0.587				
	LID	3	4.81	0.41	0.533	t-test	0.865	6	0.420
3-OMD	non-LID	5	3.87	0.49	0.676				
	LID	3	8.21	0.97	0.559	t-test	8.599	6	< 0.001
DA	non-LID	5	4.92	0.93	0.837				
	LID	3	7.52	0.95	0.702	t-test	3.804	6	0.009
DOPAC	non-LID	5	4.32	0.85	0.494				
	LID	3	5.35	0.96	0.822	t-test	1.582	6	0.165
NE	non-LID	5	5.73	1.13	0.483				
	LID	3	6.16	0.74	0.953	t-test	0.570	6	0.589
DOPEG	non-LID	5	2.97	1.05	0.358				
	LID	3	3.30	0.74	0.678	t-test	0.476	6	0.651
L-DOPA	non-LID	5	3.24	2.95	0.608				
	LID	3	10.92	1.83	0.924	t-test	3.993	6	0.007

Region: PrG		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.11	0.40	0.855				
	LID	6	10.22	0.20	0.878	t-test	0.633	10	0.541
Taurine	non-LID	6	6.99	0.49	0.428				
	LID	6	7.00	0.37	0.883	t-test	0.045	10	0.965
3-MT	non-LID	6	-0.71	1.65	0.322				
	LID	6	1.84	1.60	0.106	t-test	2.717	10	0.022
5-HIAL	non-LID	6	0.55	0.70	0.283				
	LID	6	1.11	1.09	0.748	t-test	1.050	10	0.319
5-HT	non-LID	6	4.48	0.64	0.841				
	LID	6	3.81	1.12	0.411	t-test	1.262	10	0.236
HVA	non-LID	6	5.59	0.91	0.762				
	LID	6	6.04	0.74	0.538	t-test	0.933	10	0.373
MOPEG	non-LID	6	1.34	0.73	0.744				
	LID	6	1.37	0.78	0.266	t-test	0.074	10	0.942
5-HIAA	non-LID	6	3.85	0.94	0.755				
	LID	6	4.33	0.78	0.039	Mann-Whitney U	13.000	NA	0.485
3-OMD	non-LID	6	3.72	0.62	0.725				
	LID	6	7.86	1.29	0.164	t-test	7.087	7.169	< 0.001
DA	non-LID	6	5.93	0.96	0.543				
	LID	6	7.48	1.19	0.673	t-test	2.481	10	0.033
DOPAC	non-LID	6	4.45	0.83	0.143				
	LID	6	5.22	1.07	0.763	t-test	1.383	10	0.197
NE	non-LID	6	6.16	1.04	0.408				
	LID	6	6.32	0.65	0.800	t-test	0.308	10	0.764
DOPEG	non-LID	6	3.29	0.90	0.496				
	LID	6	3.24	0.70	0.122	t-test	0.104	10	0.919
L-DOPA	non-LID	6	3.53	3.00	0.190				
	LID	6	10.29	1.93	0.793	t-test	4.636	10	0.001

Region: Put		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.54	0.37	0.939				
	LID	6	10.60	0.19	0.589	t-test	0.331	10	0.747
Taurine	non-LID	6	7.88	0.44	0.349				
	LID	6	7.85	0.33	0.852	t-test	0.107	10	0.917
3-MT	non-LID	6	5.43	1.61	0.316				
	LID	6	5.60	1.56	0.512	t-test	0.190	10	0.853
5-HIAL	non-LID	6	2.14	0.87	0.844				
	LID	6	2.19	0.74	0.287	t-test	0.105	10	0.918
5-HT	non-LID	6	5.95	0.53	0.994				
	LID	6	5.97	0.64	0.686	t-test	0.050	10	0.961
HVA	non-LID	6	8.82	1.11	0.695				
	LID	6	8.65	1.17	0.805	t-test	0.262	10	0.798
MOPEG	non-LID	6	1.72	0.29	0.398				
	LID	6	1.62	0.74	0.923	t-test	0.321	10	0.755
5-HIAA	non-LID	6	6.42	0.69	0.320				
	LID	6	6.45	0.42	0.314	t-test	0.087	10	0.932
3-OMD	non-LID	6	4.19	0.54	0.514				
	LID	6	8.03	1.24	0.133	t-test	6.961	6.81	< 0.001
DA	non-LID	6	8.17	1.96	0.351				
	LID	6	9.93	2.34	0.601	t-test	1.416	10	0.187
DOPAC	non-LID	6	5.64	1.22	0.304				
	LID	6	6.66	1.61	0.141	t-test	1.237	10	0.244
NE	non-LID	6	3.43	0.52	0.756				
	LID	6	3.43	0.80	0.481	t-test	0.010	10	0.992
DOPEG	non-LID	6	2.34	0.78	0.672				
	LID	6	2.57	0.89	0.607	t-test	0.458	10	0.657
L-DOPA	non-LID	6	4.31	1.56	0.847				
	LID	6	10.15	1.97	0.956	t-test	5.712	10	< 0.001

Region: STG		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.10	0.35	0.747				
	LID	6	10.05	0.16	0.558	t-test	0.351	10	0.733
Taurine	non-LID	6	7.56	0.33	0.269				
	LID	6	7.47	0.41	0.553	t-test	0.429	10	0.677
3-MT	non-LID	6	-1.15	1.06	0.243				
	LID	6	1.48	2.23	0.285	t-test	2.615	10	0.026
5-HIAL	non-LID	6	1.26	0.50	0.346				
	LID	6	1.75	0.65	0.397	t-test	1.474	10	0.171
5-HT	non-LID	6	5.28	0.49	0.755				
	LID	6	4.93	0.83	0.132	t-test	0.893	10	0.393
HVA	non-LID	6	5.71	0.73	0.397				
	LID	6	5.97	0.71	0.085	t-test	0.643	10	0.535
MOPEG	non-LID	6	1.87	0.40	0.922				
	LID	6	1.78	0.65	0.962	t-test	0.298	10	0.771
5-HIAA	non-LID	6	4.84	0.90	0.157				
	LID	6	5.07	0.60	0.169	t-test	0.513	10	0.619
3-OMD	non-LID	6	4.36	0.47	0.201				
	LID	6	8.13	1.22	0.223	t-test	7.082	10	< 0.001
DA	non-LID	6	4.91	0.55	0.686				
	LID	6	7.20	1.02	0.326	t-test	4.849	10	0.001
DOPAC	non-LID	6	4.27	0.72	0.532				
	LID	6	4.81	1.02	0.801	t-test	1.056	10	0.316
NE	non-LID	6	4.90	1.19	0.620				
	LID	6	4.88	0.80	0.981	t-test	0.035	10	0.973
DOPEG	non-LID	6	3.06	0.79	0.438				
	LID	6	2.96	0.70	0.721	t-test	0.232	10	0.821
L-DOPA	non-LID	6	3.77	3.18	0.144				
	LID	6	10.30	1.88	0.772	t-test	4.335	10	0.001

Region: StT		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.97	0.41	0.327				
	LID	6	11.00	0.32	0.322	t-test	0.146	10	0.887
Taurine	non-LID	6	7.33	0.49	0.523				
	LID	6	7.40	0.29	0.269	t-test	0.315	10	0.759
3-MT	non-LID	6	4.07	0.96	0.780				
	LID	6	4.65	1.53	0.203	t-test	0.778	10	0.455
5-HIAL	non-LID	6	4.35	0.71	0.255				
	LID	6	4.11	0.42	0.704	t-test	0.713	10	0.492
5-HT	non-LID	6	8.46	0.53	0.848				
	LID	6	8.27	0.47	0.040	Mann-Whitney U	15.000	NA	0.699
HVA	non-LID	6	7.93	0.96	0.276				
	LID	6	8.25	1.05	0.565	t-test	0.551	10	0.593
MOPEG	non-LID	6	3.54	0.59	0.788				
	LID	6	3.65	0.83	0.409	t-test	0.249	10	0.808
5-HIAA	non-LID	6	6.80	0.47	0.660				
	LID	6	6.81	0.38	0.732	t-test	0.049	10	0.962
3-OMD	non-LID	6	4.67	0.51	0.309				
	LID	6	8.47	1.35	0.295	t-test	6.449	6.41	0.001
DA	non-LID	6	8.73	1.28	0.250				
	LID	6	10.48	1.12	0.406	t-test	2.526	10	0.030
DOPAC	non-LID	6	6.49	1.23	0.742				
	LID	6	7.60	1.29	0.605	t-test	1.527	10	0.158
NE	non-LID	6	10.04	0.79	0.327				
	LID	6	10.14	0.64	0.990	t-test	0.223	10	0.828
DOPEG	non-LID	6	5.02	1.26	0.656				
	LID	6	5.27	1.06	0.579	t-test	0.385	10	0.708
L-DOPA	non-LID	6	3.94	1.46	0.516				
	LID	6	9.71	2.04	0.898	t-test	5.631	10	< 0.001

Region: Thal		Descriptive statistics			Normality test Shapiro-Wilk	Hypothesis test between non-LID and LID			
	Group	N	Mean	Std. dev	p-value	Hypothesis test	t/U-value	df	p-value
GABA	non-LID	6	10.15	0.36	0.542				
	LID	6	10.07	0.29	0.101	t-test	0.426	10	0.679
Taurine	non-LID	6	6.75	0.39	0.978				
	LID	6	6.64	0.32	0.519	t-test	0.543	10	0.599
3-MT	non-LID	6	-2.33	1.84	0.219				
	LID	6	2.25	2.10	0.349	t-test	4.021	10	0.002
5-HIAL	non-LID	6	1.80	1.36	0.004				
	LID	6	1.55	0.50	0.911	Mann-Whitney U	8.000	NA	0.132
5-HT	non-LID	6	6.71	0.75	0.712				
	LID	6	6.36	0.62	0.445	t-test	0.890	10	0.394
HVA	non-LID	6	6.81	0.84	0.130				
	LID	6	7.30	0.99	0.101	t-test	0.930	10	0.374
MOPEG	non-LID	6	2.26	0.93	0.770				
	LID	6	2.31	0.82	0.414	t-test	0.104	10	0.919
5-HIAA	non-LID	6	6.93	0.69	0.984				
	LID	6	6.85	0.71	0.196	t-test	0.197	10	0.848
3-OMD	non-LID	6	3.40	0.55	0.335				
	LID	6	7.36	1.47	0.614	t-test	6.199	10	< 0.001
DA	non-LID	6	5.21	1.64	0.753				
	LID	6	7.95	1.37	0.941	t-test	3.140	10	0.011
DOPAC	non-LID	6	4.38	0.83	0.781				
	LID	6	5.52	1.30	0.831	t-test	1.818	10	0.099
NE	non-LID	6	8.87	1.66	0.231				
	LID	6	7.59	1.09	0.533	t-test	1.580	10	0.145
DOPEG	non-LID	6	3.66	1.00	0.886				
	LID	6	3.34	0.80	0.064	t-test	0.615	10	0.552
L-DOPA	non-LID	6	3.86	1.60	0.019				
	LID	6	9.22	2.07	0.385	Mann-Whitney U	0.000	NA	0.002

The table shows number of samples in each group (N), means, standard deviations, results from normality test, test was used to compare metabolite abundance between non-LID and LID, t-value (Student's t-test), U-value (Mann-Whitney U test), degrees of freedom (df, not obtained from Mann-Whitney U test) and p-value of the hypothesis test. A Shapiro-Wilk normality test was performed to determine whether to use a parametric (Student's t-test, $P > 0.05$) or non-parametric (Mann-Whitney U, $P < 0.05$) test for differences between non-LID and LID in 18 brain regions. α of 0.05 was used.

Table S3. One-way ANOVA and Tukey post-hoc test of differences in dopamine, L-DOPA, norepinephrine, serotonin and GABA abundance between control, MPTP, non-LID and LID in ten selected regions.

a) Dopamine

Dopamine - Amyg
ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	6.839	2.280	2.568	8.47E-02	.
Residuals	19	16.868	0.888			

Dopamine - Cd
ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	195.200	65.050	30.29	1.91E-07	***
Residuals	19	40.800	2.150			

Tukey post hoc

	diff	lwr	upr	p adj
LID-Ctrl	-5.192	-7.571	-2.813	3.71E-05
MPTP-Ctrl	-7.147	-9.642	-4.652	8.53E-07
non-LID-Ctrl	-6.982	-9.361	-4.603	5.95E-07
MPTP-LID	-1.955	-4.450	0.540	0.158099171
non-LID-LID	-1.790	-4.169	0.589	0.183980102
non-LID-MPTP	0.166	-2.329	2.661	0.997612122

Dopamine - GPe
ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	37.104	12.368	6.486	3.31E-3	**
Residuals	19	36.228	1.907			

Tukey post hoc

	diff	lwr	upr	p adj
LID-Ctrl	0.436	-1.806	2.678	0.946251647
MPTP-Ctrl	-2.752	-5.103	-0.401	0.018405734
non-LID-Ctrl	-1.759	-4.000	0.483	0.157459061
MPTP-LID	-3.188	-5.539	-0.837	0.005912153
non-LID-LID	-2.195	-4.436	0.047	0.056280316
non-LID-MPTP	0.994	-1.358	3.345	0.641308435

Dopamine - GPi

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	44.460	14.819	8.443	9.03E-04	***
Residuals	19	33.350	1.755			

Tukey post hoc

	diff	lwr	upr	p adj
LID-Ctrl	1.929	-0.222	4.080	0.088408622
MPTP-Ctrl	-1.626	-3.882	0.630	0.213244814
non-LID-Ctrl	-1.270	-3.421	0.881	0.370900897
MPTP-LID	-3.555	-5.811	-1.299	0.001499554
non-LID-LID	-3.199	-5.349	-1.048	0.002611343
non-LID-MPTP	0.356	-1.900	2.612	0.969979764

Dopamine - Hip

Anova table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3.000	73.570	24.522	14.57	5.94E-05	***
Residuals	17.000	28.610	1.683			

Tukey post hoc

	diff	lwr	upr	p adj
LID-Ctrl	3.610	1.377	5.843	0.0013334
MPTP-Ctrl	-1.186	-3.518	1.146	0.4899451
non-LID-Ctrl	-0.016	-2.349	2.316	0.9999971
MPTP-LID	-4.796	-7.029	-2.563	6.313E-05
non-LID-LID	-3.626	-5.859	-1.393	0.0012769
non-LID-MPTP	1.170	-1.163	3.502	0.5013787

Dopamine - Hy

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	17.220	5.740	5.464	7.03E-03	**
Residuals	19	19.960	1.051			

Tukey post hoc

	diff	lwr	upr	p adj
LID-Ctrl	1.828	0.164	3.492	0.028274228
MPTP-Ctrl	-0.444	-2.190	1.301	0.889570791
non-LID-Ctrl	0.121	-1.543	1.785	0.996834409
MPTP-LID	-2.272	-4.017	-0.527	0.008260413
non-LID-LID	-1.707	-3.370	-0.043	0.043221392
non-LID-MPTP	0.566	-1.179	2.311	0.799002155

Dopamine - PrG

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	18.130	6.045	5.445	7.13E-03	**
Residuals	19	21.090	1.110			

Tukey post hoc

	diff	lwr	upr	p adj
LID-Ctrl	1.719	0.008	3.429	0.048659429
MPTP-Ctrl	-0.743	-2.537	1.051	0.65572121
non-LID-Ctrl	0.169	-1.542	1.879	0.9923099
MPTP-LID	-2.461	-4.255	-0.667	0.005352515
non-LID-LID	-1.550	-3.261	0.160	0.084027432
non-LID-MPTP	0.911	-0.883	2.705	0.497839125

Dopamine - Put

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	144.730	48.240	17.75	9.72E-06	***
Residuals	19	51.630	2.720			

Tukey post hoc

	diff	lwr	upr	p adj
LID-Ctrl	-4.239	-6.915	-1.563	0.001423885
MPTP-Ctrl	-6.068	-8.874	-3.261	4.18E-05
non-LID-Ctrl	-6.122	-8.798	-3.446	2.01E-05
MPTP-LID	-1.828	-4.635	0.978	0.289837261
non-LID-LID	-1.883	-4.559	0.793	0.230775067
non-LID-MPTP	-0.054	-2.861	2.752	0.999939867

Dopamine - StT

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	16.610	5.538	4.825	1.16E-02	*
Residuals	19	21.810	1.148			

Tukey post hoc

	diff	lwr	upr	p adj
LID-Ctrl	0.203	-1.536	1.942	0.98743318
MPTP-Ctrl	-1.685	-3.509	0.139	0.076371313
non-LID-Ctrl	-1.510	-3.249	0.230	0.102984123
MPTP-LID	-1.888	-3.712	-0.064	0.040928627
non-LID-LID	-1.712	-3.452	0.027	0.05454061
non-LID-MPTP	0.176	-1.649	2.000	0.992832713

Dopamine - Thal

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	6.839	2.280	2.568	8.47E-02	.
Residuals	19	16.868	0.888			

b) L-DOPA

L-DOPA - Amyg

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	271.920	90.640	35.85	5.04E-08	***
Residuals	19	48.030	2.530			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	7.857	5.275	10.438	3.42858E-07
MPTP-Ctrl	-1.027	-3.734	1.681	0.713451962
non-LID-Ctrl	2.324	-0.258	4.905	0.086780449
MPTP-LID	-8.883	-11.590	-6.176	1.07E-07
non-LID-LID	-5.533	-8.114	-2.952	4.66E-05
non-LID-MPTP	3.350	0.643	6.057	0.012267308

L-DOPA - Cd

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	295.100	98.370	32.39	1.13E-07	***
Residuals	19	57.700	3.040			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	6.273	3.444	9.102	3.02093E-05
MPTP-Ctrl	-3.931	-6.898	-0.964	0.007170624
non-LID-Ctrl	0.642	-2.187	3.471	0.918443848
MPTP-LID	-10.204	-13.171	-7.237	5.12E-08
non-LID-LID	-5.631	-8.460	-2.802	1.16E-04
non-LID-MPTP	4.573	1.606	7.540	0.001862507

L-DOPA - GPe

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	342.300	114.110	38.42	2.89E-08	***
Residuals	19	56.400	2.970			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	9.184	6.386	11.982	1.06795E-07
MPTP-Ctrl	-0.425	-3.360	2.509	0.976451269
non-LID-Ctrl	2.809	0.011	5.606	0.048921248
MPTP-LID	-9.610	-12.544	-6.675	1.11E-07
non-LID-LID	-6.376	-9.174	-3.578	2.11E-05
non-LID-MPTP	3.234	0.300	6.168	0.027680644

L-DOPA - GPi

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	354.500	118.170	35.59	5.34E-08	***
Residuals	19	63.100	3.320			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	9.332	6.374	12.290	1.98019E-07
MPTP-Ctrl	-0.441	-3.543	2.662	0.977787391
non-LID-Ctrl	2.641	-0.317	5.599	0.09023911
MPTP-LID	-9.773	-12.875	-6.670	2.03E-07
non-LID-LID	-6.691	-9.649	-3.733	2.33E-05
non-LID-MPTP	3.082	-0.020	6.184	0.05189595

L-DOPA - Hip

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	293.200	97.730	35.35	1.59E-07	***
Residuals	17	47.000	2.760			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	8.651	5.789	11.513	7.58793E-07
MPTP-Ctrl	-0.262	-3.251	2.727	0.994343249
non-LID-Ctrl	2.160	-0.829	5.150	0.207659354
MPTP-LID	-8.913	-11.775	-6.051	4.99E-07
non-LID-LID	-6.490	-9.352	-3.628	3.29E-05
non-LID-MPTP	2.423	-0.566	5.412	0.13631055

L-DOPA - Hy

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	160.370	53.460	16.35	1.70E-05	***
Residuals	19	62.130	3.270			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	5.860	2.925	8.796	0.000112201
MPTP-Ctrl	-1.088	-4.166	1.991	0.75498313
non-LID-Ctrl	2.033	-0.902	4.969	0.242384582
MPTP-LID	-6.948	-10.027	-3.869	2.40E-05
non-LID-LID	-3.827	-6.763	-0.892	8.17E-03
non-LID-MPTP	3.121	0.042	6.200	0.046282204

L-DOPA - PrG

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	401.400	133.790	40.95	1.72E-08	***
Residuals	19	62.100	3.270			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	9.893	6.959	12.828	7.01863E-08
MPTP-Ctrl	-0.578	-3.656	2.500	0.951179589
non-LID-Ctrl	3.371	0.437	6.305	0.020981181
MPTP-LID	-10.471	-13.549	-7.394	6.07E-08
non-LID-LID	-6.522	-9.457	-3.588	2.93E-05
non-LID-MPTP	3.949	0.871	7.027	0.009276699

L-DOPA - Put

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	245.290	81.760	27.72	3.78E-07	***
Residuals	19	56.040	2.950			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	5.552	2.764	8.340	0.000115619
MPTP-Ctrl	-3.708	-6.632	-0.783	0.010187509
non-LID-Ctrl	-0.132	-2.920	2.656	0.999121497
MPTP-LID	-9.260	-12.184	-6.336	1.87E-07
non-LID-LID	-5.684	-8.473	-2.896	8.69E-05
non-LID-MPTP	3.575	0.651	6.500	0.013430817

L-DOPA - StT

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	315.180	105.060	27.39	4.15E-07	***
Residuals	19	72.890	3.840			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	8.731	5.552	11.911	1.58897E-06
MPTP-Ctrl	-0.576	-3.911	2.759	0.961327835
non-LID-Ctrl	3.166	-0.014	6.346	0.051256847
MPTP-LID	-9.307	-12.642	-5.972	1.25E-06
non-LID-LID	-5.565	-8.745	-2.386	5.06E-04
non-LID-MPTP	3.742	0.407	7.077	0.024603763

L-DOPA - Thal

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	271.920	90.640	35.85	5.04E-08	***
Residuals	19	48.030	2.530			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	7.857	5.275	10.438	3.42858E-07
MPTP-Ctrl	-1.027	-3.734	1.681	0.713451962
non-LID-Ctrl	2.324	-0.258	4.905	0.086780449
MPTP-LID	-8.883	-11.590	-6.176	1.07E-07
non-LID-LID	-5.533	-8.114	-2.952	4.66E-05
non-LID-MPTP	3.350	0.643	6.057	0.012267308

c) norepinephrine (NE)

NE - Amyg

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	2.795	0.932	2.135	0.129	
Residuals	19	8.291	0.436			

NE - Cd

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	14.520	4.839	4.476	0.0154	*
Residuals	19	20.540	1.081			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	-1.763	-3.451	-0.075	0.0387653
MPTP-Ctrl	-1.781	-3.551	-0.010	0.0483839
non-LID-Ctrl	-1.872	-3.560	-0.184	0.0265458
MPTP-LID	-0.018	-1.788	1.753	0.9999919
non-LID-LID	-0.109	-1.797	1.579	0.9977794
non-LID-MPTP	-0.092	-1.862	1.679	0.998857

NE - GPe

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	5.643	1.881	1.325	0.296
Residuals	19	26.984	1.420		

NE - GPi

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	1.270	0.425	0.179	0.909
Residuals	19	44.960	2.367		

NE - Hip

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	0.818	0.273	0.372	0.774
Residuals	17	12.474	0.734		

NE - Hy

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	3.150	1.051	0.489	0.694	
Residuals	19	40.860	2.150			

NE - PrG

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	3.225	1.075	1.343	0.29	
Residuals	19	15.214	0.801			

NE - Put

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	12.620	4.208	3.866	0.0258	*
Residuals	19	20.680	1.088			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	-1.466	-3.159	0.228	0.1043669
MPTP-Ctrl	-1.991	-3.768	-0.215	0.024747
non-LID-Ctrl	-1.467	-3.161	0.226	0.1038695
MPTP-LID	-0.526	-2.302	1.251	0.8386107
non-LID-LID	-0.002	-1.695	1.692	1
non-LID-MPTP	0.524	-1.252	2.300	0.8397713

NE - StT

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	0.358	0.119	0.169	0.916
Residuals	19	13.433	0.707		

NE - Thal

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	2.795	0.932	2.135	0.129
Residuals	19	8.291	0.436		

d) serotonin (5-HT)

5-HT - Amyg
ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	0.384	0.128	0.593	0.627
Residuals	19.000	4.099	0.216		

5-HT - Cd
ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	2.500	0.833	1.126	0.363
Residuals	19	14.060	0.740		

5-HT - GPe
ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	1.660	0.553	0.489	0.694
Residuals	19	21.500	1.132		

5-HT - GPi
ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	2.055	0.685	0.766	0.527
Residuals	19	16.996	0.895		

5-HT - Hip
ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	0.709	0.236	0.709	0.56
Residuals	17	5.668	0.333		

5-HT - Hy
ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	0.555	0.185	0.247	0.863
Residuals	19	14.237	0.749		

5-HT - PrG

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	8.825	2.942	2.96	0.0584
Residuals	19	18.881	0.994		

5-HT - Put

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	1.993	0.664	1.289	0.307
Residuals	19	9.794	0.516		

5-HT - StT

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	0.794	0.265	0.578	0.636
Residuals	19	8.691	0.457		

5-HT - Thal

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	0.384	0.128	0.593	0.627
Residuals	19	4.099	0.216		

e) GABA

GABA - Amyg

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	0.7821	0.2607	1.583	0.226	
Residuals	19	3.1283	0.1646			

GABA - Cd

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	2.117	0.7056	5.976	0.00478	**
Residuals	19	2.244	0.1181			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	0.511	-0.047	1.069	0.0798039
MPTP-Ctrl	-0.215	-0.800	0.370	0.7319558
non-LID-Ctrl	0.470	-0.088	1.028	0.117656
MPTP-LID	-0.726	-1.311	-0.141	0.012018
non-LID-LID	-0.041	-0.599	0.517	0.9967848
non-LID-MPTP	0.685	0.100	1.270	0.0183663

GABA - GPe

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	3.519	1.1729	8.352	0.000956	***
Residuals	19	2.668	0.1404			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	0.560	-0.049	1.168	0.07807
MPTP-Ctrl	-0.431	-1.069	0.207	0.2615525
non-LID-Ctrl	0.495	-0.114	1.103	0.1366587
MPTP-LID	-0.990	-1.629	-0.352	0.0017373
non-LID-LID	-0.065	-0.673	0.543	0.9902841
non-LID-MPTP	0.926	0.287	1.564	0.0032833

GABA - GPi

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	3.414	1.1379	6.672	0.0029	**
Residuals	19	3.24	0.1705			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	0.570	-0.100	1.241	0.1127725
MPTP-Ctrl	-0.489	-1.192	0.214	0.2388033
non-LID-Ctrl	0.326	-0.344	0.997	0.5326821
MPTP-LID	-1.060	-1.763	-0.356	0.0023077
non-LID-LID	-0.244	-0.914	0.427	0.7385811
non-LID-MPTP	0.816	0.113	1.519	0.019592

GABA - Hip

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	0.744	0.2479	1.268	0.317
Residuals	17	3.325	0.1956		

GABA - Hy

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	1.154	0.3847	1.976	0.152
Residuals	19	3.699	0.1947		

GABA - PrG

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	2.996	0.9985	4.428	0.016	*
Residuals	19	4.285	0.2255			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	0.539	-0.232	1.310	0.2356129
MPTP-Ctrl	-0.402	-1.210	0.407	0.5160486
non-LID-Ctrl	0.419	-0.352	1.190	0.4409796
MPTP-LID	-0.941	-1.749	-0.132	0.0192247
non-LID-LID	-0.120	-0.891	0.651	0.9713484
non-LID-MPTP	0.821	0.012	1.629	0.0458442

GABA - Put

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
Group	3	2.848	0.9492	8.161	0.00108	**
Residuals	19	2.21	0.1163			

Tukey post-hoc

	diff	lwr	upr	p adj
LID-Ctrl	0.626	0.073	1.180	0.0232971
MPTP-Ctrl	-0.195	-0.775	0.386	0.7823074
non-LID-Ctrl	0.578	0.024	1.131	0.0389428
MPTP-LID	-0.821	-1.402	-0.240	0.004123
non-LID-LID	-0.048	-0.602	0.505	0.9945763
non-LID-MPTP	0.773	0.192	1.353	0.0069257

GABA - StT

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	1.732	0.5773	1.95	0.156
Residuals	19	5.625	0.2961		

GABA - Thal

ANOVA table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Group	3	0.7821	0.2607	1.583	0.226
Residuals	19	3.1283	0.1646		

ANOVA tests of dopamine, L-DOPA, norepinephrine, serotonin, GABA in control (Ctrl), MPTP, non-LID and LID groups. Significant ANOVA test was followed by a Tukey post-hoc. Diff, difference of the means; lwr, lower level of confidence interval; upr, upper level of the confidence interval; Sq, squares.

Table S4. Linear regression analysis of conversion of L-DOPA to 3-OMD, L-DOPA to DA and summarised results from hypothesis tests of metabolite ratios between non-LID and LID.

a) L-DOPA to 3-OMD

LID	Int	SE int	P-int	Sl	SE sl	P-sl	Res SE	Adj R^2	DF	Mult R^2	n
Amyg	2.758	1.431	0.1262	0.566	0.146	0.0179	0.6317	0.7369	4	0.7896	n=6
Cd	2.296	1.358	0.166	0.5796	0.1276	0.0105	0.5485	0.797	4	0.8376	n=6
Clau	1.753	1.2995	0.24865	0.609	0.1318	4.621	0.00988	0.8028	4	0.8422	n=6
Ctx	1.798	1.3916	0.2659	0.6027	0.1334	0.0107	0.5619	0.7952	4	0.8362	n=6
Ent	1.9263	1.5427	0.2899	0.6097	0.1488	0.0149	0.6168	0.7595	4	0.8076	n=6
GPe	1.8502	1.2219	0.20456	0.6102	0.1237	0.00785	0.6182	0.8236	4	0.8589	n=6
GPi	1.7267	1.2804	0.24878	0.6182	0.2187	0.00863	0.6572	0.8153	4	0.8522	n=6
Hip	2.1414	1.2053	0.15026	0.6039	0.1185	0.00701	0.5407	0.8331	4	0.8665	n=6
Hy	2.0679	1.5229	0.246	0.6137	0.1594	0.0183	0.7192	0.7344	4	0.7875	n=6
Put	2.2546	1.3993	0.1824	0.5685	0.1357	0.0138	0.5963	0.768	4	0.8144	n=6
StT	2.4717	1.1879	0.10592	0.6183	0.1202	0.00677	0.5475	0.8359	4	0.8687	n=6
Tha	1.327	1.2842	0.35982	0.6539	0.1364	0.00869	0.6307	0.8147	4	0.8517	n=6

non-LID	Int	SE int	P-int	Sl	SE sl	P-sl	Res SE	Adj R^2	DF	Mult R^2	n
Amyg	3.528	0.579	0.00888	0.249	0.126	0.14265	0.2987	0.4206	3	0.5654	n=5
Cd	3.3918	0.3440	0.00059	0.2606	0.0692	0.01973	0.263	0.7246	4	0.7797	n=6
Clau	3.1249	0.8087	0.0609	0.1791	0.1826	0.4301	0.2961	-0.0127	2	0.3248	n=4
Ctx	2.8913	0.3387	0.0134	0.2857	0.0618	0.0438	0.1271	0.8716	2	0.9144	n=4
Ent	3.3996	0.8172	0.0532	0.2473	0.1466	0.2337	0.2231	0.3807	2	0.5871	n=4
GPe	2.9779	0.1601	0.00288	0.2973	0.0387	0.01648	0.06883	0.951	2	0.9673	n=4
GPi	2.5142	0.7645	0.0813	0.3723	0.1843	0.1807	0.3074	0.5068	2	0.6712	n=4
Hip	3.8597	0.2451	0.0404	0.1566	0.0493	3.178	0.1941	0.8198	1	0.9099	n=3
Hy	3.5632	1.9720	0.145	0.0951	0.3663	0.808	0.5944	-0.2293	4	0.5944	n=6
Put	2.8439	0.3194	0.00088	0.3136	0.0705	0.01123	0.2455	0.79	4	0.832	n=6
StT	3.3561	0.2248	0.00012	0.3330	0.0540	0.00352	0.1769	0.8809	4	0.9047	n=6
Tha	3.8477	1.5094	0.084	-0.0559	0.3345	0.878	0.319	-0.321	3	0.0092	n=5

Results from linear regression analysis. 3-OMD was set as y-variable and L-DOPA was set as x-variable. DF, degrees of freedom; Int, intercept; Res, residuals; SE, Standard error; Sl, Slope.

b) L-DOPA to DA

LID	Int	SE int	P-int	Sl	SE sl	P-sl	Res SE	Adj R^2	Mult R^2	DF	n
Amyg	7.6962	0.83095	0.000756	0.37288	0.08478	0.011709	0.3668	0.7858	0.8286	4	n=6
Cd	0.2255	3.3152	0.949	0.8411	0.3115	0.0541	1.339	0.5573	0.6458	4	n=6
Clau	2.56685	0.9474	0.05357	0.53849	0.09611	0.00498	0.4202	0.8587	0.887	4	n=6
Ctx	1.34612	0.52488	0.062333	0.58243	0.05031	0.000318	0.2119	0.9638	0.971	4	n=6
Ent	0.06774	0.51457	0.901627	0.74896	0.04963	0.000112	0.2057	0.9784	0.9827	4	n=6
GPe	0.3206	1.6434	0.85482	0.7847	0.1663	0.00919	0.8314	0.8096	0.8477	4	n=6
GPi	1.9477	0.8297	0.07873	0.678	0.0834	0.00125	0.4259	0.9287	0.9429	4	n=6
Hip	2.04153	0.88558	0.08246	0.57125	0.08709	0.00279	0.3973	0.8937	0.9149	4	n=6
Hy	4.393	1.2317	0.02345	0.632	0.1289	0.00803	0.5817	0.8217	0.8573	4	n=6
Put	1.9124	4.5844	0.698	0.7896	0.4446	0.15	1.954	0.3011	0.4409	4	n=6
StT	5.7084	1.1962	0.00883	0.4918	0.121	0.0153	0.5513	0.7562	0.805	4	n=6
Thal	2.3717	1.2641	0.1339	0.6049	0.1343	0.0108	0.6208	0.7942	0.8353	4	n=6

non-LID	Int	SE int	P-int	Sl	SE sl	P-sl	Res SE	Adj R^2	Mult R^2	DF	n
Amyg	11.023	0.8143	0.000872	-0.201	0.1772	0.338922	0.42	0.06712	0.3003	3	n=5
Cd	7.8728	2.8702	0.0517	-0.1597	0.5779	0.796	2.194	-0.2266	0.01873	4	n=6
Clau	3.2972	2.4133	0.305	0.3816	0.5449	0.556	0.8836	-0.2046	0.1969	2	n=4
Ctx	2.8507	1.1858	0.138	0.4034	0.2164	0.203	0.4449	0.4521	0.6347	2	n=4
Ent	-3.982	10.861	0.776	1.49	1.825	0.564	0.7145	-0.2001	0.3999	1	n=3
GPe	5.34827	4.17652	0.329	-0.0734	1.00795	0.949	1.795	-0.496	0.00264	2	n=4
GPi	3.0744	3.9616	0.519	0.5654	0.9548	0.614	1.593	-0.2763	0.1491	2	n=4
Hip	-0.5575	2.5595	0.863	0.8633	0.5145	0.342	0.9153	0.4758	0.7379	1	n=3
Hy	6.7375	1.1641	0.00486	0.3635	0.2218	0.1766	0.3599	0.2521	0.4017	4	n=6
Put	10.7044	2.5229	0.0132	-0.5896	0.5564	0.3491	1.939	0.02395	0.2192	4	n=6
StT	6.3672	1.313	0.00834	0.6007	0.3156	0.12675	1.033	0.344	0.4752	4	n=6
Thal	1.2076	7.885	0.888	0.9752	1.7475	0.616	1.667	-0.2079	0.094	3	n=5

Results from linear regression analysis. DA was set as y-variable and L-DOPA was set as x-variable. DF, degrees of freedom; Int, intercept; Res, residuals; SE, Standard error; Sl, Slope.

c) Summarised results from hypothesis tests of metabolite ratios between non-LID and LID.

Ratios Cd	Mean Rank non-LID	Sum of Ranks non-LID	Mean Rank LID	Sum of Ranks LID	U-statistics	p-value
DOPAC/DA	8.333	50	4.667	28	7	0.09
3-MT/DA	9	54	4	24	3	0.0152

Ratios Put	Mean Rank non-LID	Sum of Ranks non-LID	Mean Rank LID	Sum of Ranks LID	U-statistics	p-value
DOPAC/DA	8.333	50	4.667	28	7	0.09
3-MT/DA	9	54	4	24	3	0.02

Summary of results from Mann-Whitney U test, ratios of DOPAC/DA and 3-MT/DA in Cd and Put.

Table S5. Two-way ANOVA test of dopamine in cortical layers.

Cortical area: Precentral gyrus				
ANOVA table	% of total variation	DF	F (DFn, DFd)	P value
Cortical layer	8.77	2	F (2, 20) = 29.21	P=0.0001
Dyskinesia	45.94	1	F (1, 10) = 11.56	P=0.0068
Interaction: Cortical layer x Dysinesia	2.55	2	F (2, 20) = 8.485	P=0.0021

	Mean non-LID	Mean LID
Outer	6.295	7.608
Middle	5.575	7.466
Deep	4.763	7.151

Sidak's multiple comparisons test - non-LID vs LID in cortical layers				
non-LID - LID	Mean Diff.	95.00% CI of diff.	Adjusted P Value	DF
Outer	-1.313	-2.751 to 0.1241	0.0815	30
Middle	-1.891	-3.329 to -0.4537	0.007	30
Deep	-2.388	-3.826 to -0.9503	<0.001	30

Cortical area: Insula				
ANOVA table	% of total variation	DF	F (DFn, DFd)	P value
Cortical layer	4.82	2	F (2, 20) = 36.8	P<0.001
Dyskinesia	35.12	1	F (1, 10) = 6.05	P=0.034
Interaction: Cortical layer x Dyskinesia	0.72	2	F (2, 20) = 5.501	P=0.013

	Mean non-LID	Mean LID
Outer	5.442	7.076
Middle	4.201	6.465
Deep	4.603	6.85

Sidak's multiple comparisons test - non-LID vs LID in cortical layers				
non-LID - LID	Mean Diff.	95.00% CI of diff.	Adjusted P Value	DF
Outer	-1.633	-3.762 to 0.4952	0.174	30
Middle	-2.264	-4.392 to -0.1352	0.034	30
Deep	-2.248	-4.376 to -0.119	0.036	30

Cortical area: Temporal gyrus				
ANOVA table	% of total variation	DF	F (DFn, DFd)	P value
Cortical layer	11.29	2	F (2, 20) = 14.55	P=0.0001
Dyskinesia	54.94	1	F (1, 10) = 21.16	P=0.001
Interaction: Cortical layer x Dyskinesia	0.053	2	F (2, 20) = 0.068	P=0.934

	Mean non-LID	Mean LID
Outer	5.935	8.041
Middle	4.69	6.911
Deep	5.018	7.286

Sidak's multiple comparisons test - non-LID vs LID in cortical layers				
non-LID - LID	Mean Diff.	95.00% CI of diff.	Adjusted P Value	DF
Outer	-2.106	-3.483 to -0.7287	0.0017	30
Middle	-2.221	-3.598 to -0.8442	<0.001	30
Deep	-2.268	-3.645 to -0.8911	<0.001	30

Results from investigation of differential distribution of DA in outer, middle and deep cortical layers in non-LID and LID performed using two-way ANOVA with Sidak's multiple comparisons test. CI, confidence interval; DF, degrees of freedom.