Supporting information

Control of motor coordination by astrocytic tonic GABA release through modulation of excitation/inhibition balance in cerebellum

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This PDF file includes:

Materials and Methods

Animals

Adult (8~10 week) male and female wild-type of Best1 KO (Balb/C background), MAOB KO (129 background) and GFAP-MAOB(1) (C57BL/6 background) mice were used. In GFAP-MAOB mice, astrocyte-specific transgene expression of MAOB was induced by feeding animals with doxycycline at 3000 ppm provided in pre-mixed Purina chow (Research Diets) for a three weeks period. All experimental procedures described below were performed in accordance with KIST (Seoul, Korea, approval number: 2016-051) and Dankook University Animal Experimentation Guidelines (Cheonan, Korea, approval number: DKU-17-022).

Immunohistochemistry

Adult mice were deeply anesthetized with 2% avertin (20 μg/g) and perfused with 0.1M PBS (Phosphate buffered saline) followed by ice cold 4 % PFA (paraformaldehyde). Excised brains were post-fixed overnight in 4 % PFA at 4 °C and immersed in 30% sucrose for 48 hrs for cryo-protection. Parasagittal cerebellar sections (30 μm), rinsed in PBS three times and incubated 1 hr at RT with blocking solution (0.3% Triton-X, 2 % normal serum in 0.1 M PBS). Sections were incubated overnight in a mixture of the following primary antibodies with blocking solution at 4 °C on shaker; rabbit anti bestrophin antibody (1:200; produced by Young In Frontier), rabbit anti MAOB antibody (1:200), chicken anti GFAP antibody (1:500; Millipore) and guinea-pig anti GABA (1:200; Sigma). After washing three times in PBS, sections were incubated with corresponding secondary antibodies; conjugated Alexa 647 goat anti guinea-pig antibody (1:200; Jackson ImmunoResearch Inc.), Alexa 555 goat anti rabbit (1:200; Jackson ImmunoResearch Inc.) and Alexa 488 donkey anti chicken antibody (1:200;

Jackson ImmunoResearch Inc.), for two and a half hours, followed by one rinse in PBS, and incubated one time DAPI (1:1,000) in PBS. After incubated with DAPI, followed by one rinse in PBS. Then mounted with an anti-fade mounting medium. A series of fluorescence images were obtained with a confocal microscope (Zeiss, LSM 700) and images were processed for later analysis using ImageJ program and ZEN 2010 imaging software.

Slice recording

Animals were deeply anesthetized with halothane. After decapitation, the brain was quickly excised from the skull and submerged in an ice-cold cutting solution that contained (in mM): 130 NaCl, 24 $NaHCO_3$, 1.25 NaH_2PO_4, 3.5 KCl, 1.5 $CaCl_2$, 1.5 $MgCl_2$, and 10 D(+)-glucose, pH 7.4. The whole solution was gassed with 95 % O_2-5 % CO_2. After trimming the cerebellar brain, 250 μm parasagittal slices were cut using a vibratome (DSK Linear Slicer, Kyoto, Japan) with a blade (DORCO, Seoul, Korea) and transferred to extracellular ACSF solution (in mM): 130 NaCl, 24 $NaHCO_3$, 1.25 NaH_2PO_4, 3.5 KCl, 1.5 $CaCl_2$, 1.5 $MgCl_2$, and 10 D(+)-glucose, pH 7.4.

Slices were incubated at room temperature for at least one hour prior to recording. Slices were transferred to a recording chamber that was continuously perfused with ASCF solution (flow rate = 2 ml/min). The slice chamber was mounted on the stage of an upright Olympus microscope and viewed with a 60X water immersion objective (NA = 0.90) with infrared differential interference contrast optics. Cellular morphology was visualized by CCD camera and Axon Imaging Workbench software. Whole-cell recordings were made from cerebellar granule cell somata located in lobules 2-5. The holding potential was -60 mV. Pipette resistance was typically 8-10 MΩ for GCs and 4-5 MΩ for PCs. The pipette was filled with an internal solution (in mM): 135 CsCl, 4

NaCl, 0.5 $CaCl_2$, 10 HEPES, 5 EGTA, 2 Mg-ATP, 0.5 Na_2-GTP, 10 QX-314, pH adjusted to 7.2 with CsOH (278-285 mOsmol) for current measurement; 140 K-gluconate, 10 HEPES, 7 NaCl, and 2 MgATP adjusted to pH 7.4 with CsOH for voltage measurement. Electrical signals were digitized and sampled at 50 μs intervals with Digidata 1440A and Multiclamp 700B amplifier (Molecular Devices) using pCLAMP 10.2 software. Data were filtered at 2 kHz.

Evoked responses were obtained by concentric bipolar tungsten stimulating electrodes placed in the white matter to activate mossy fibers or in the molecular layer to activate parallel fibers as previously described (2). Trains of stimuli (200 μA) were 200 ms in duration and delivered only every 30 s to prevent changes in synaptic efficacy (3). To avoid the response change by the position of stimulating electrode, the distance between stimulating electrode and recording electrode was matched. This was monitored by the amplitude of stimulating artifact with the same intensity of stimulation (200 μA). PCs were patched with an internal solution (in mM): 140 K-gluconate, 10 HEPES, 7 NaCl, and 2 MgATP adjusted to pH 7.4 with CsOH and their membrane potential were set at -65 mV. LTP in PCs was measured by evoked EPSC responses in recording solution without the antagonists for $GABA_AR$ and $GABA_BR$ and induced by 1Hz, 5 minutes stimulation (90 stimuli) at paraller fiber in the current clamp mode.

Data analysis and statistical analysis

Off-line analysis was carried out using Clampfit, Minianalysis, SigmaPlot and Excel software. The significance of data for comparison was assessed by Student's two-tailed unpaired t test. Exact *P* values are clearly indicated in the Supplementary Tables. In general, data distribution was assumed to be normal but this was not formally tested.

The data distribution was assumed to be normal. Data are presented as mean ± SEM (standard error of the mean). Levels of statistical significance are indicated as follows:

* ($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$).

In vivo microdialysis

Mice were anesthetized with 2 % avertin (20 μg/g) and mounted in a stereotaxic frame. After exposing the skull and drilling a hole, a CMA7 guide cannula (CMA Microdialysis) was inserted in the mid cerebellum (AP: -2.0 mm; ML: 0.0 mm from lambda; DV, -2.0 mm). In addition, anchor screws were located in the skull and fixed with Zinc Polycarboxylate dental cement. After mice recovered from anesthesia, a CMA7 microdialysis probe (membrane diameter 0.24 mm, length 1 mm; stainless-steel shaft diameter 0.38 mm) was implanted through the guide cannula. The probe was connected to a CMA100 microinjection pump (CMA Microdialysis) with polyethylene tubing (PE 50) and FEP tubing (INSTECH). Then the probe was perfused with artificial cerebrospinal fluid (ACSF) (in mM: 149 NaCl, 2.8 KCl, 1.2 $MgCl_2$, 1.2 $CaCl_2$, and 5.4 glucose, pH7.4) into the inlet of the probe at a flow rate of 1.5 μl/min. Perfusates from the outlet of the tubing were automatically collected in plastic vials at 8 °C using CMA 470 refrigerated fraction collector. Dialysates were collected over 20 min intervals for 4 hr and used for measurement glutamate, putrescine and GABA from the second samples. Dialysates were stored at -80 °C and then analyzed using Mass spectrometry and HPLC.

Glutamate and GABA measurement using HPLC

1 mg/ml stock solutions of GABA/glutamate standards were prepared in HPLC-grade

water, aliquoted out and stored at −20 °C. Working solutions (1 µg/ml and 5 µg/ml for glutamate; 100 ng/ml and 500 ng/ml for GABA) were prepared daily by dilutions of those stock solutions, aliquoted out and stored at 4 °C until derivatization and analysis. Briefly, the derivatization was performed by mixing 100 µl in vivo microdialysate or standard solutions, 20 µl of daily prepared methanolic o-phthalaldehyde (5 mg/ml), 75 µl borate buffer (pH 9.9) and 5 µl 3-mercaptopropionic acid. The resulting solution was vortexed and analyzed after 1 min at room temperature. The HPLC system consisted of a Waters chromatograph (Waters) with a 200-µl loop (Rheodyne 7725-I) and a fluorescence detector (FLD-Waters spectrofluorometric detector 2475), coupled to an LC-10 AD pump. The system was equipped with a 3-µm particle size (150 mm × 4.6 mm, ID) C18 analytical column (Hibar-Futigsanle RT) and a prepacked column (RT 250-4 E, Merck). An integrator (Empower 2) was used to analyze the chromatographic data. The mobile phase consisted of 0.05 M sodium acetate, tetrahydrofuran and methanol (50:1:49, v:v:v) adjusted to pH 4.0. The mobile phase was filtered through Millipore 0.45-µm Durapore membrane filters and vacuum degassed before use. Chromatographic analyses were performed at 25 ± 2 °C. Compounds were eluted isocratically over a 9-min runtime at a flow rate of 1 ml/min. The fluorescence detector was set at an excitation wavelength of 337 nm and an emission wavelength of 454 nm, low sensitivity and range GABA/glutamate were identified by their characteristic retention times as determined by standard injections. Sample peak areas were measured through the integrator system and compared with the calibration curve standard in order to quantify the amino acid concentrations.

Glutamate, GABA and putrescine measurement using LC-MS/MS

The LC-MS/MS system consisted of an Agilent 1290 series rapid resolution LC system

and a triple quadrupole linear ion trap mass spectrometer (4000 QTRAP) (AB Sciex, Foster City, CA, USA). Chromatographic separation was achieved using a Luna C8 column (100 mm × 2.0 mm, 3 µm, Phenomenex, Torrance, CA, USA). The mobile phases A and B consisted of 0.1% formic acid in water (LC-MS grade) and acetonitrile (LC-MS grade), respectively. The isocratic elution profile was chosen to assay microdialysis samples: 5% B for GABA and glutamate, 75% B for putrescine. The flow rate was run at 0.3 mL/min and the injection volume was 10 µL. The mass spectrometer was optimized for multiple reaction monitoring (MRM) mode using electrospray ionization (ESI) in positive mode. The ion spray voltage was set at 5000 V and the source temperature at 500°C. The m/z transitions were set as 104.0 → 87.0 for GABA, 148.0 → 84.0 for glutamate and 89.0 → 72.0 for putrescine. Data were acquired and analyzed using the software Analyst® version 1.6 (AB Sciex, Foster City, CA, USA).

Rotarod test

The rotarod test was based on a rod with forced motor activity. Mice were handled for 7 days and were trained to walk on the five station rotarod (MED Associates Inc., USA) for 3 days and then tested for 2 days. The rotarod consists of a cylinder with a diameter 5.5 cm on 5 animals can run simultaneously, separated by panels. The test processed constant 32 rpm during 300 seconds for 2 days. Values for latency to fall were averaged results for 2 days. Mice were placed on the stationary rod and recorded time of latency to fall. Interval time of each trial is 10 mins. In accelerating mode, mice were placed on a rotarod that accelerated from 4 to 40 rpm in 5 mins. Mice were trained for 4 sessions (60 seconds per 1 session) in a day at gradually increasing speed day by day (day 1: 24 rpm; day 2: 28 rpm; day 3: 32 rpm) with 60 seconds for 3 days. The

protocol was based on the previous study (4) with our modification as described above. During training sessions, we allowed each animal to have up to three trials to perform additional rotarod test if a mouse falls within 10 seconds. We excluded any mouse that failed to satisfy this criterion. The tests were done for 2 days. In the test session, each trial ended when mice fell off the rod or when the mice ran for 600 seconds. The time when mice dropped form the rod was recorded. The maximal velocity is the rpm was calculated by recorded time. The equation is (40-4)rpm/300sec * (recorded seconds) + 4 rpm.

Supplementary Figures

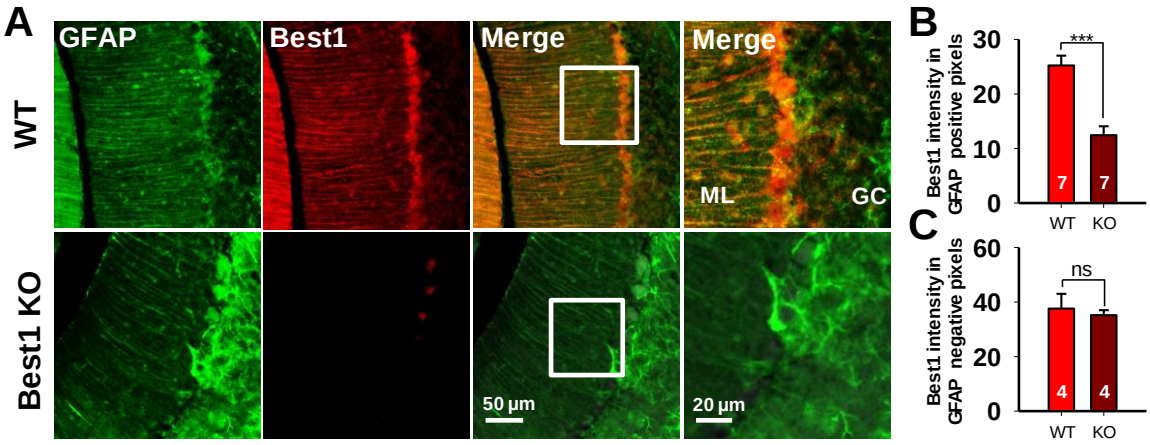

Fig. S1. Confirmation of genetic deletion of Best1 in Best1 KO mice by immunohistochemistry.
(A) Immunostaining from cerebellar slices with wild type and Best1 KO mice. (Green: GFAP; Red: Best1, ML: molecular layer, GC: granule cell layer). **(B and C)** Quantification of Best1 immunoreactivity in GFAP positive pixels (B, WT: 25.21 ± 1.82; KO: 12.91 ± 1.67; *P* = 0.0003) and negative pixels (C, WT: 37.58 ± 5.41; KO: 35.19 ± 1.81; *P* = 0.6904, unpaired t test).

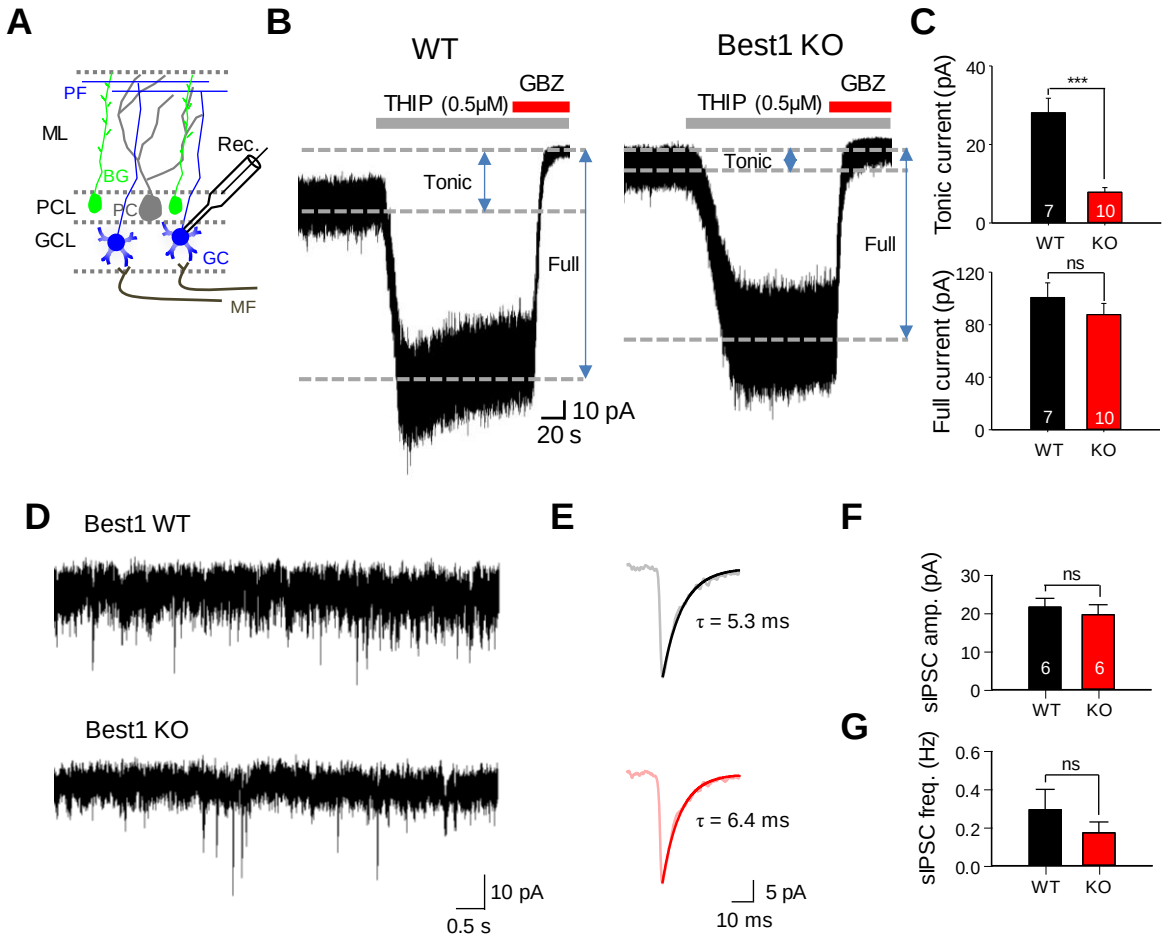

Fig. S2. No significant difference in THIP-induced tonic current and synaptic responses in WT and Best1 KO mice.

(A) Schematic illustration for tonic current recording in cerebellar GCs by whole-cell patch clamp. **(B)** Representative traces of tonic current in cerebellar GCs from WT and Best1 KO mice. **(C)** Magnitude of GABAzine sensitive tonic current (upper, WT: 27.06 ± 2.77 pA; KO: 7.84 ± 1.19 pA; *P* = 0.00003) and full current (bottom, WT: 97.51 ± 8.52; KO: 87.70 ± 8.53 pA; *P* = 0.4248) as indicated (unpaired t test). **(D)** Representative traces of sIPSC from WT and Best1 KO mice. **(E)** Averaged sIPSCs after normalization by peak. Decay was fitted to one-expenential functions. **(F,G)** Summary data of amplitude (F, WT: 21.59 ± 2.28; KO: 19.59 ± 2.59 pA; *P* = 0.5573) and frequency (G, WT: 0.29 ± 0.11; KO: 0.17 ± 0.06 pA; *P* = 0.3043) of sIPSCs. (unpaired t test).

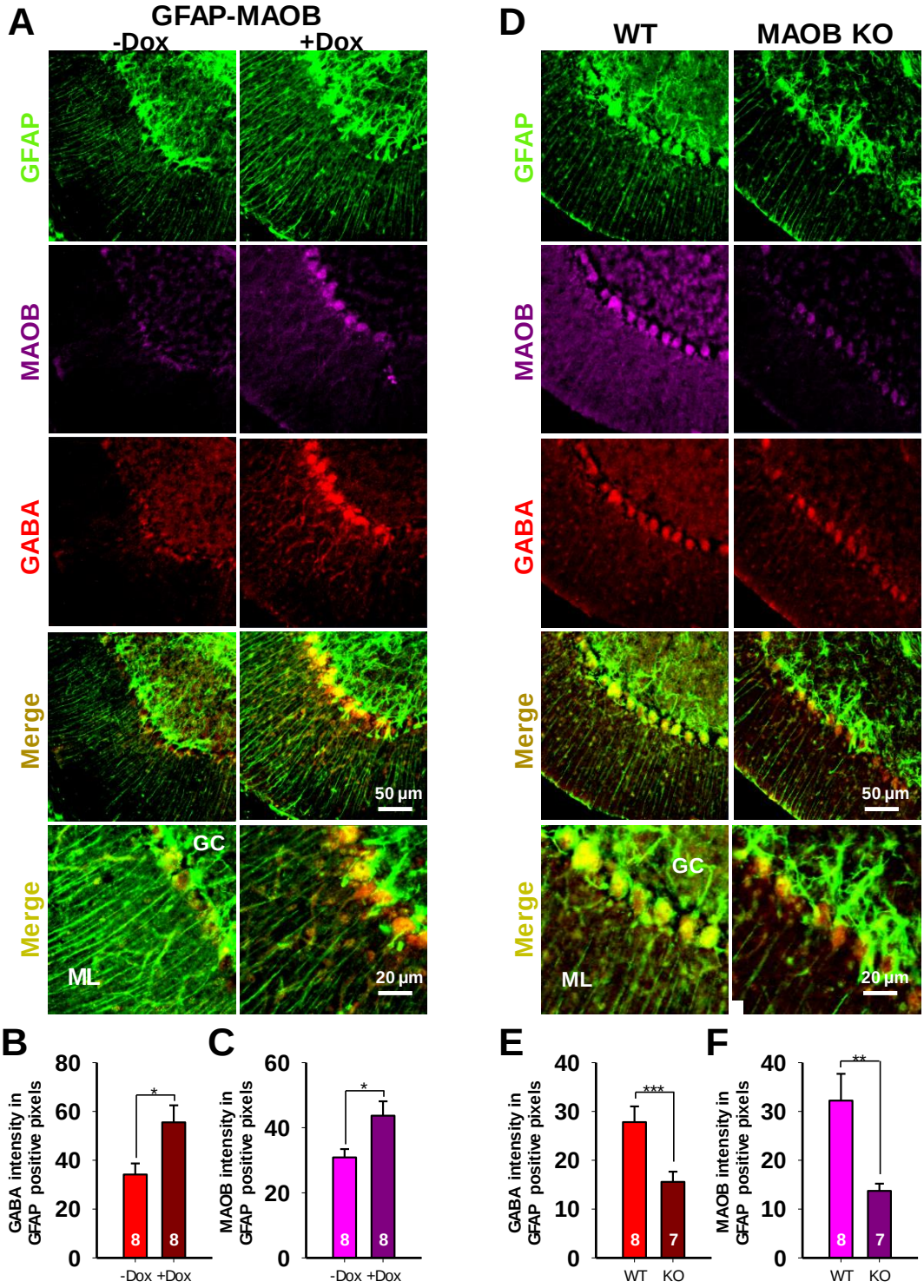

Fig. S3. GABA content is suppressed by genetic deletion of MAOB and enhanced by overexpression of MAOB in Bergmann glial cells and lamellar astrocytes.

(A) Immunostaining from cerebellar slices from GFAP-MAOB mice in off-doxycycline (- Dox) and on-doxycycline (+ Dox) conditions. (Green: GFAP; Purple: MAOB, Red: GABA). **(B and C)** Quantification of GABA (b, - Dox: 34.16 ± 4.82; + Dox: 55.53 ± 7.43, GFAP (+); *P* = 0.022) and MAOB (c, - Dox: 30.87 ± 2.75; + Dox: 43.71 ± 4.72; *P* =

0.025, unpaired t test) immunoreactivity in GFAP positive pixels. **(D)** Immunostaining from cerebellar slices from wild type and MAOB KO mice. (Green: GFAP; Purple: MAOB, Red: GABA). **(E and F)** Quantification of GABA (e, WT: 27.82 ± 3.42; KO: 15.57 ± 2.09; *P* = 0.0084) and MAOB (f, WT: 32.22 ± 5.86; KO: 13.72 ± 1.49; *P* = 0.0009; unpaired t test) immunoreactivity in GFAP positive pixels.

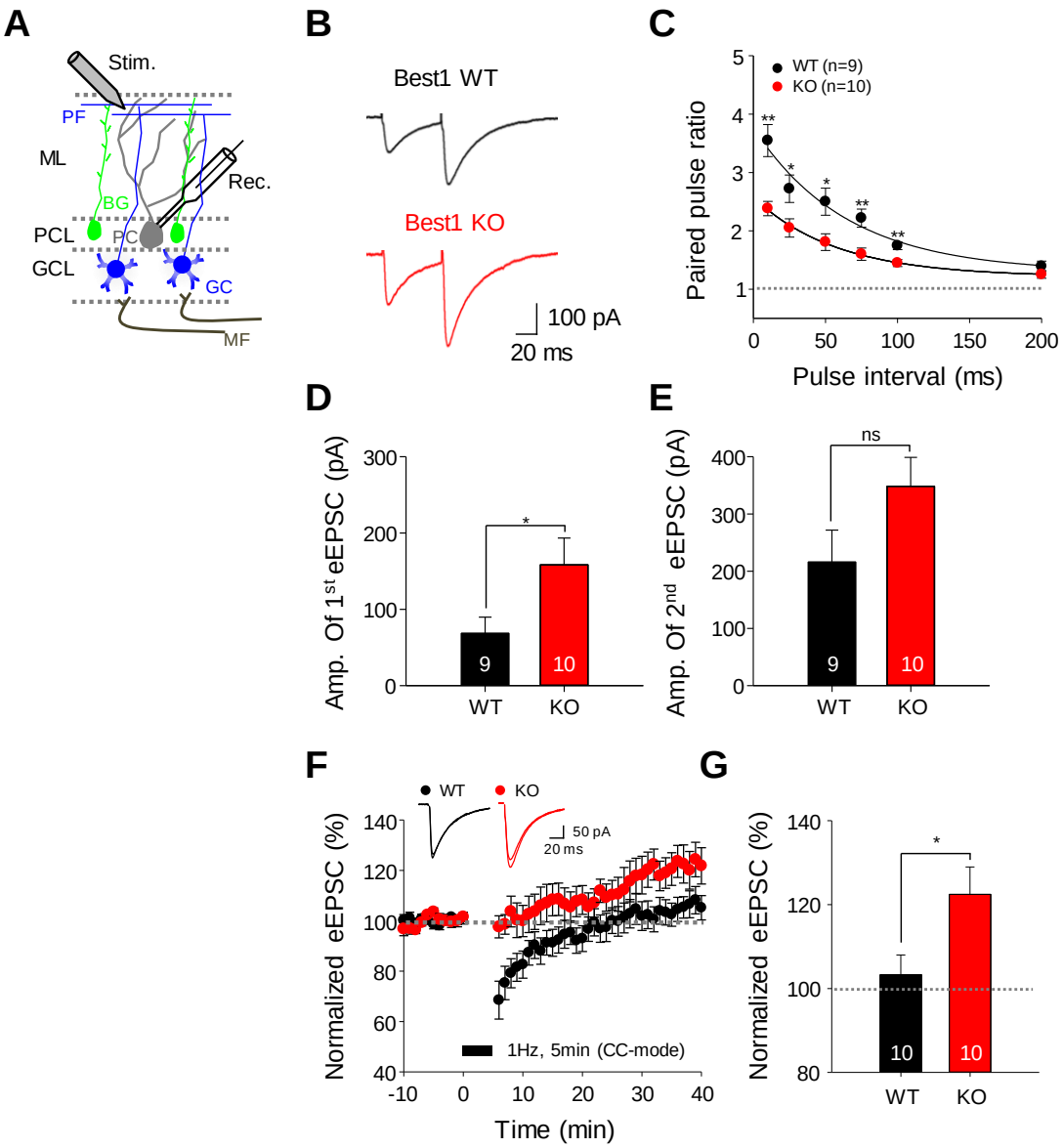

Fig. S4. Release probability and synaptic plasticity are increased in Best1 KO mice.

(A) Schematic illustration for evoked EPSC (eEPSC) in cerebellar PCs by electrical stimulation of PF. **(B)** Representative traces of PPR in PCs from WT and Best1 KO mice. **(C)** Suammary data of PPR in PCs upon various pulse interval (unpaired t test). **(D, E)** Averaged amplitude of eEPSCs in 1st (WT: 68.7 ± 21.16; KO: 158.39 ± 35.09 pA; *P* = 0.046) and 2nd (WT: 99.69 ± 30.41; KO: 178.14 ± 39.46 pA; *P* = 0.014) responses at 10 ms stimulation interval. **(F)** Averaged eEPSC upon LTP protrocol (1Hz, 5 min in current-clamp mode) from WT and Best1 KO mice. **(G)** Summary data of LTP (averaging responses for the last 5 min, WT: 103.29 ± 4.69; KO: 122.46 ± 6.53 %; *P* = 0.0283, unpaired t test).

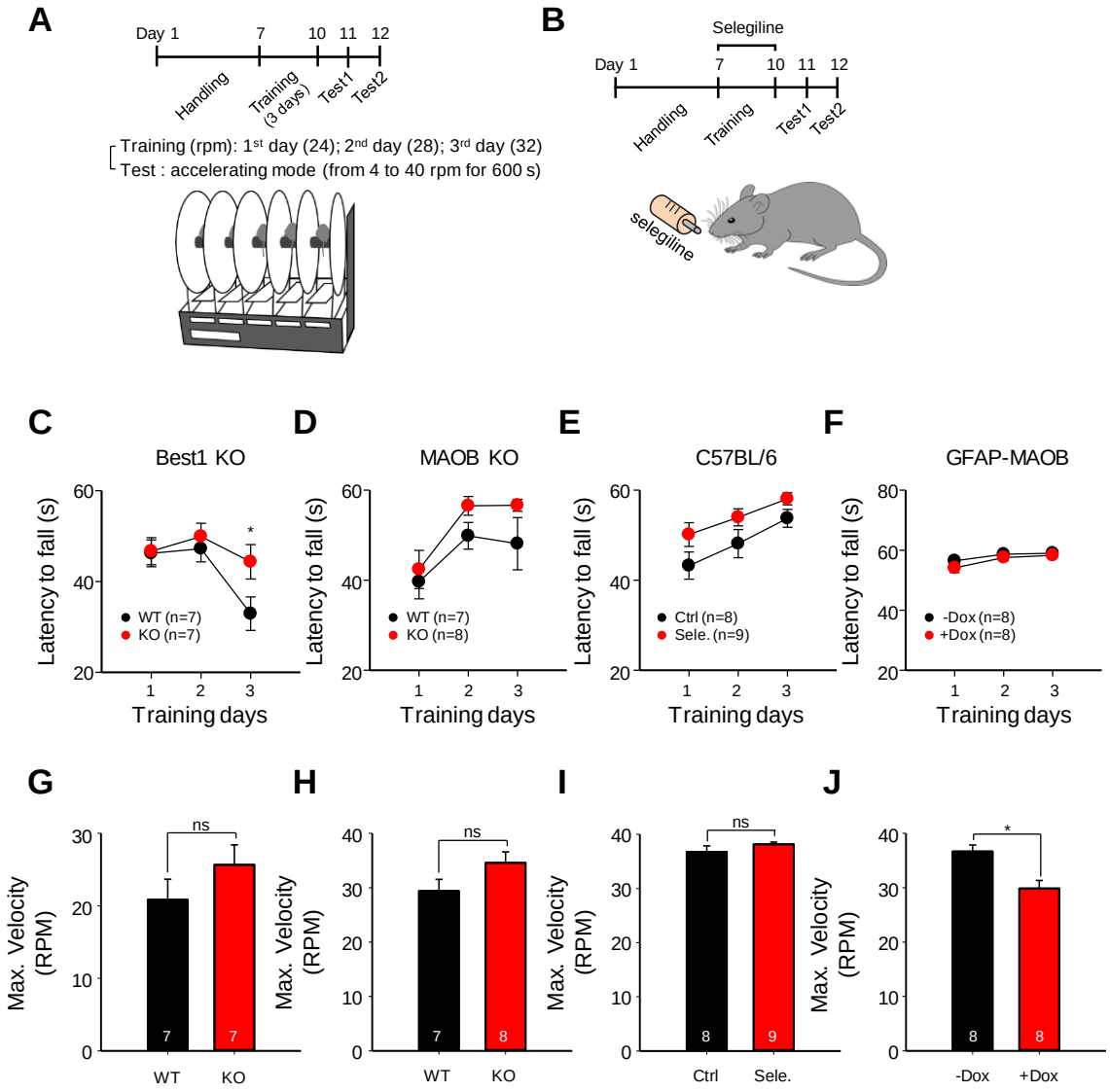

Fig. S5. Initial motor performance and maximum velocity to stay on from rotarod test.

(A) Experimental timeline and schematic illustration for rotarod test. **(B)** Experimental timeline for selegiline treatment and rotarod test. **(C-F)** Summary graph showing latency to fall during training sessions. **(G-J)** Summary graph maximum velocity (unpaired t test). Error bars are s.e.m., * indicates $P < 0.05$, ns indicates $P > 0.05$.

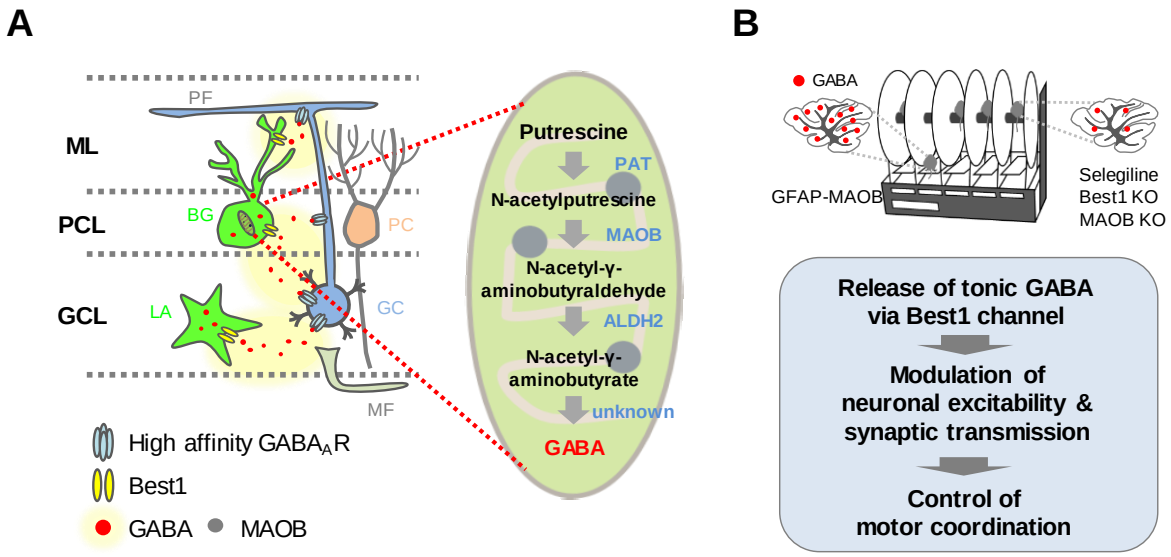

Fig. S6. Schematic model for astrocytic GABA-mediated control of motor coordination.
(A) Schematic for GABA synthesis pathway in cerebellum. PAT: putrescine acetyltransferase; MAOB: monoamine oxidase B; ALDH2: aldehyde dehydrogenase 2. **(B)** Schematic model showing modulation of glial GABA, neuronal excitability, synaptic transmission, and motor coordination.

Supplementary Table 1

	GFAP intensity (a.u.)			
	Avg	SEM	n (slices)	*P* value
Best1 WT	57.02	3.6	7	0.78
Best1 KO	57.15	5.89	7	
MAOB WT	69.07	7.08	8	0.15
MAOB KO	54.69	5.99	7	
GFAP-MAOB (-Dox)	102.55	4.95	8	0.09
GFAP-MAOB (+Dox)	119.47	8.02	8	

Quantification of GFAP intentisity in Best1 KO, MAOB KO, and GFAP-MAOB mice (related to supplementary figure 2). *P*-values were derived from two-tailed unpaired t tests (Avg: mean; SEM: standard error of the mean).

Supplementary Table 2

	sIPSC amplitude (pA)				sIPSC frequency (Hz)			
	Avg	SEM	n (slices)	*P* value	Avg	SEM	n (slices)	*P* value
Best1 WT	15.29	2.05	6	0.58	0.34	0.07	6	0.16
Best1 KO	13.48	2.33	7		0.25	0.02	7	
GFAP-MAOB (-Dox)	16.05	2.09	12	0.16	0.28	0.03	12	0.68
GFAP-MAOB (+Dox)	21.48	3.16	10		0.24	0.09	10	

Results of the amplitude and frequency spontaneous IPSC (sIPSC) from Best1 wildtype, KO mice and GFAP-MAOB (-Dox / +Dox) mice. *P*-values were derived from two-tailed unpaired t tests (Avg: mean; SEM: standard error of the mean).

Supplementary Table 3

Tonic current (pA)					
	Avg	SEM	n (slices)	N (mice)	*P* value
Best1 WT	21.17	1.62	6	3	0.0005
Best1 KO	6.28	2.38	9	3	
Tonic current (pA) in the presence of 5 µM					
	Avg	SEM	n (slices)	N (mice)	*P* value
Best1 WT	93.23	12.07	6	3	0.6023
Best1 KO	87.4	11.05	8	3	

Tonic current (pA)					
	Avg	SEM	n (slices)	N (mice)	*P* value
GFAP-MAOB (-Dox)	15.25	3.97	11	4	0.0384
GFAP-MAOB (+Dox)	28.34	4.88	11	4	
Tonic current (pA) in the presence of 5 µM					
	Avg	SEM	n (slices)	N (mice)	*P* value
GFAP-MAOB (-Dox)	70.94	8.91	5	3	0.2411
GFAP-MAOB (+Dox)	91.34	13.43	5	3	

Results of the tonic current (illustrated in **Fig. 1D,G,K,N**) without or with 5 µM GABA in recording ACSF from Best1 wildtype, KO mice (upper) and GFAP-MAOB (-Dox / +Dox) mice (bottom). *P*values were derived from two-tailed unpaired t tests (Avg: mean; SEM: standard error of the mean).

Supplementary Table 4

EPSP (mV) in GCs by current injection					
	Best1 WT (n=11; N=3)		Best1 KO (n=11; N=3)		
Current (pA)	Avg	SEM	Avg	SEM	*P* value
0	0.00	0.00	0.00	0.00	N/D
5	0.00	0.00	0.00	0.00	N/D
10	1.82	1.82	0.00	0.00	0.3293
15	6.36	3.64	4.55	1.84	0.6603
20	14.55	4.29	20.00	4.32	0.3807
25	23.18	4.83	32.27	5.37	0.2224
30	31.82	4.06	48.64	6.43	0.0389
35	43.18	5.73	59.09	6.25	0.0752
40	49.55	5.90	70.91	6.32	0.0225
45	57.27	7.15	79.09	7.19	0.0438
50	59.09	6.43	85.91	6.67	0.0089
	GFAP-MAOB (-Dox) (n=9; N=3)		GFAP-MAOB (+Dox) (n=12; N=3)		
Current (pA)	Avg	s.e.m.	Avg	s.e.m.	*P* value
0	0.00	0.00	0.00	0.00	N/D
5	0.00	0.00	0.00	0.00	N/D
10	1.11	1.11	0.00	0.00	0.2384
15	4.44	2.94	0.00	0.00	0.0810
20	5.00	3.33	0.00	0.52	0.1484
25	6.67	4.00	2.14	2.32	0.5798
30	8.33	4.33	4.29	2.95	0.6704
35	16.67	3.54	7.86	3.42	0.2288
40	27.78	5.01	10.00	3.80	0.0517
45	40.56	5.03	14.29	5.11	0.0293
50	47.78	6.78	19.29	5.76	0.0360

EPSP (mV) in PCs by current injection					
	Best1 WT (n=13; N=3)		Best1 KO (n=11; N=3)		
Current (pA)	Avg	SEM	Avg	SEM	*P* value
0	0.00	0.00	0.00	0.00	N/D
50	6.15	5.38	1.82	1.39	0.4776
100	18.08	9.14	17.27	4.74	0.9417
150	33.08	11.80	31.82	6.51	0.9301
200	48.08	11.06	45.91	7.74	0.8783
250	62.31	13.10	56.36	7.30	0.7100
300	70.77	13.61	63.64	6.98	0.6633
350	75.38	14.79	70.00	8.06	0.7644
400	75.00	14.18	76.82	8.35	0.9170
450	73.08	13.46	80.45	11.09	0.6835

	GFAP-MAOB (-Dox) (n=5; N=3)		GFAP-MAOB (+Dox) (n=7; N=3)		
Current (pA)	Avg	s.e.m.	Avg	s.e.m.	*P* value
0	0.00	0.00	0.00	0.00	N/D
50	0.00	0.00	0.00	0.00	N/D
100	0.00	0.00	0.00	0.00	N/D
150	4.00	2.92	3.57	2.37	0.9108
200	18.00	8.89	15.71	5.82	0.8263
250	42.00	8.00	27.86	8.15	0.2590
300	58.00	4.90	43.57	8.84	0.2329
350	76.00	4.30	60.00	6.81	0.1031
400	83.00	6.82	70.00	7.07	0.2310
450	78.00	4.90	70.00	6.64	0.3918

Results of the EPSP of GCs by current injection from Best1 WT, KO mice and GFAP-MAOB (-Dox), GFAP-MAOB (+Dox) mice (illustrated in **Fig. 2C, E**, top). Results of the EPSP of PCs by current injection from Best1 WT, KO mice and GFAP-MAOB (-Dox), GFAP-MAOB (+Dox) mice (illustrated in **Fig. 2H, J**, bottom). *P*-values were derived from two-tailed unpaired t tests (Avg: mean; SEM: standard error of the mean; N/D: no detected).

Supplementary Table 5

Evoked EPSP (mV) by MF stimulation					
	Best1 WT (n=16; N=4)		Best1 KO (n=16; N=4)		
Stim. (Hz)	Avg	SEM	Avg	SEM	*P* value
5	1.88	0.9	8.13	1.7	0.0029
10	3.44	1.63	20	5.12	0.0044
20	8.75	3.49	34.06	5.92	0.0009
50	22.81	7.46	67.19	8.93	0.0008
100	32.19	12.24	65.31	9.45	0.0404
200	35	14.54	76.25	16.74	0.0726
Evoked EPSP (mV) by PF stimulation					
	Best1 WT (n=13; N=4)		Best1 KO (n=14; N=4)		
Stim. (Hz)	Avg	s.e.m.	Avg	s.e.m.	*P* value
5	5.38	1.44	8.93	2.23	0.2019
10	12.69	3.03	17.14	4.01	0.3903
20	26.16	6.48	39.29	7.81	0.2112
50	26	6.1	48.93	7.09	0.0177
100	20.38	4.58	57.14	12.84	0.0149
200	20.38	5.32	5.14	13.81	0.0235

Evoked EPSP (mV) by MF stimulation					
	GFAP-MAOB (-Dox) (n=11; N=4)		GFAP-MAOB (+Dox) (n=15; N=4)		
Stim. (Hz)	Avg	SEM	Avg	SEM	*P* value
5	9.09	3.62	3	1.45	0.0959
10	16.82	6.37	5.67	2.62	0.0860
20	33.18	10.21	9.67	4.98	0.0341
50	47.27	15.13	15.67	6.13	0.0423
100	44.55	11.55	33.33	8.72	0.4371
200	60.45	17.44	40	9.93	0.2889
Evoked EPSP (mV) by PF stimulation					
	GFAP-MAOB (-Dox) (n=10; N=4)		GFAP-MAOB (+Dox) (n=13; N=4)		
Stim. (Hz)	Avg	s.e.m.	Avg	s.e.m.	*P* value
5	6.5	1.5	2.69	1.34	0.0731
10	14.5	3.37	5.77	2.46	0.0437
20	29	6.53	18.08	4.48	0.1686
50	57.5	9.29	35	6.23	0.0493
100	53.5	11.55	40.77	9.82	0.4085
200	53.5	15.77	35.83	12.35	0.3310

Results of the evoked EPSP by mossy fiber and parallel fiber stimulation from Best1 wildtype and KO mice (illustrated in **Fig. 3C, H**, top) and GFAP-MAOB (-Dox) and

GFAP-MAOB (+Dox) mice (illustrated in **Fig. 3E, J,** bottom). *P*-values were derived from two-tailed unpaired t tests (Avg: mean; SEM: standard error of the mean).

Supplementary Table 6

Evoked EPSP (mV) by MF stimulation from Best1 WT					
	Control (n=16; N=4)		GABAzine (n=7; N=2)		
Stim. (Hz)	Avg	SEM	Avg	SEM	*P* value
5	2.00	0.95	5.63	1.99	0.0589
10	3.67	1.72	10.00	2.50	0.0338
20	9.33	3.68	21.88	4.32	0.0344
50	24.33	8.12	49.38	5.93	0.0349
100	34.33	12.88	100.00	10.39	0.0017
Evoked EPSP (mV) by MF stimulation from Best1 KO					
	Control (n=16; N=4)		GABAzine (n=7; N=2)		
Stim. (Hz)	Avg	s.e.m.	Avg	s.e.m.	*P* value
5	7.33	1.61	2.86	1.49	0.0983
10	19.00	5.37	9.29	2.30	0.2451
20	32.00	5.93	20.71	3.52	0.2295
50	65.67	9.41	55.00	3.78	0.4607
100	65.33	10.10	90.71	14.94	0.1730

Evoked EPSP (mV) by PF stimulation from Best1 WT					
	Control (n=13; N=4)		GABAzine (n=8; N=2)		
Stim. (Hz)	Avg	SEM	Avg	SEM	*P* value
5	5.38	1.44	8.57	1.43	0.1709
10	12.69	3.03	17.86	2.86	0.2817
20	26.15	6.48	41.43	5.31	0.1336
50	25.00	6.10	74.29	12.79	0.0009
100	20.38	4.58	114.29	17.06	0.0000
Evoked EPSP (mV) by PF stimulation from Best1 KO					
	Control (n=14; N=4)		GABAzine (n=8; N=2)		
Stim. (Hz)	Avg	s.e.m.	Avg	s.e.m.	*P* value
5	8.93	2.23	3.13	1.32	0.0797
10	17.14	4.02	11.88	2.49	0.3646
20	39.29	7.81	25.00	5.43	0.2162
50	48.93	7.09	55.00	8.07	0.5943
100	57.14	12.84	73.13	10.69	0.4078

Results of the evoked EPSP by mossy fiber and parallel fiber stimulation from Best1 wildtype and KO mice (illustrated in **Fig. 4C, E**, bottom) and GFAP-MAOB (-Dox) and GFAP-MAOB (+Dox) mice (illustrated in **Fig. 4H, J**). *P*-values were derived from two-tailed unpaired t tests (Avg: mean; SEM: standard error of the mean).

Supplementary Table 7

Extracellular concertation by microdialysis (%, after normalization)												
	GABA				Glutamate				Putrescine			
	Avg	SEM	N (mice)	*P* value	Avg	SEM	N	*P*	Avg	SEM	N	*P*
Best1 WT	100	18.78	21	0.0183	100	18.73	21	0.3174	100	17.22	22	0.1713
Best1 KO	17.23	13.59	6		75.32	8.68	11		60.26	13.86	7	
MAOB WT	100	33.85	8	0.0441	100	35.56	8	0.4362	100	5.11	14	0.2500
MAOB KO	27.03	9.04	9		71.21	12.59	8		116.69	12.50	16	
GFAP-MAOB (-Dox)	100	30.71	12	0.3339	100	9.18	12	0.0599	100	13.99	12	0.1512
GFAP-MAOB (+Dox)	180.35	64.79	17		134.55	16.69	17		80.75	4.86	17	

Results of the extracellular concentration of GABA, Glutamate, and Putrescine measured by microdialysis (illustrated in **Fig. 5B to D**). *P*-values were derived from two-tailed unpaired t tests (Avg: mean; SEM: standard error of the mean).

Supplementary Table 8

Latency to fall in rotarod test (%, after normalization)				
	Avg	SEM	N (mice)	*P* value
Best1 WT	100	6.62	23	0.0176
Best1 KO	119.51	5.73	26	
MAOB WT	100	26.27	8	0.0989
MAOB KO	162.82	23.99	11	
Control	100	18.65	9	0.0453
Selegiline	137.54	6.37	10	
GFAP-MAOB (-Dox)	100	6.2	8	0.081
GFAP-MAOB (+Dox)	71.97	7.12	11	

Results of the rotarod test (illustrated in **Fig. 6C to F**). *P*-values were derived from two-tailed unpaired t tests (Avg: mean; SEM: standard error of the mean).

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