

Supplementary Materials and Methods

Novel object recognition test

The ORT was performed in 3 consecutive days, consisting of the habituation phase, the familiarization phase, and the testing phase. First, animals were habituated to an empty open field box with transparent walls (45 x 45 x 30 cm) for 4 min. For 3 consecutive days the ORT was repeated with increasing inter-trial intervals between the familiarization and testing phases (30 min on day 1, 1h on day 2, and 2h on day 3), performed as follows: during the familiarization phase, two identical objects (calcium eggs, tea-light holders, yellow plastic ice cream cones, or bottles filled with sand) (F1 and F2) were placed equidistant from the center of the box. After 4 min of free exploration, the mice returned to their home-cage. Thirty minutes later, mice were placed into the same arena, with one of the familiar objects (F3) and one novel object (N1) that differed in shape and appearance (testing phase). Again, each mouse was allowed to explore the objects for 4 minutes. The position of the novel object (i.e., left or right) was counterbalanced across trials.

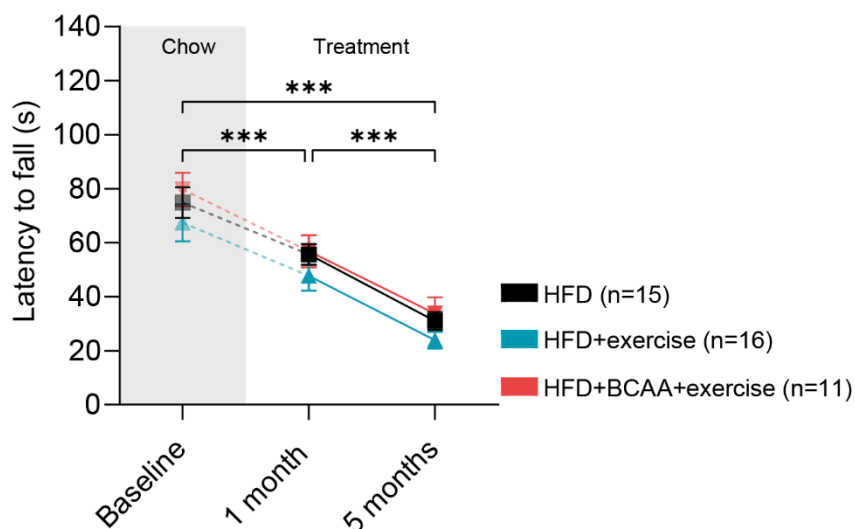
Exploratory behavior of the mice was measured using EthoVision XT 16 (Noldus, Wageningen, the Netherlands) as direct contact with the object, or movement within a 2cm diameter around the object. Several indexes were calculated that describe the relationship between the exploration of the familiar objects and subsequent object recognition of the novel object during the testing phase. First, the recognition index reflects the percentage of time spent exploring the novel object (N1) relative to the total time spent exploring both, the novel (N1) and the familiar object (F3) ($RI = N1/(N1 + F3)$). Second, the discrimination index (DI) reflects the discrimination between the novel object (F3) and the familiar object (N1) ($DI = (N1 - F3)/(N1 + F3)$). The index between +1 and -1 is obtained. A positive result indicates that the animals spent more time around the novel object, while a negative score indicates that the mice spent more time exploring the familiar object, and a score of 0 indicates a null preference. Third, the preference index for any one of the two objects (novel (N1) or familiar (F3)) was calculated as proportion of the total time spent exploring both objects ($PI = 100 \times ([N1 \text{ or } F3]/(N1 + F3))$). When N1 is the numerator, a value closer to 100% indicates a preference for N1, 50% indicates no preference, and less than 50% indicates a preference for F3 (vice versa when F3 is the numerator).

Polarized light imaging

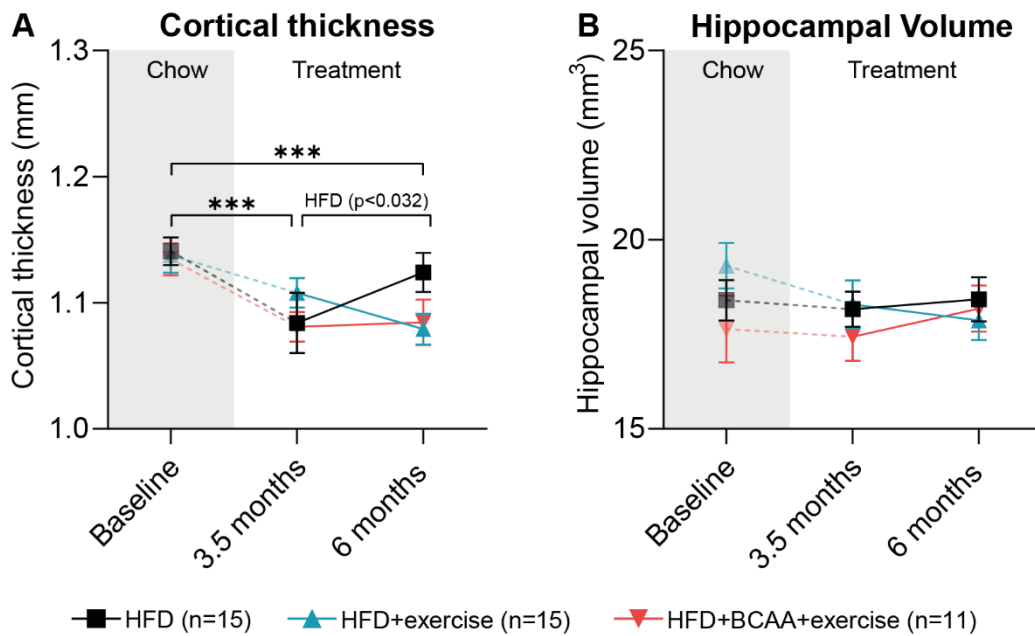
Different PLI maps were derived from the raw images by fitting them to the Jones formula: 1) transmittance, (2) retardance, (3) in-plane, (4) inclination, and (5) FOM-HSV map [1, 2]. The transmittance map resembles the average light intensity across all polarizer orientations and thereby represents the absorption of light by the brain tissue [1, 2]. On the obtained images, the myelin dense white matter appears dark, while grey matter appears brighter. The

retardance map measures the magnitude of the phase shift induces to the light wave because of birefringent tissue. Assuming that most of the birefringence in nervous tissue arises from myelin, PLI is an indirect measure for myelin density[3]. Therefore, a decrease in retardance is indicative for myelin loss. Importantly, the retardance map can also be influenced by tissue thickness, inclination angle (i.e., the out-of-plane angle in the third dimension) of the myelinated fiber, and the local birefringent properties of myelin. Furthermore, crossing fiber (orthogonal) cancel out the birefringence effect, which results in lower retardance values. The in-plane orientation map describes the in-section direction angle of each myelinated fiber (x-y orientation) [2]. The inclination map measures the out-of-section angle because it measures the vertical component of each fiber [2]. Finally, the fiber orientation map (FOM)-HSV map is a color-coded adaptation of the retardance map and the in-plane orientation map. The FOM is color-coded representation of the direction of fibers with its intensity modulated by the myelin density [3].

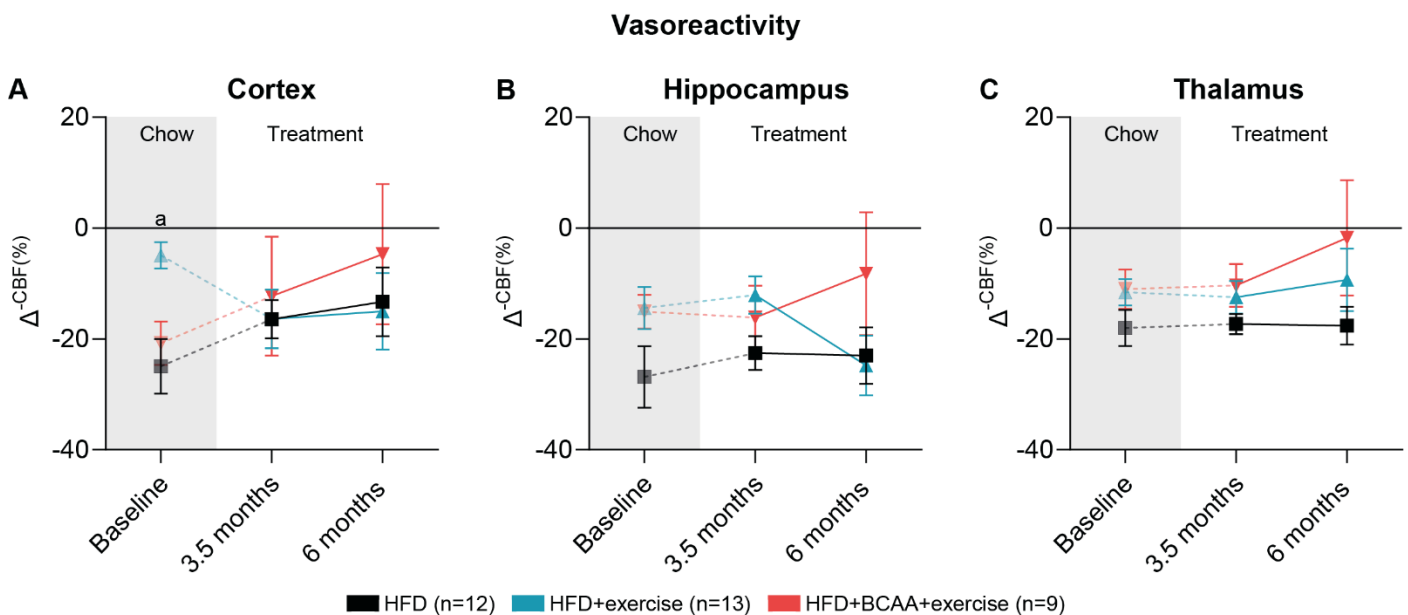
Supplementary Results



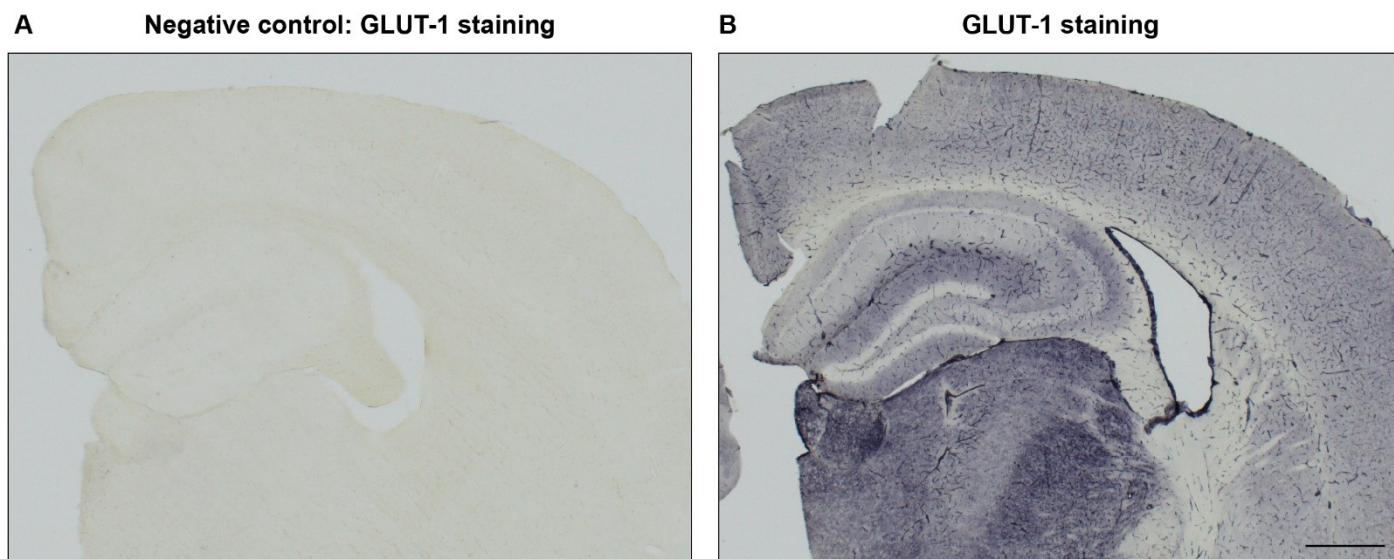
Supplementary Figure S1. Rotarod. The rotarod test was conducted during baseline measurements and again after 1 month and 5 months of treatment to assess the impact of HFD, HFD+exercise, and HFD+BCAA+exercise on motor balance. In all experimental groups, the latency to fall decreased, and after 6 months of treatment, the latency to fall was even lower than during baseline measurements. However, no significant treatment effects were observed. High-fat diet (HFD), branched-chain amino acids (BCAA). Data are presented as mean \pm SEM. *** $p < 0.001$.



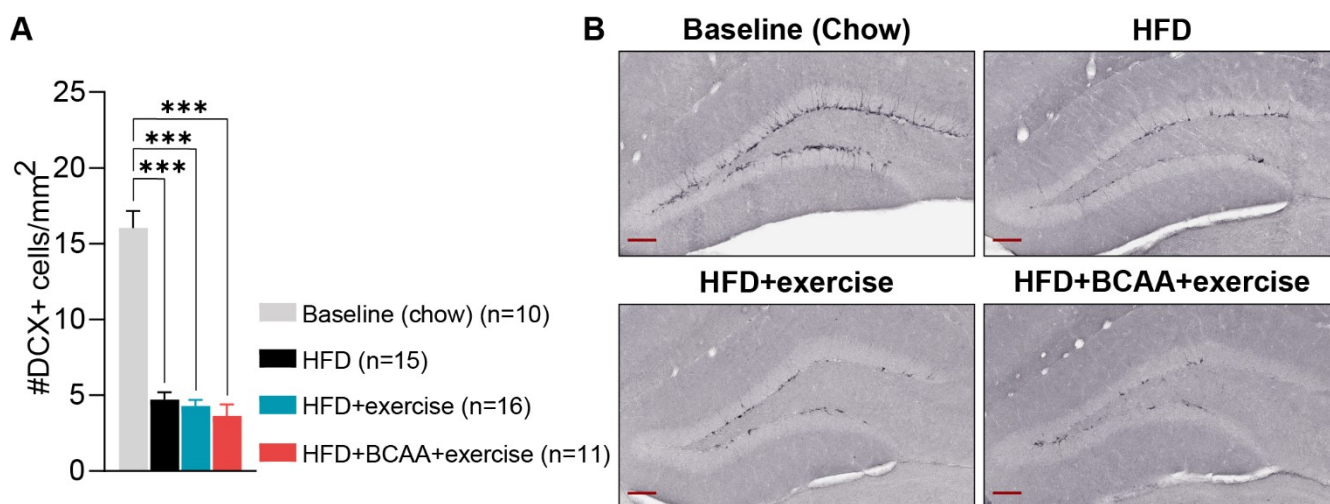
Supplementary Figure S2. Cortical thickness and hippocampal volume. (A) Cortical thickness and (B) hippocampal volume at baseline (chow) and after 3.5 and 6 months of treatment with HFD, HFD+exercise and HFD+BCAA+exercise. A decrease in cortical thickness was observed in all mice between baseline and 3.5 months of treatment and between baseline and 6 months of treatment. Only HFD-fed mice showed an increase in cortical thickness between 3.5 and 6 months of treatment. No changes in hippocampal volumetry were detected. High-fat diet (HFD), branched-chain amino acids (BCAA). Data are presented as mean \pm SEM. *** $p < 0.001$.



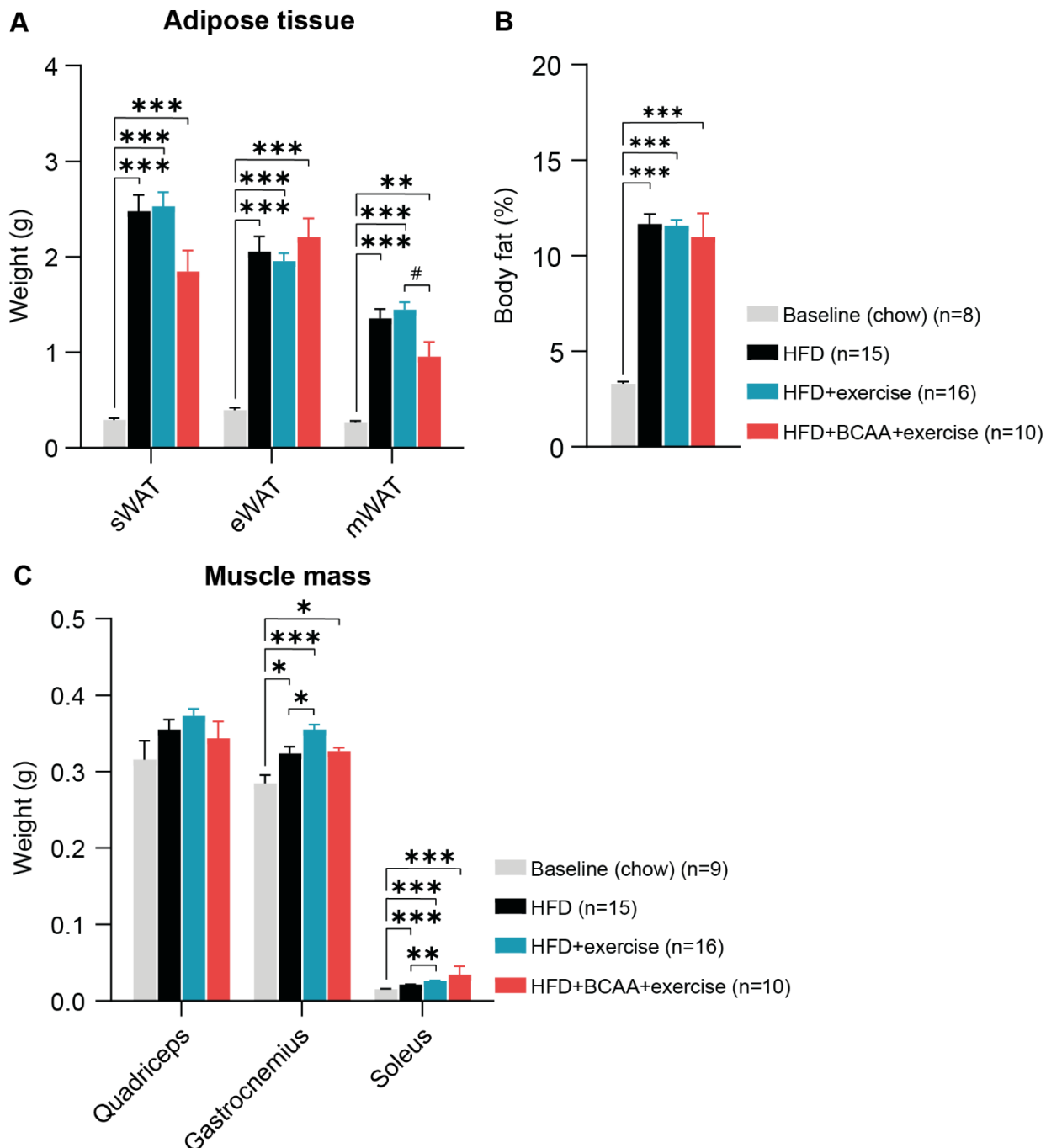
Supplementary Figure S3. Cerebrovascular reactivity. Cerebral blood flow (CBF) was measured by arterial spin labeling during baseline (chow) and after 3.5 and 6 months of treatment with HFD, HFD+exercise and HFD+BCAA+exercise. Vasodilative and vasoconstrictive CBF levels were used to calculate cerebral vasoreactivity in the cortex (A), hippocampus (B) and thalamus (C). High-fat diet (HFD), branched-chain amino acids (BCAA), cerebral blood flow (CBF). Data are presented as mean \pm SEM. a: significant difference HFD vs. HFD+exercise group.



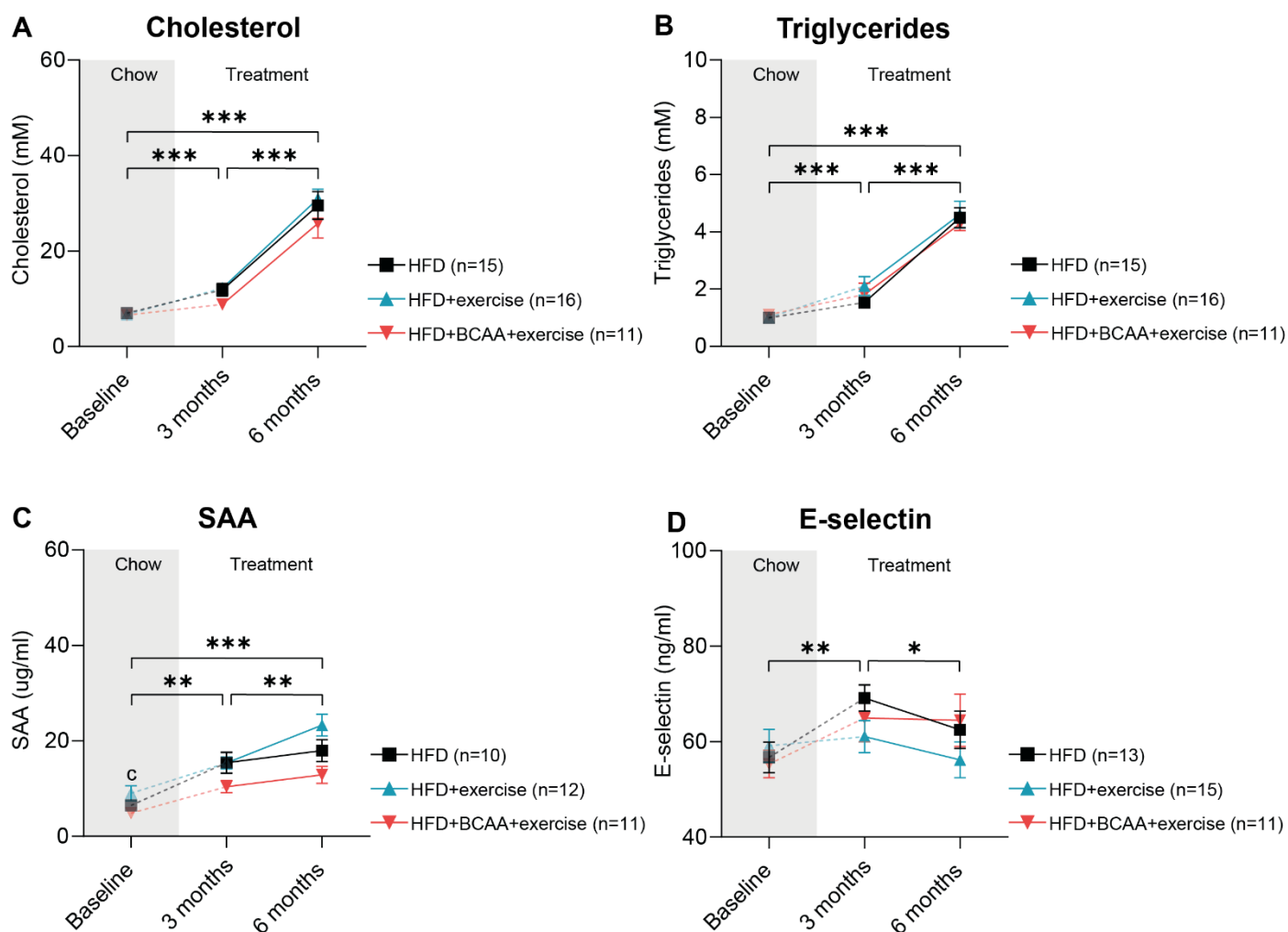
Supplementary Figure S4. (A) A high-resolution image of the negative control for GLUT-1 immunohistochemical staining and (B) a representative image of the brain section stained for GLUT-1 (2.5× magnification). Scale bar: 1 mm.



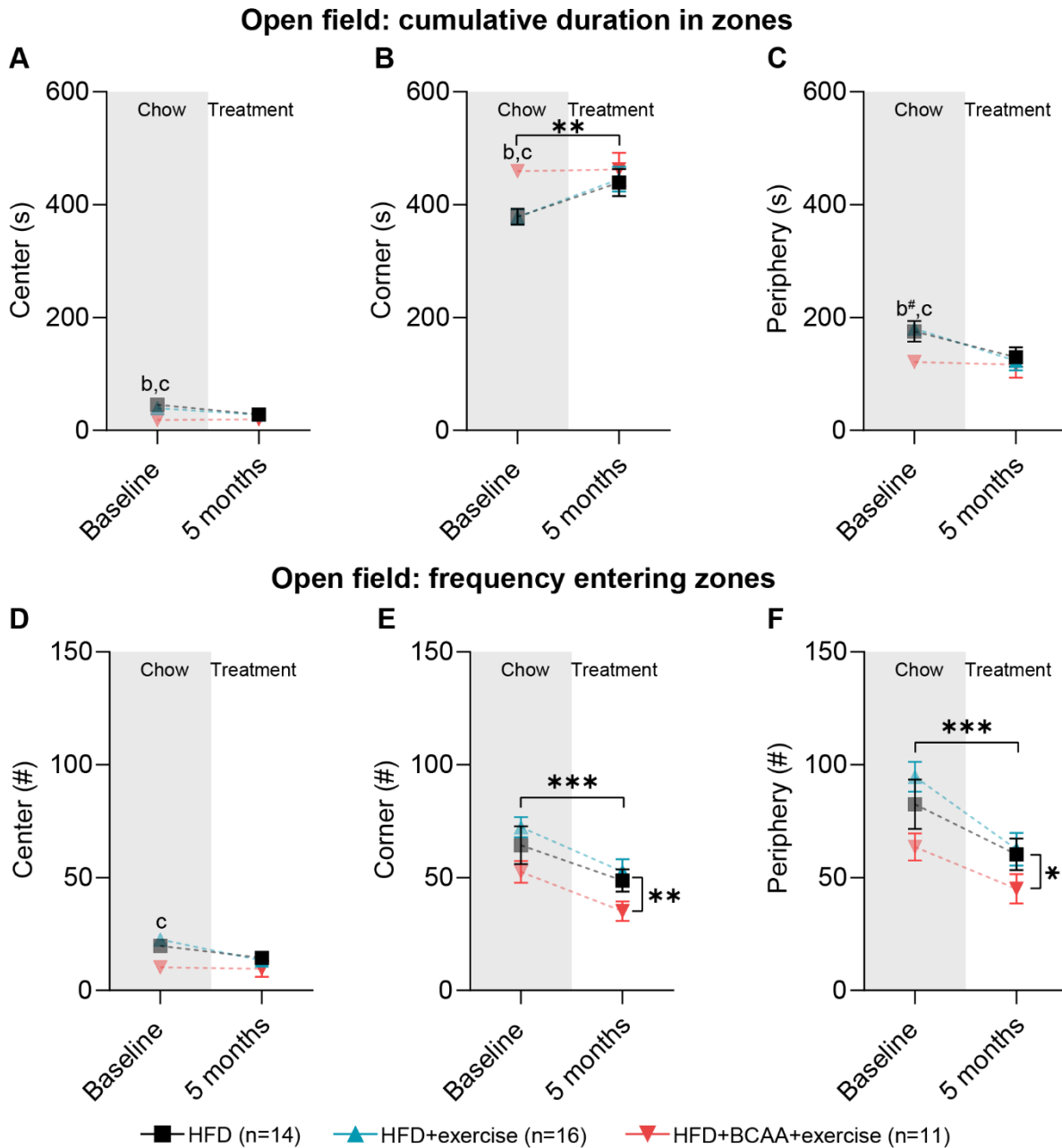
Supplementary Figure S5. Neurogenesis. (A) Immunohistochemical staining for newly formed neurons by staining doublecortin (DCX) in the dentate gyrus of the hippocampus of young chow-fed animals (baseline), HFD, HFD+exercise, and HFD+BCAA+exercise mice. Neurogenesis was higher in young chow-fed mice at baseline measurements compared to the other treatment groups after 6 months of treatment. No other treatment differences were observed. (B) Representative images of the DCX staining in the dentate gyrus (scale bar = 100 μ m). High-fat diet (HFD), branched-chain amino acids (BCAA). Data are presented as mean \pm SEM. *** $p < 0.001$.



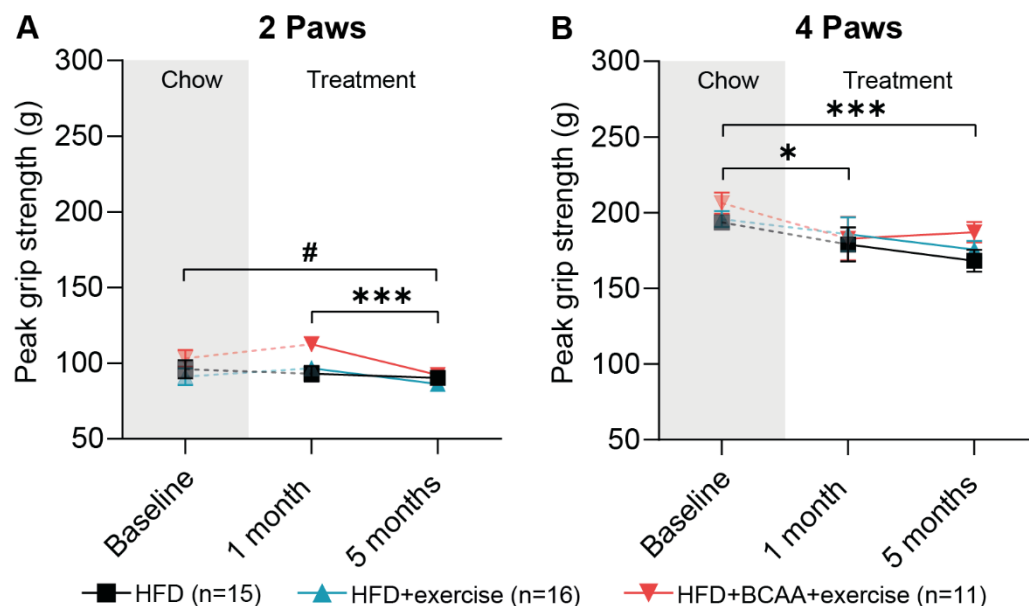
Supplementary Figure S6. White adipose tissue, body fat and muscle mass. (A) Weights of white adipose tissue depots (subcutaneous adipose tissue (sWAT), epididymal white adipose tissue (eWAT), mesenteric white adipose tissue (mWAT)) and (B) weights of the hind leg muscles (quadriceps, gastrocnemius, soleus) measured in young chow-fed mice and mice treated with HFD, HFD+exercise, or HFD+BCAA+exercise for 6 months. All HFD-fed mice developed adiposity in the different fat depots. In HFD+BCAA+exercise mice mWAT mass tended to be less heavy than in the HFD+exercise group. In all mice, the gastrocnemius and soleus muscle mass was heavier after 6 months of treatment in comparison to young chow animals (Figure 2D). Notably, after 6 months of HFD feeding, exercising mice had a heavier gastrocnemius and soleus than non-exercising animals, whereas the combination of exercise with BCAA had no effect on muscle mass. (C) Body fat percentage increased in all HFD-fed mice compared to young chow-fed mice. High-fat diet (HFD), branched-chain amino acids (BCAA). Data are present as mean \pm SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, # $0.05 < p < 0.08$ (trend); b: significant difference HFD vs. HFD+BCAA+exercise group; c: significant difference HFD+exercise vs. HFD+BCAA+exercise group.



Supplementary Figure S7. Metabolic markers. (A) Cholesterol, (B) triglycerides, (C) serum amyloid (SAA), and (D) E-selectin were measured in the blood plasma of HFD, HFD+exercise, and HFD+BCAA+exercise treated animals at baseline (chow), and after 3 months and 6 months of treatment. Plasma levels of cholesterol, triglycerides, and serum amyloid A (SAA) increased steadily throughout the treatment period. After an initial increase in E-selectin after 2 months of treatment, plasma E-selectin levels decreased again, resulting in plasma levels comparable to the baseline measurements after 6 months of treatment. No significant treatment effect was measured for any of the markers. High-fat diet (HFD), branched-chain amino acids (BCAA). Data are presented as mean \pm SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

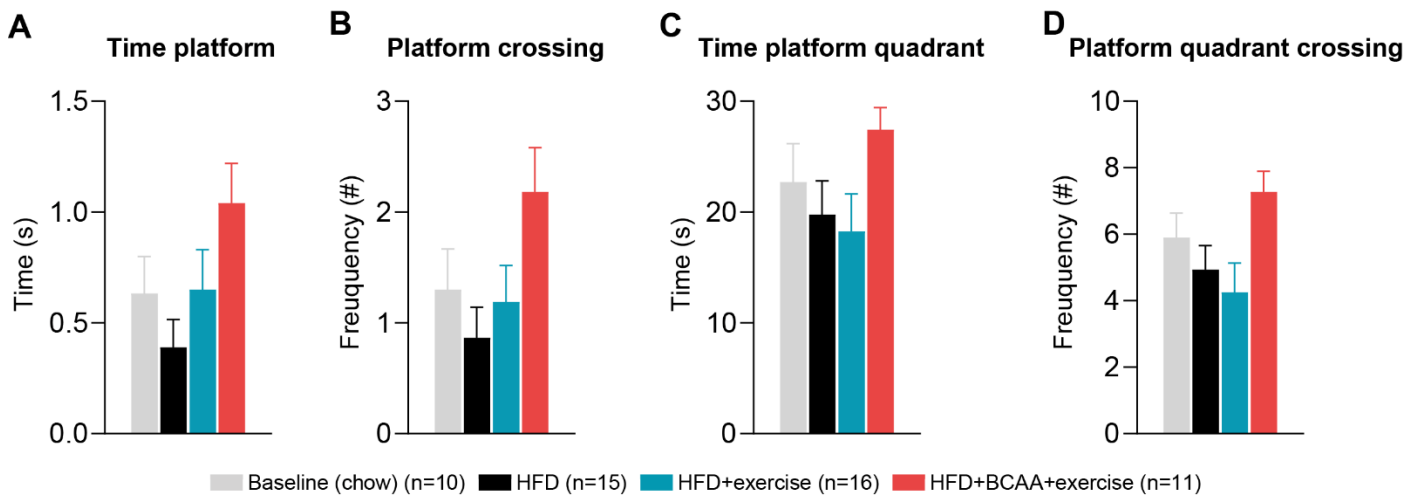


Supplementary Figure S8. Open field test. Spontaneous behavior and exploratory locomotion were measured at baseline measurements and again after 5 months of treatment with HFD, HFD+exercise, or HFD+BCAA+exercise. The cumulative time spent in the (A) center (B) corner (C) periphery and the frequency of entering the (D) center (E) corner (F) periphery of the open field arena were analyzed. After 5 months of treatment, all mice spent more time in the corners of the open field, and the frequency of mice entering the corners and periphery of the arena decreased. Notably, the frequency of entering the corners and periphery of the open field was significantly lower in the HFD+BCAA+exercise mice compared to the HFD+exercise mice. High-fat diet (HFD), branched-chain amino acids (BCAA). Data are presented as mean \pm SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, # $0.05 < p < 0.08$ (trend); b: significant difference HFD vs. HFD+BCAA+exercise group, c: significant difference HFD+exercise vs. HFD+BCAA+exercise group.

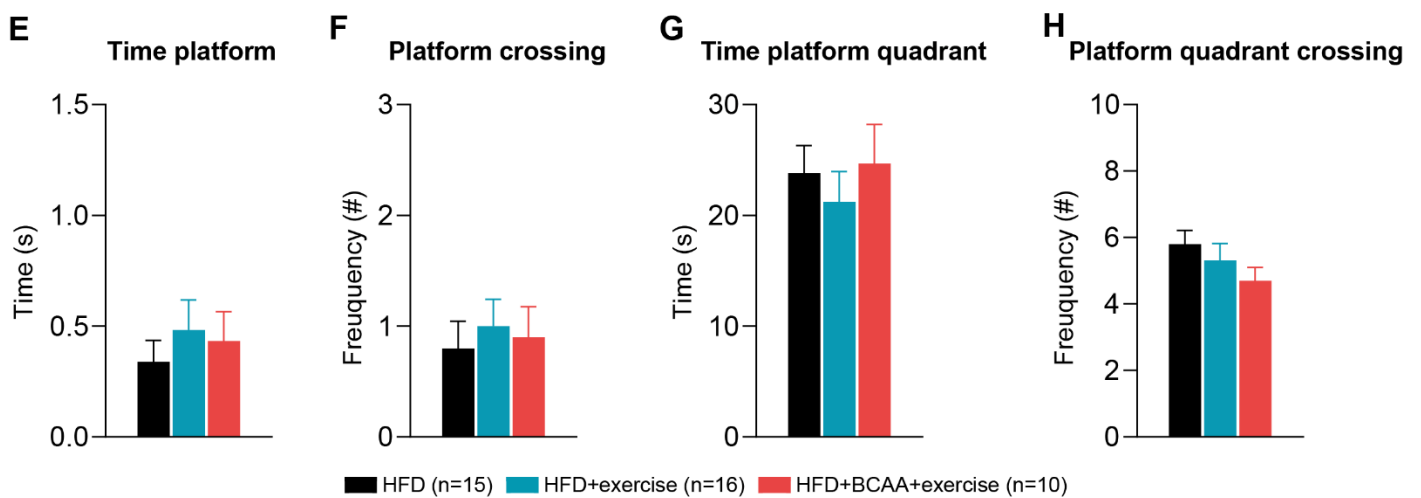


Supplementary Figure S9. Grip strength test. Total peak strength of (A) forelimbs (2 paws) and (B) fore- and hindlimbs together (4 paws) was measured at baseline (chow) and after 1 and 5 months of treatment with exercise (HFD+exercise) and exercise in combination with BCAA supplementation (HFD+BCAA+exercise). Forelimb peak force decreased between treatment months 1 and 5 in all groups. After 5 months of treatment, peak force was lower in all animals compared to baseline measurements. Peak grip strength of fore- and hindlimbs combined (4 paws) of all experimental groups started to decrease already after 1 month of treatment and was significantly lower after 5 months of treatment compared to baseline measurements. High-fat diet (HFD), branched-chain amino acids (BCAA). Data are presented as mean \pm SEM. * $p < 0.01$, *** $p < 0.001$, # $0.05 < p < 0.08$ (trend).

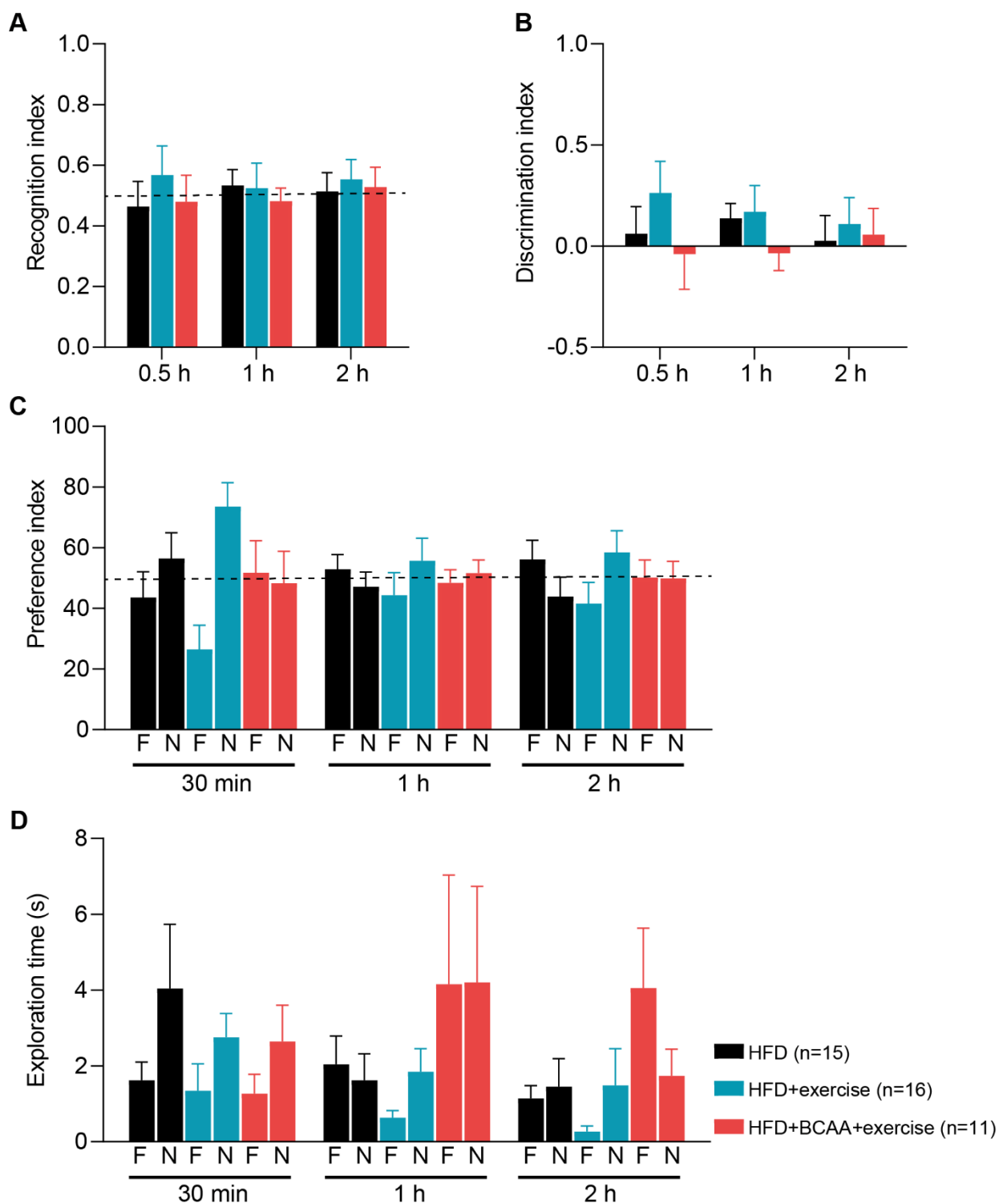
Baseline MWM: Probe (baseline young chow)



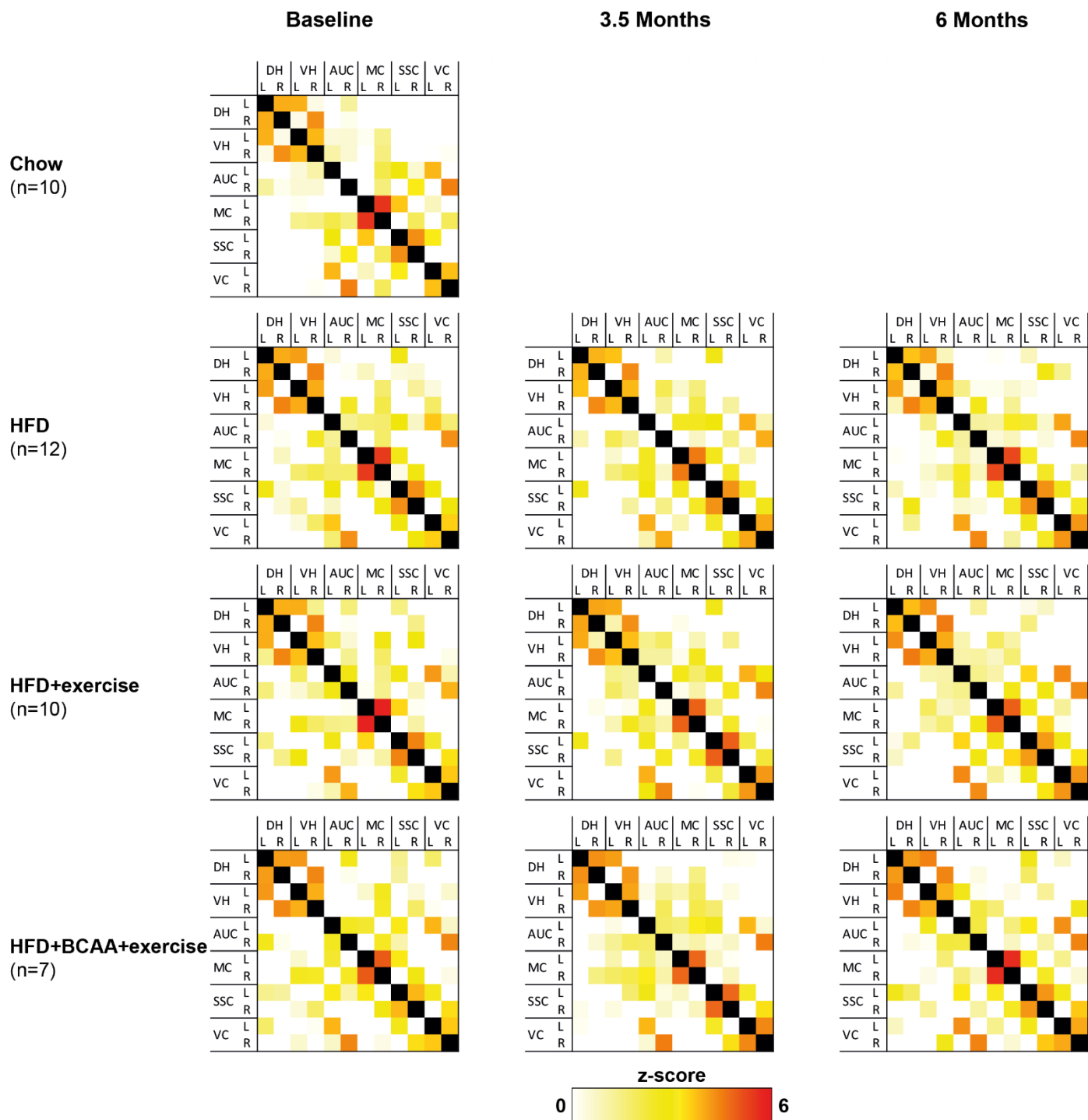
reverseMWM: Probe - former platform location (5 Months treatment)



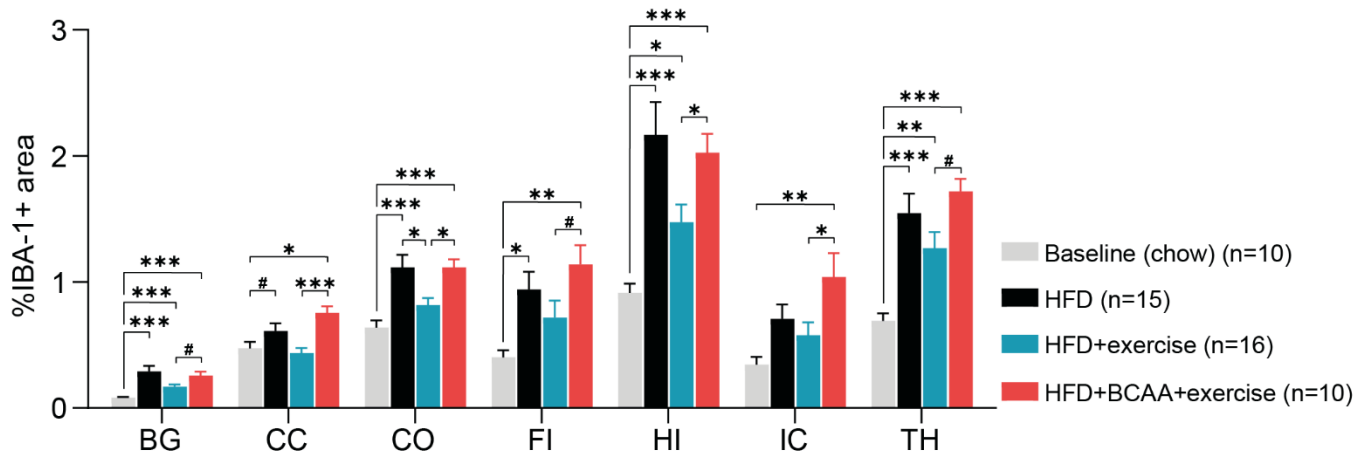
Supplementary Figure S10. (Reverse) Morris water maze. In a baseline Morris water maze (MWM) probe trial, the time animals spent in (A) the former platform location and (C) platform quadrant, as well as the frequency with which mice crossed (C) the former platform location and (D) the platform quadrant was assessed (platform location: north-east). After 5 months of treatment, the probe trial was repeated (reverse Morris water maze) and long-term spatial memory of the former platform location (north-east) was analyzed by again measuring the time the animals spent in (E) the former platform location and (G) the platform quadrant as well as the frequency the mice crossed (F) the former platform location and (H) the platform quadrant. No treatment differences were found. Data are presented as mean \pm SEM. High-fat diet (HFD), branched-chain amino acids (BCAA).



Supplementary Figure S11. Novel object recognition test. After 3 months of treatment, the novel object recognition test was performed and the (A) recognition index, (B) discrimination index, and (C) preference index and (D) exploration time around the familiar object (F) and the novel object (N) during the testing phase measured in the HFD, HFD+exercise, and HFD+BCAA+exercise group were calculated. No treatment effects were detected. Data are presented as mean \pm SEM. High-fat diet (HFD), branched-chain amino acids (BCAA).



Supplementary Figure S12. Resting-state functional connectivity based on partial correlations. Functional connectivity between brain regions was measured by resting-state fMRI at baseline (chow) and after 3.5 and 6 months of treatment with HFD, HFD+exercise and HFD+BCAA+exercise. Partial correlation matrixes show the connectivity between the dorsal hippocampus (DH), ventral hippocampus (VH), auditory cortex (AC), motor cortex (MC), somatosensory cortex (SSC), and visual cortex (VC) for the left (L) and right (R) hemispheres, respectively at each neuroimaging time point. All significant results are summarized in the main article and summarized in Supplementary Table 12. High-fat diet (HFD), branched-chain amino acids (BCAA).



Supplementary Figure S13. Neuroinflammation. Immunohistochemical analysis of ionized calcium-binding adapter molecule (IBA-1) as measure of neuroinflammation in several brain regions of interest (basal ganglia (BG), corpus callosum (CC), cortex (C), fimbria (FI), hippocampus (HI), internal capsule (IC), thalamus (TH)). The IBA-1+ area was analyzed in young chow-fed animals (baseline), HFD, HFD+exercise, and HFD+BCAA+exercise groups. All HFD-fed groups showed a larger IBA-1+ area in the basal ganglia, hippocampus, and thalamus compared to young chow-fed mice. In addition, HFD and HFD+BCAA+exercise animals showed a larger IBA-1+ area in the corpus callosum, cortex, and fimbria compared to young chow-fed mice. In the internal capsule, HFD+BCAA+exercise animals had a larger IBA-1+ area than young chow-fed mice. Notably, exercise alone could counteract an HFD-induced enlargement of IBA-1+ area in the cortex. In contrast, HFD-BCAA+exercise mice showed significantly larger relative IBA-1+ area than exercising mice that did not receive BCAA supplementation in several ROI, including basal ganglia, corpus callosum, cortex, fimbria, hippocampus, internal capsule, and thalamus. High-fat diet (HFD), branched-chain amino acids (BCAA). Data are presented as mean \pm SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, # 0.05.

Supplementary Table S1. Ingredients and composition of special diets. High-fat diet (HFD, D12451 Research Diets, New Brunswick) and branched-chain amino acid enriched high-fat diet (HFD+BCAA, Research Diets, New Brunswick, USA). Percentages of macronutrients in the food are based on mass (gm %) and kilocalories (kcal %).

	HFD		HFD+BCAA	
	gm %	kcal %	gm %	kcal %
Protein	21	18	21	18
Carbohydrates	41	36	42	36
Fat	24	46	24	46
Total		100		100
kcal/g	4.6		4.7	
Ingredients	gm	kcal	gm	kcal
Casein	200	704	137.832	485
L-Alanine	0	0	0.139	1
L-Arginine	0	0	1.811	7
L-Asparagine	0	0	0.195	1
L-Aspartic Acid	0	0	0.139	1
L-Cysteine	3	12	3.333	13
L-Glutamine	0	0	0.473	2
L-Glutamic Acid	0	0	0.579	2
Glycine	0	0	0.083	0
L-Histidine	0	0	1.389	6
L-Isoleucine	0	0	8.613	34
L-Leucine	0	0	17.475	70
L-Lysine	0	0	3.928	16
DL-Methionine	0	0	1.513	6
L-Phenylalanine	0	0	2.539	10
L-Proline	0	0	0.486	2
L-Serine	0	0	0.278	1
L-Threonine	0	0	2.175	9
L-Tryptophan	0	0	0.603	2
L-Tyrosine	0	0	2.721	11
L-Valine	0	0	9.159	37
Corn starch	72.8	291	72.8	291
Maltodextrin-10	100	400	100	400
Sucrose	172.8	691	172.8	691
Cellulose	50	0	50	0
Soybean oil	25	225	25	225
Lard	177.5	1598	177.5	1598
Mineral mix S10026	10	0	10	0
Di-calcium phosphate	13	0	13	0
Calcium carbonate	5.5	0	5.5	0
Potassium citrate	16.5	0	16.5	0
Vitamin Mix V10001	10	40	10	40
Choline bitartrate	2	0	2	0

	gm/kg	%	gm/kg	%
Alanine	5.83	0.583	4.21	0.421
Arginine	6.99	0.699	6.99	0.699
Asparagine	8.16	0.816	5.9	0.59
Aspartic Acid	5.83	0.583	4.21	0.42
Cysteine	4.89	0.489	7.89	0.489
Glutamine	19.81	1.981	14.33	1.433
Glutamic Acid	24.24	2.424	17.53	1.753
Glycine	3.5	0.35	2.53	0.253
Histidine	5.36	0.536	5.36	0.536
Isoleucine	8.62	0.862	16.12	1.612
Leucine	18.18	1.818	33.18	3.318
Lysine	15.15	1.515	15.15	1.515
Methionine	5.83	0.583	5.83	0.583
Phenylalanine	9.79	0.979	9.79	0.979
Proline	20.51	2.051	14.83	1.483
Serine	11.65	1.165	8.43	0.843
Threonine	8.39	0.839	8.39	0.839
Tryptophan	2.33	0.233	2.33	0.233
Tyrosine	10.49	1.049	10.49	1.049
Valine	10.72	1.072	18.22	1.822

Supplementary Table S2. Imaging parameters.

	Anatomical T2*w	ASL	DTI	rsfMRI	T2w
Imaging method	GE	FAIR-ASL	4-shot spin-echo PI	Spin-echo EPI	T2 TurboRARE
Echo time (ms)	7.35	10.08	21	10	30
Repetition time (s)	0.86	12	7.75	1.8	2.5
Image matrix (pixel x pixel)	512 × 512	128 × 96	128 × 128	96 × 96	256 x 256
Field-of-view (mm)	40 × 40	25 × 25	20 × 20	25 × 25	20 x 20
Spatial resolution (μm/pixel)	78 × 78 × 500	195 × 260 × 1000	156 × 156 × 500	260 × 260 × 500	78 × 78 × 500
Number of slices	20 × 3	16	20	20	20
Total acquisition time (min)	8	13	35	11	4

Supplementary Table S3. Average area \pm SEM of the regions of interest that were manually selected using the freehand tool in ImageJ group on the brain sections used for immunohistochemistry (IHC) and polarized light imaging (PLI). High-fat diet (HFD), branched-chain amino acids (BCAA).

Parameter	Bregma	ROI	Baseline chow		HFD		HFD+exercise		HFD+BCAA+exercise	
			Area (μm)	\pm SEM	Area (μm)	\pm SEM	Area (μm)	\pm SEM	Area (μm)	\pm SEM
IHC	0.5	Anterior commissure	151.87	35.04	233.98	57.32	144.74	39.88	487.54	154.17
		Basal ganglia	19746.19	4509.61	23384.39	4008.46	15816.18	3249.01	47150.49	14910.29
		Corpus callosum	647.61	99.39	574.43	75.39	491.09	58.00	672.81	212.76
		Cortex	27362.59	4289.74	28307.79	4379.68	20074.72	2242.99	44846.42	14181.68
		External capsule	693.08	177.67	581.32	108.12	387.85	87.10	821.95	259.92
	1.94	Corpus callosum	410.55	67.38	407.42	98.04	305.90	21.76	680.92	215.33
		Cortex	16793.07	2805.41	21043.36	2953.49	16253.70	2017.73	29194.26	9232.03
		External capsule	1159.82	189.62	887.26	120.53	884.44	122.26	1571.61	496.99
		Fimbria	1131.08	159.14	1436.19	131.39	1027.91	101.40	1392.53	440.36
		Hippocampus	62898.62	9829.14	73807.80	6070.54	65916.90	6299.24	90313.62	28559.68
		Internal capsule	1177.93	357.41	1283.61	176.59	969.14	257.27	1357.34	452.45
		Optic tract	396.84	74.25	518.29	51.97	452.02	80.84	443.98	140.40
		Thalamus	44237.45	5215.97	55673.12	14803.91	35466.59	4358.35	64849.18	20507.11
PLI	0.5	Anterior commissure	940.60	110.59	1011.78	78.16	1127.43	100.53	5729.58	1727.53
		Basal ganglia	22846.16	1578.46	22472.87	1242.40	22125.10	976.55	22795.57	6873.12
		Corpus callosum	1952.07	158.71	2345.47	200.41	1806.60	206.68	2155.41	649.88
		External capsule	847.85	69.89	935.18	50.81	1012.53	75.15	1052.22	317.26
		Motor cortex	5584.07	284.41	4897.53	307.22	4458.86	256.00	4273.50	1288.51
		Somatosensory cortex	17355.41	932.30	13563.87	830.41	14320.85	812.12	18200.21	5487.57
	0.14	Anterior commissure	4345.10	385.47	5549.01	406.47	4852.21	309.23	1052.29	317.28
		Basal ganglia	22940.74	866.56	23356.89	712.01	21447.89	1488.44	22290.14	6720.73
		Corpus callosum	1750.25	120.18	2005.34	114.83	1764.82	120.93	2607.18	786.09
		External capsule	1028.12	62.91	1069.82	50.08	1092.92	45.60	965.20	291.02
		Motor cortex	4650.52	353.45	4269.29	316.74	4287.57	420.08	4747.88	1431.54
		Somatosensory cortex	16425.19	999.11	17240.44	817.15	17375.15	556.73	16725.36	5042.88
		Fornix	2298.39	131.07	2148.33	157.18	1886.26	201.23	2686.88	849.67
		Corpus callosum	1706.53	187.14	2134.20	288.41	2622.86	226.99	2451.05	739.02
	1.94	Cortex	20523.80	1091.83	19825.40	786.39	19240.64	817.54	19225.38	5796.67
		External capsule	1857.21	218.35	2243.75	190.01	2651.50	130.04	2662.98	842.11

		Fimbria	1626.03	130.99	1561.07	129.97	1869.74	162.30	1443.35	435.19
		Hippocampus	1095.95	344.31	962.77	109.65	947.47	96.77	954.34	287.74
		Internal capsule	23785.64	1628.24	24136.57	1094.65	26013.48	1004.44	25360.74	7646.55
		Optic tract	924.55	138.22	1021.83	130.12	1197.82	111.23	1135.71	342.43

Supplementary Table S4. Sample size (number of mice or cages) per experiment. In total 4 animals of the HFD+BCAA+exercise group were excluded from analysis because they did not use the running wheel throughout the experiment. Furthermore, 2 mice died before the end of the experiment. The final group sample size was baseline(chow) n=10, HFD n=15, HFD+exercise n=16, HFD+BCAA+exercise n=11. Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA), digital ventilated cages (DVC), reverse Morris Water Maze ((r)MWM), functional magnetic resonance imaging (fMRI), glucose transporter 1 (GLUT-1), ionized calcium-binding adapter molecule (IBA-1), doublecortin (DCX).

Parameter	Baseline (chow)	HFD	HFD+exercise	HFD+BCAA+exercise
Body weight	10	15	16	10
Caloric intake (cage level)	5	8	8	6
Muscle weight	9	15	16	10
Fat depots and percentage	8	15	16	10
Glucose	10	15	16	11
Insulin	10	14	15	11
Cholesterol	10	15	16	11
Triglycerides	10	15	16	11
Serum amyloid A	10	10	12	11
E-selectin	10	13	15	11
Systolic blood pressure	10	15	16	11
DVC activity (cage level)	6	8	8	6
DVC running wheel distance (cage level)			6	4
Open field	10	14	16	11
Grip test	10	15	16	11
Rotarod	10	15	16	11
MWM - Acquisition	10	15	16	11
MWM - Probe	10	15	16	11
rMWM - Acquisition		15	16	11
rMWM - Probe (old platform location)		15	16	10
rMWM - Probe (new platform location)		14	16	11
Object recognition test		15	16	11
resting-state fMRI	10	12	10	7
Cerebral blood flow	10	12	13	9
Diffusion tensor imaging	9	12	14	9
Polarized light imaging	9-10	14-15	14-16	10-11
Cortical thickness	10	15	15	11
Hippocampal volume	10	15	15	11
GLUT-1 staining	9-10	15	16	9-10
IBA-1 staining	10	15	16	10
DCX staining	10	15	16	11

Supplementary Table S5. Excluded mice per experiment and reason for exclusion. Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA), digital ventilated cages (DVC), (reverse) Morris water maze ((r)MWM), functional magnetic resonance imaging (fMRI), glucose transporter 1 (GLUT-1), ionized calcium-binding adapter molecule (IBA-1), doublecortin (DCX), # = number of mice.

Parameter	Baseline (chow)	HFD	HFD+exercise	HFD+BCAA+exercise	Reason for exclusion
Body weight	0	0	0	1	statistical outlier (single-housed) (#1)
Caloric intake (cage level)	0	0	0	0	
Muscle weight	0	0	0	1	statistical outlier (#1)
Fat depots and percentage	2	0	0	1	missing measurements (#3)
Glucose	0	0	0	0	
Insulin	0	1	1	0	statistical outlier (#1) missing measurements (#1)
Cholesterol	0	0	0	0	
Triglycerides	0	0	0	0	
Serum amyloid A	0	5	4	0	statistical outlier (#8) missing measurement (#1)
E-selectin	0	2	1	0	statistical outlier (#2) missing measurement (#1)
Systolic blood pressure	0	0	0	0	
DVC activity (cage level)	0	0	0	0	
DVC distance (cage level)			2	3	missing data due to technical problems (#4) single house moused excluded (#1)
Open field	0	1	0	0	mouse was inactive (#1)
Grip test	0	0	0	0	
Rotarod	0	0	0	0	
MWM - Acquisition	0	0	0	0	
MWM - Probe	0	0	0	0	
rMWM - Acquisition		0	0	0	
rMWM - Probe (old platform location)		0	0	1	mouse was only floating in the water (#1)
rMWM - Probe (new platform location)		1	0	0	no video available due to technical problems (#1)
Object recognition index		0	0	0	
Cerebral blood flow	0	3	3	2	low body temperature (#8)
resting-state fMRI		3	6	4	very low CBF may influence functional connectivity (#8) statistical outlier (#5)

Diffusion tensor imaging	1	3	2	2	bad realignment (#2) movement resp. EPI related artifact (#5) statistical outlier (#1)
Polarized light imaging	1	1	2	1	one or more regions of interest were not available (#5)
Cortical thickness	0	1	0	0	scan artifact (#1)
Hippocampal volume	0	1	0	0	scan artifact (#1)
GLUT-1 staining	1	0	0	2	one or more regions of interest were not available (#2) technical issues (#1)
IBA-1 staining	0	0	0	1	one or more regions of interest were not available (#1)
DCX staining	0	0	0	0	

Supplementary Table S6. Summary statistics of body weight, caloric intake, muscle weight, and fat tissue analysis. Abbreviations: subcutaneous adipose tissue (sWAT), epididymal white adipose tissue (eWAT), mesenteric white adipose tissue (mWAT), high-fat diet (HFD), branched-chain amino acids (BCAA).

Parameters		Overall	HFD > Baseline (chow)		HFD+exercise > Baseline (chow)		HFD+BCAA+exercise > Baseline (chow)		HFD+exercise > HFD	HFD+BCAA+exercise < HFD	HFD+BCAA+exercise < HFD+exercise
			p-value	relative change (%)	p-value	relative change (%)	p-value	relative change (%)	p-value	p-value	p-value
Body weight	Baseline	F(3,47)=2.406, p<0.079									
	Month 1	F(2,38)=6.833, p<0.003								p<0.002	p<0.079
	Month 2	F(2,38)=3.889, p<0.029								p<0.029	p<0.075
	Month 3	F(2,38)=8.050, p<0.001								p<0.003	p<0.001
	Month 4	F(2,38)=6.375, p<0.004								p<0.013	p<0.005
	Month 5	F(2,38)=6.868, p<0.003								p<0.014	p<0.003
	Month 6	F(2,38)=10.373, p<0.001								p<0.002	p<0.001
Caloric intake	Baseline	F(3,23)=1.122, p<0.361									
Muscle weight	Gastrocnemius	F(3,46)=12.015, p<0.001	p<0.011	113.7	p<0.001	124.7	p<0.010	114.9	p<0.018		
	Soleus	F(3,46)=19.813, p<0.001	p<0.001	139.1	p<0.001	168.8	p<0.001	153.9	p<0.007		
	Quadriceps	F(3,46)=2.086, p<0.115									
Fat	sWAT weight	F(3,45)=30.228, p<0.001	p<0.001	846.1	p<0.001	863.7	p<0.001	630.7			
	eWAT weight	F(3,45)=26.538, p<0.001	p<0.001	518.7	p<0.001	494.3	p<0.001	557.0			
	mWAT weight	F(3,45)=23.845, p<0.001	p<0.001	504.0	p<0.001	538.2	p<0.007	355.9			p<0.062
	Fat percentage	F(3,45)=44.878, p<0.001	p<0.001	353.0	p<0.001	347.1	p<0.001	346.7			
		Overall	HFD < Baseline (chow)		HFD+exercise < Baseline (chow)		HFD+BCAA+exercise < Baseline (chow)		HFD+exercise > HFD	HFD+BCAA+exercise > HFD	HFD+BCAA+exercise > HFD+exercise
Muscle (% total BW)	Gastrocnemius	F(3,46)=27.978, p<0.001	p<0.001	67.3	p<0.001	71.7	p<0.001	113.0		p<0.003	p<0.062
	Soleus	F(3,46)=5.071, p<0.004	p<0.002	82.5					p<0.078	p<0.054	
	Quadriceps	F(3,46)=10.985, p<0.001	p<0.007	66.8	p<0.009	67.9					
		Overall	HFD > Baseline (chow)		HFD+exercise > Baseline (chow)		HFD+BCAA+exercise > Baseline (chow)		HFD+exercise > HFD	HFD+BCAA+exercise < HFD	HFD+BCAA+exercise > HFD+exercise
Fat (% total BW)	sWAT	F(3,45)=36.672, p<0.001	p<0.001	482.2	p<0.001	483.9	p<0.001	86.5			
	eWAT	F(3,45)=20.996, p<0.001	p<0.001	305.4	p<0.001	280.7	p<0.001	133.1			p<0.02
	mWAT	F(3,45)=21.214, p<0.001	p<0.001	286.9	p<0.001	300.2	p<0.008	77.7			

Parameter	Effects	Baseline → 1 months		1 months → 6 months	Baseline → 6 months	
		p-value	relative change (%)	p-value	p-value	relative change (%)
Body weight	Time effect all groups	↑F(1,38)=158.324, p<0.001	122.3	↑F(5,190)=270.208, p<0.001	↑F(1,38)=745.986, p<0.001	177.0
	HFD+BCAA+exercise < HFD	p<0.003		p<0.004	p<0.004	
	HFD+BCAA+exercise < HFD-exercise			p<0.002	p<0.002	
Caloric intake	Time effect all groups	↑F(1,19)=45.637, p<0.001	116.0	↓F(5,95)=13.358, p<0.001	↑F(1,19)=8.637, p<0.008	106.3

Supplementary Table S7. Summary statistics of fasting blood and plasma markers and systolic blood pressure analysis. Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA).

Parameters			Overall	HFD > Baseline (chow)	HFD+RW > Baseline (chow)	HFD+BCAA+RW > Baseline (chow)	HFD+RW > HFD	HFD+BCAA+RW < HFD	HFD+BCAA+RW < HFD+RW
Fasting blood	Glucose	Baseline	F(3,48)=0.681; p<0.568						
Fasting Plasma	Insulin	Baseline	F(3,46)=0.963; p<0.418						
		3 Months	F(2,37)=3.609; p<0.037						p<0.031
		6 Months	F(2,37)=6.134; p<0.005					p<0.047	p<0.004
	Cholesterol	Baseline	F(3,48)=0.306; p<0.821						
	Triglycerides	Baseline	F(3,48)=0.081; p<0.970						
	Serum amyloid A	Baseline	F(3,39)=3.909; p<0.016			p<0.034			p<0.042
	E-selectin	Baseline	F(3,45)=0.283; p<0.837						
Systolic blood pressure		Baseline	F(3,48)=0.630; p<0.599						

Parameter		Effects	Baseline → 3 months		3 months → 6 months	Baseline → 6 months	
			p-value	relative change (%)	p-value	p-value	relative change (%)
Blood plasma	Glucose	Time effect all groups	↑F(1,39)=33.431, p<0.001	125.7	↓F(1,39)=3.708, p<0.061	↑F(1,39)=17.338, p<0.001	114.3
	Insulin	Time effect all groups	↑F(1,37)=165.843, p<0.001	659.0	↑F(1,37)=8.335, p<0.006	↑F(1,37)=161.119, p<0.001	1034.5
		HFD+BCAA+exercise < HFD				p<0.061	
		HFD+BCAA+exercise < HFD+exercise			p<0.004	p<0.023	
	Cholesterol	Time effect all groups	↑F(1,39)=36.227, p<0.001	162.7	↑F(1,39)=376.410, p<0.001	↑F(1,39)=476.049, p<0.001	425.1
	Triglycerides	Time effect all groups	↑F(1,39)=18.863, p<0.001	178.1	↑F(1,39)=149.310, p<0.001	↑F(1,39)=254.231, p<0.001	437.4
	SAA	Time effect all groups	↑F(1,30)=10.610, p<0.003	200.4	↑F(1,30)=11.062, p<0.002	↑F(1,30)=16.280, p<0.001	265.6
	E-selectin	Time effect all groups	↑F(1,36)=7.659, p<0.009	113.3	↓F(1,36)=4.835, p<0.034		
			Baseline → 2 months		2 months → 6 months	Baseline → 6 months	
Systolic blood pressure		Time effect all groups	↑F(1,39)=17.360, p<0.001	115.8	↑F(2,78)=6.292, p<0.003	↑F(1,39)=49.525, p<0.001	125.0

Supplementary Table S8. Summary statistics of DVC metrics and open field parameters. Abbreviations: digital ventilated cages (DVC), high-fat diet (HFD), branched-chain amino acids (BCAA).

Parameters			Overall	HFD > Baseline (chow)	HFD+RW > Baseline (chow)	HFD+BCAA+RW > Baseline (chow)	HFD+RW > HFD	HFD+BCAA+RW < HFD	HFD+BCAA+RW > HFD+RW
DVC	Activity daytime	Baseline	F(3,24)=0.044, p<0.987						
		Month 6	F(2,19)=3.19, p<0.004					p<0.003	
				HFD > Baseline (chow)	HFD+RW > Baseline (chow)	HFD+BCAA+RW > Baseline (chow)	HFD+RW > HFD	HFD+BCAA+RW > HFD	HFD+BCAA+RW > HFD+RW
	Activity nighttime	Baseline	F(3,24)=0.588, p<0.629						
		Month 1	F(2,19)=1.751, p<0.200						
		Month 2	F(2,19)=2.054, p<0.156						
		Month 3	F(2,19)=2.566, p<0.103						
		Month 4	F(2,19)=5.838, p<0.011					p<0.01	p<0.042
		Month 5	F(2,19)=0.620, p<0.548						
		Month 6	F(2,19)=3.060, p<0.070						
Open field	Distance	Baseline	F(3,47)=1.399, p<0.255						
	Velocity	Baseline	F(3,47)=1.428, p<0.246						
				HFD > Baseline (chow)	HFD+RW > Baseline (chow)	HFD+BCAA+RW > Baseline (chow)	HFD+RW > HFD	HFD+BCAA+RW < HFD	HFD+BCAA+RW < HFD+RW
	Center (frequency)	Baseline	F(3,47)=3.825, p<0.016						p<0.010
	Corner (frequency)	Baseline	F(3,47)=1.659, p<0.189						
	Periphery (frequency)	Baseline	F(3,47)=2.216, p<0.099						
	Center (time)	Baseline	F(3,47)=3.344, p<0.027					p<0.030	p<0.049
	Periphery (time)	Baseline	F(3,47)=3.198, p<0.032					p<0.064	p<0.028
				HFD > Baseline (chow)	HFD+RW > Baseline (chow)	HFD+BCAA+RW > Baseline (chow)	HFD+RW > HFD	HFD+BCAA+RW < HFD	HFD+BCAA+RW < HFD+RW
	Corner (time)	Baseline	F(3,47)=5.924, p<0.002			p<0.063		p<0.003	p<0.002

Parameter		Effects	Baseline → 1 months		1 month → 6 months	Baseline → 6 months	
			p-value	relative change (%)	p-value	p-value	relative change (%)
DVC	Activity - daytime	Time effect all groups	↑F(1,19)=5.216, p<0.034	171.8	↑F(5,95)=9.237, p<0.001		
		Time effect HFD group				↑F(1,7)=8.528, p<0.022	147.6
		Time effect HFD+RW group				↑F(1,7)=4.865, p<0.063	128.6
		HFD+BCAA+exercise < HFD			p<0.048	p<0.005	
	Activity - nighttime	Time effect all groups	↑F(1,19)=18.943, p<0.001	188.4			
		Time effect HFD+BCAA+RW group			↓F(5,25)=15.582, p<0.001		
			1 months → 6 months				
DVC	Distance - daytime	Time effect all groups	↓F(5,40)=13.078, p<0.001	38.7			
	Distance - nighttime	Time effect all groups	↓F(5,40)=23.144, p<0.001	21.8			
			Baseline → 5 months				
Open field	Distance	Time effect all groups	↓F(1,39)=22.467, p<0.001	81.0			
		HFD+BCAA+exercise < HFD+exercise	p<0.033				
	Velocity	Time effect all groups	↓F(1,38)=22.584, p<0.001	81.3			
		HFD+BCAA+exercise < HFD+exercise	p<0.031				
	Center (time)	Time effect all groups					
	Corner (time)	Time effect all groups	↑F(1,38)=9.072, p<0.005	111.9			
	Periphery (time)	Time effect all groups					
	Center (frequency)	Time effect all groups					
	Corner (frequency)	Time effect all groups	↓F(1,38)=12.710, p<0.001	72.5			
		HFD+BCAA+exercise < HFD+exercise	p<0.006				
	Periphery (frequency)	Time effect all groups	↓F(1,38)=14.606, p<0.001	69.4			
		HFD+BCAA+exercise < HFD+exercise	p<0.011				

Supplementary Table S9. Summary statistics of the grip strength test and Rotarod. Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA).

Parameters			Overall	HFD > Baseline (chow)	HFD+exercise > Baseline (chow)	HFD+BCAA+exercise > Baseline (chow)	HFD+exercise > HFD	HFD+BCAA+exercise > HFD	HFD+BCAA+exercise > HFD+exercise
Grip test - 2 Paws	Total force	Baseline	F(3,48)=1.130, p<0.347						
		Month 1	F(2,39)=6.377, p<0.004					p<0.006	p<0.012
		Month 5	F(2,39)=0.962, p<0.391						
	Peak force	Baseline	F(3,48)=0.693, p<0.561						
Grip test - 4 Paws	Total force	Baseline	F(3,48)=0.719, p<0.546						
		Month 1	F(2,39)=3.781, p<0.032					p<0.038	p<0.065
		Month 5	F(2,39)=1.047, p<0.361						
	Peak force	Baseline	F(3,48)=0.916, p<0.440						
Rotarod	Latency to fall	Baseline	F(3,48)=1.159, p<0.335						

Parameter		Effects	Baseline → 1 month		1 month → 5 months	Baseline → 5 months	
			p-value	relative change (%)	p-value	p-value	relative change (%)
Grip test - 2 Paws	Total force	Time effect all groups	↑F(1,39)=7.952, p<0.008	112.4		↓F(1,39)=6.855, p<0.013	85.1
		Time effect HFD+exercise group			↓F(1,15)=5.513, p<0.033		
		Time effect HFD+BCAA+exercise group			↓F(1,10)=56.767, p<0.001		
		HFD+BCAA+exercise > HFD	p<0.055				
		HFD+BCAA+exercise > HFD+exercise	p<0.015				
	Peak force	Time effect all groups			↓F(1,39)=15.765, p<0.001	↓F(1,39)=3.961, p<0.054	92.9
Grip test - 4 Paws	Total force	Time effect all groups	↑F(1,39)=27.287, p<0.001	131.8		↑F(1,39)=36.558, p<0.001	133.0
		Time effect HFD+BCAA+exercise group			↓F(1,10)=9.548, p<0.011		
		HFD+BCAA+exercise > HFD	p<0.049				
		HFD+BCAA+exercise > HFD+exercise	p<0.073				
	Peak force	Time effect all groups	↓F(1,39)=4.274, p<0.045	92.3		↓F(1,39)=26.076, p<0.001	89.0
Rotarod	Latency to fall	Time effect all groups	↓F(1,39)=27.757, p<0.001	72.2	↓F(1,39)=96.396, p<0.001	↓F(1,39)=128.777, p<0.001	39.6

Supplementary Table S10. Summary statistics of the (reverse) Morris Water Maze. Abbreviations: (reverse) Morris water maze ((r)MWM), high-fat diet (HFD), branched-chain amino acids (BCAA).

Parameter		Effects	Acquisition day 1 → Acquisition day 4	
			p-value	relative change (%)
Morris water maze - baseline	Escape latency	Time effect all groups	↓ F(3,144)=4.311, p<0.006	85.7
	Distance	Time effect all groups	↓ F(3,144)=32.280, p<0.001	59.5
	Velocity	Time effect all groups	↓ F(3,144)=44.186, p<0.001	74.1
			Acquisition day 1 → Acquisition day 2	
reverse Morris water maze - month 5	Escape latency	Time effect all groups	↓ F(1,39)=6.654, p<0.014	80.1
		HFD+BCAA+exercise < HFD	p<0.061	
	Distance	Time effect all groups	↓ F(1,39)=9.872, p<0.003	75.5
	Velocity	Time effect all groups	↓ F(1,39)=16.824, p<0.001	91.0

Parameters		Overall	HFD > Baseline (chow)	HFD+exercise > Baseline (chow)	HFD+BCAA+exercise > Baseline (chow)	HFD+exercise > HFD	HFD+BCAA+exercise > HFD	HFD+BCAA+exercise > HFD+exercise
MWM - Probe	Platform location (time)	$\chi^2(3)=7.154$, p<0.067						
	Platform (frequency)	$\chi^2(3)=7.476$, p<0.058						
	Platform quadrant (time)	F(3,48)=1.592, p<0.204						
	Platform quadrant (frequency)	F(3,48)=2.722, p<0.055						
rMWM- Probe Day1	Platform location (time)	$\chi^2(2)=0.396$, p<0.820						
	Platform (frequency)	$\chi^2(2)=0.807$, p<0.807						
	Platform quadrant (time)	F(2,38)=0.055, p<0.946						
	Platform quadrant (frequency)	F(2,38)=0.967, p<0.390						
rMWM - Probe Day 2	Platform location (time)	F(2,38)=1.392, p<0.261						
	Platform (frequency)	$\chi^2(2)=1.578$, p<0.454						
	Platform quadrant (time)	F(2,38)=0.693, p<0.506						
	Platform quadrant (frequency)	F(2,38)=4.098, p<0.024					p<0.025	

Supplementary Table S11. Summary statistics of the resting-state functional connectivity analysis based on total correlations. Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA), left (L), right (R).

Connection			Effects	Baseline → 3.5 months	3.5 months → 6 months	Baseline → 6 months
Intrahemispheric	Auditory cortex L	Ventral hippocampus L	Time effect all groups	↓F(1,26)=6.694, p<0.016		↓F(1,26)=13.294, p<0.001
	Auditory cortex L	Dorsal hippocampus L	Time effect all groups			↓F(1,26)=6.484, p<0.017
	Auditory cortex R	Dorsal hippocampus R	Time effect all groups	↓F(1,26)=3.985, p<0.056		
	Motor cortex R	Ventral hippocampus R	Time effect all groups		↓F(1,26)=5.061, p<0.033	
	Somatosensory cortex L	Ventral hippocampus L	Time effect all groups			↓F(1,26)=7.715, p<0.01
	Somatosensory cortex L	Auditory cortex L	Time effect all groups	↓F(1,26)=21.238, p<0.025		↓F(1,26)=5.772, p<0.024
	Visual cortex L	Ventral hippocampus L	Time effect all groups	↓F(1,26)=8.064, p<0.009		↓F(1,26)=19.112, p<0.001
	Visual cortex L	Auditory cortex L	Time effect all groups	↓F(1,26)=6.351, p<0.018		↓F(1,26)=5.785, p<0.024
	Visual cortex L	Motor cortex L	Time effect all groups			↓F(1,26)=4.038, p<0.055
	Visual cortex L	Somatosensory cortex L	Time effect all groups	↓F(1,26)=6.983, p<0.014		↓F(1,26)=9.52, p<0.005
	Visual cortex L	Dorsal hippocampus L	Time effect all groups	↓F(1,26)=4.119, p<0.053		↓F(1,26)=7.506, p<0.011
	Visual cortex R	Dorsal hippocampus R	Time effect all groups	↓F(1,26)=5.205, p<0.031		
	Visual cortex R	Ventral hippocampus R	Time effect all groups	↓F(1,26)=7.022, p<0.014		↓F(1,26)=5.6, p<0.026
	Visual cortex R	Auditory cortex R	Time effect all groups	↓F(1,26)=5.121, p<0.032		
	Visual cortex R	Motor cortex R	Time effect all groups	↓F(1,26)=1.15, p<0.037		
	Visual cortex R	Somatosensory cortex R	Time effect all groups	↓F(1,26)=4.133, p<0.052		
	Motor cortex L	Dorsal hippocampus L	HFD+BCAA+exercise < HFD			p<0.041
			HFD+BCAA+exercise < HFD+exercise			p<0.054
Interhemispheric	Auditory cortex L	Dorsal hippocampus R	Time effect all groups	↓F(1,26)=4.991, p<0.034		↓F(1,26)=6.335, p<0.018
	Auditory cortex L	Ventral hippocampus R	Time effect all groups	↓F(1,26)=5.662, p<0.025		↓F(1,26)=16.852, p<0.001
	Auditory cortex R	Auditory cortex L	Time effect all groups	↓F(1,26)=9.673, p<0.004		↓F(1,26)=9.621, p<0.005
	Motor cortex R	Ventral hippocampus L	Time effect all groups		↓F(1,26)=5.127, p<0.032	
	Somatosensory cortex L	Ventral hippocampus R	Time effect all groups			↓F(1,26)=8.719, p<0.007
	Somatosensory cortex L	Auditory cortex R	Time effect all groups			↓F(1,26)=4.75, p<0.039
	Somatosensory cortex L	Motor cortex R	Time effect all groups			↓F(1,26)=3.44, p<0.075
	Somatosensory cortex R	Auditory cortex L	Time effect all groups			↓F(1,26)=4.165, p<0.052
	Somatosensory cortex R	Somatosensory cortex L	Time effect all groups			↓F(1,26)=4.595, p<0.042
	Visual cortex L	Dorsal hippocampus R	Time effect all groups	↓F(1,26)=6.01, p<0.021		↓F(1,26)=8.402, p<0.008
	Visual cortex L	Ventral hippocampus R	Time effect all groups	↓F(1,26)=8.202, p<0.008		↓F(1,26)=24.554, p<0.001
	Visual cortex L	Auditory cortex R	Time effect all groups	↓F(1,26)=4.393, p<0.046		↓F(1,26)=34.008, p<0.008
	Visual cortex L	Motor cortex R	Time effect all groups			↓F(1,26)=6.108, p<0.02
	Visual cortex L	Somatosensory cortex R	Time effect all groups			↓F(1,26)=5.424, p<0.028
	Visual cortex R	Dorsal hippocampus L	Time effect all groups	↓F(1,26)=4.188, p<0.051		
	Visual cortex R	Ventral hippocampus L	Time effect all groups	↓F(1,26)=8.815, p<0.006		↓F(1,26)=6.46, p<0.017
	Visual cortex R	Auditory cortex L	Time effect all groups	↓F(1,26)=8.189, p<0.008		↓F(1,26)=7.07, p<0.013
	Visual cortex R	Motor cortex L	Time effect all groups	↓F(1,26)=3.667, p<0.067		
	Visual cortex R	Somatosensory cortex L	Time effect all groups	↓F(1,26)=7.681, p<0.01		↓F(1,26)=3.895, p<0.059

	Visual cortex R	Visual cortex L	Time effect all groups			↓F(1,26)=4.686, p<0.04
	Ventral hippocampus R	Dorsal hippocampus L	HFD+BCAA+exercise < HFD			p<0.03
			HFD+BCAA+exercise < HFD+exercise			p<0.034
	Motor cortex L	Auditory cortex R	HFD+BCAA+exercise < HFD			p<0.051
			HFD+BCAA+exercise < HFD+exercise			p<0.027

Supplementary Table S12. Summary statistics of the resting-state functional connectivity analysis based on partial correlations. Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA), left (L), right (R).

Connection			Effects	Baseline → 3.5 months	3.5 months → 6 months	Baseline → 6 months
Intrahemispheric	Auditory cortex L	Ventral hippocampus L	Time effect all groups			↑F(1,26)=7.006, p<0.014
	Motor cortex L	Dorsal hippocampus L	Time effect all groups			↑F(1,26)=4.541, p<0.043
	Motor cortex L	Auditory cortex L	Time effect all groups	↑F(1,26)=3.6, p<0.069	↓F(1,26)=6.578, p<0.016	
	Motor cortex R	Dorsal hippocampus R	Time effect all groups	↑F(1,26)=14.281, p<0.001	↑F(1,26)=3.912, p<0.059	
	Somatosensory cortex L	Motor cortex L	Time effect all groups		↑F(1,26)=4.803, p<0.038	
	Somatosensory cortex R	Auditory cortex R	Time effect all groups	↑F(1,26)=5.316, p<0.029		↑F(1,26)=4.12, p<0.053
	Ventral hippocampus L	Dorsal hippocampus L	Time effect all groups		↑F(1,26)=4.802, p<0.038	
	Visual cortex L	Auditory cortex L	Time effect all groups		↑F(1,26)=6.262, p<0.019	↑F(1,26)=3.548, p<0.071
	Auditory cortex L	Ventral hippocampus L	Time effect HFD group			↑F(1,11)=12, p<0.005
			Time effect HFD+BCAA+exercise group			↑F(1,6)=8, p<0.03
			HFD+exercise < HFD	p<0.027		
	Motor cortex L	Auditory cortex L	Time effect HFD+exercise group	↑F(1,9)=12.204, p<0.007		
			Time effect HFD+BCAA+exercise group			↓F(1,6)=7.169, p<0.037
	Somatosensory cortex L	Motor cortex L	Time effect HFD+exercise group	↓F(1,9)=28.593, p<0.001		
			Time effect HFD+BCAA+exercise group			
	Somatosensory cortex R	Ventral hippocampus R	Time effect HFD group	↑F(1,11)=4.448 p<0.035	↓F(1,11)=4.448 p<0.031	
			Time effect HFD+BCAA+exercise group	↓F(1,6)=9.801 p<0.02		
Interhemispheric	Auditory cortex R	Dorsal hippocampus L	Time effect all groups	↑F(1,26)=3.960, p<0.057		
	Auditory cortex R	Ventral hippocampus L	Time effect all groups	↑F(1,26)=13.091, p<0.001		
	Auditory cortex R	Auditory cortex L	Time effect all groups	↓F(1,26)=6.374, p<0.018		
	Motor cortex L	Ventral hippocampus R	Time effect all groups			↑F(1,26)=5.704, p<0.024
	Motor cortex R	Auditory cortex L	Time effect all groups		↑F(1,26)=3.39, p<0.077	
			HFD+exercise < HFD		p<0.002	p<0.029
			HFD+BCAA+exercise < HFD			p<0.006
			HFD+exercise < HFD+BCAA+exercise		p<0.065	
	Motor cortex R	Motor cortex L	Time effect all groups	↓F(1,26)=16.162, p<0.014		
	Somatosensory cortex L	Dorsal hippocampus R	Time effect all groups		↑F(1,26)=7.104, p<0.013	
	Somatosensory cortex R	Dorsal hippocampus L	Time effect all groups	↑F(1,26)=3.476, p<0.074		↑F(1,26)=3.531, p<0.072
	Somatosensory cortex R	Somatosensory cortex L	Time effect all groups	↑F(1,26)=3.486, p<0.073		
	Visual cortex L	Ventral hippocampus R	Time effect all groups	↑F(1,26)=3.931, p<0.058		↓F(1,26)=8.008, p<0.009
	Visual cortex R	Ventral hippocampus L	Time effect all groups	↑F(1,26)=3.308, p<0.08		

	Visual cortex R	Auditory cortex L	Time effect all groups		↓F(1,26)=5.155, p<0.032	
	Visual cortex R	Visual cortex L	Time effect all groups	↑F(1,26)=10.783, p<0.003		↑F(1,26)=4.636, p<0.041
	Motor cortex R	Auditory cortex L	Time effect HFD+BCAA+exercise group	↑F(1,6)=22.859 p<0.003		
	Ventral hippocampus R	Dorsal hippocampus L	HFD+exercise > HFD			p<0.07
			HFD+BCAA+exercise < HFD+exercise			p<0.014
	Somatosensory cortex L	Motor cortex R	HFD+exercise < HFD			p<0.026
	Visual cortex L	Dorsal hippocampus L	HFD+BCAA+exercise > HFD+exercise			p<0.034

Supplementary Table S13. Summary statistics of cerebral blood flow analysis. Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA).

Parameter		Effects	Baseline → 1 months	1 months → 6 months	Baseline → 6 months	
			p-value	p-value	p-value	relative change (%)
Vasodilation	Cortex	Time effect all groups		↓F(1,31)=4.823, p<0.036	↓F(1,31)=5.682, p<0.023	89.7
	Hippocampus	Time effect all groups		↓F(1,31)=9.177, p<0.005		
		Time HFD+exercise group			↓F(1,12)=6.737, p<0.023	72.0
		Time HFD+BCAA+exercise group			↓F(1,8)=9.568, p<0.015	70.6
		HFD+exercise < HFD		p<0.047		
	Thalamus	Time effect all groups		↓F(1,31)=9.741, p<0.004	↓F(1,31)=7.104, p<0.012	85.0
Vasoconstriction	Cortex	Time effect all groups				
		Time HFD+exercise group			↓F(1,12)=7.178, p<0.020	75.7
	Hippocampus	Time effect all groups		↓F(1,31)=5.757, p<0.023		
		Time HFD+exercise group			↓F(1,12)=9.692, p<0.009	70.1
	Thalamus	Time effect all groups		↓F(1,31)=5.322, p<0.028	↓F(1,31)=3.572, p<0.068	92.24
Vasoreactivity	Cortex	Time effect all groups				
	Hippocampus	Time effect all groups				
	Thalamus	Time effect all groups				

Parameters			Overall	HFD < Baseline (chow)	HFD+RW > Baseline (chow)	HFD+BCAA+RW < Baseline (chow)	HFD+RW < HFD	HFD+BCAA+RW < HFD	HFD+BCAA+RW > HFD+RW
Vasodilation	Cortex	Baseline	F(3,40)=1.834, p<0.157						
		Month 6	F(2,31)=1.622, p<0.214						
	Hippocampus	Baseline	F(3,40)=1.660, p<0.191						
		Month 6	F(2,31)=4.039, p<0.028				p<0.077	p<0.038	
	Thalamus	Baseline	F(3,40)=0.714, p<0.550						
Vasoconstriction	Cortex	Baseline	F(3,40)=3.919, p<0.015				p<0.008		
		Month 6	F(2,31)=3.365, p<0.048						
	Hippocampus	Baseline	F(3,40)=1.926, p<0.141						
		Month 6	F(2,31)=1.386, p<0.265						
	Thalamus	Baseline	F(3,40)=1.171, p<0.333						
Vasoreactivity	Cortex	Baseline	F(3,40)=6.445, p<0.001	p<0.003		p<0.026	p<0.019		
	Hippocampus	Baseline	F(3,40)=3.111, p<0.037	p<0.022					
	Thalamus	Baseline	F(3,40)=1.299, p<0.288						

Supplementary Table S14. Summary statistics of immunohistochemical analysis of glucose transporter 1 (GLUT-1). Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA).

Parameters		Overall	HFD < Baseline (chow)	HFD+exercise < Baseline (chow)	HFD+BCAA+exercise > Baseline (chow)	HFD+exercise > HFD	HFD+BCAA+exercise > HFD	HFD+BCAA+exercise > HFD+exercise
relative GLUT-1+ area	Anterior commissure	F(3,45)=2.791, p<0.051						
	Basal ganglia	$\chi^2(3)=13.024$, p<0.005						p<0.003
	Corpus callosum	F(3,45)=2.679, p<0.058						
	Cortex	F(3,45)=7.035, p<0.001			p<0.004		p<0.029	p<0.001
	External capsule	F(3,45)=3.160, p<0.034						p<0.046
	Fimbria	F(3,45)=2.957, p<0.042				p<0.067		p<0.079
	Hippocampus	F(3,45)=2.263, p<0.094						
	Internal capsule	F(3,45)=0.516, p<0.673						
	Optic tract	F(3,45)=1.115, p<0.353						
	Thalamus	$\chi^2(3)=6.739$, p<0.081						
GLUT-1 Intensity	Anterior commissure	$\chi^2(3)=7.416$, p<0.060						
	Basal ganglia	F(3,45)=5.195, p<0.004		p<0.064				p<0.003
	Corpus callosum	F(3,45)=1.954, p<0.134						
	Cortex	F(3,45)=4.084, p<0.012	p<0.006	p<0.066				
	External capsule	F(3,45)=1.413, p<0.251						
	Fimbria	F(3,45)=0.844, p<0.477						
	Hippocampus	F(3,45)=3.945, p<0.014	p<0.007					
	Internal capsule	F(3,45)=3.257, p<0.030						p<0.068
	Optic tract	F(3,45)=1.401, p<0.255						
	Thalamus	F(3,45)=1.534, p<0.219						

Supplementary Table S15. Summary statistics of Diffusion tensor imaging analysis. Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA), fractional anisotropy (FA), mean diffusivity (MD).

Parameter		Effects	Baseline → 3.5 months		3.5 months → 6 months	Baseline → 6 months	
			p-value	relative change (%)	p-value	p-value	relative change (%)
FA	Grey Matter	Time effect all groups	↑F(1,32)=6.592, p<0.015	102.1		↑F(1,32)=12.849 p<0.001	104.3
	White Matter	Time effect all groups	↑F(1,32)=29.660, p<0.001	104.1		↑F(1,32)=18.617 p<0.001	103.1
	Auditory Cortex	Time effect all groups					
	Basal Ganglia	Time effect all groups	↑F(1,32)=5.315 p<0.028	102.8		↑F(1,32)=12.853, p<0.001	104.8
	Corpus Callosum	Time effect all groups	↑F(1,32)=38.500, p<0.001	105.3	↑F(1,32)=3.472, p<0.072	↑F(1,32)=17.916, p<0.001	103.9
		HFD+exercise > HFD				p<0.043	
	Fornix	Time effect all groups	↑F(1,32)=31.807 p<0.001	104.7		↑F(1,32)=16.085, p<0.001	103.6
		HFD+exercise > HFD				p<0.018	
	Hippocampus	Time effect all groups					
	Motor Cortex	Time effect all groups					
	Optic Tract	Time effect all groups	↑F(1,32)=30.483, p<0.001	105.5		↑F(1,32)=48.166, p<0.001	106.7
	Somatosensory Cortex	Time effect all groups					
MD	Grey Matter	Time effect all groups					
	White Matter	Time effect all groups	↓F(1,32)=3.950, p<0.055	99.2	↑F(1,32)=3.712, p<0.063		
	Auditory Cortex	Time effect all groups				↓F(1,32)=3.828, p<0.059	98.1
	Basal Ganglia	Time effect all groups	↓F(1,32)=9.922, p<0.004	98.6		↓F(1,32)=6.572, p<0.015	98.7
	Corpus callosum	Time effect all groups					
		Time effect HFD group			↓F(1,11)=7.644, p<0.018		
	Fornix	Time effect all groups					
		Time effect HFD group			↓F(1,11)=9.389, p<0.011		
		HFD+exercise < HFD	p<0.031				
		HFD+BCAA+exercise < HFD	p<0.028				
	Hippocampus	Time effect all groups					
	Motor Cortex	Time effect all groups					
	Optic Tract	Time effect all groups	↓F(1,32)=7.856, p<0.009	96.4		↓F(1,32)=12.736, p<0.001	96.1
	Somatosensory Cortex	Time effect all groups	↓F(1,32)=4.101, p<0.051	97.8		↓F(1,32)=5.286, p<0.028	97.8

Supplementary Table S16. Summary statistics of Polarized light imaging analysis. Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA).

Parameters		Overall	HFD > Baseline (chow)	HFD+exercise > Baseline (chow)	HFD+BCAA+exercise < Baseline (chow)	HFD+exercise > HFD	HFD+BCAA+exercise > HFD	HFD+BCAA+exercise > HFD+exercise
Dispersion	Anterior commissure	$\chi^2(3)=3.016$, $p<0.389$						
	Basal ganglia	$F(3,48)=1.183$, $p<0.326$						
	Corpus callosum	$\chi^2(3)=1.352$, $p<0.717$						
	Cortex	$F(3,48)=3.133$, $p<0.034$						
	Cerebral peduncle	$\chi^2(3)=0.848$, $p<0.838$						
	External capsule	$F(3,48)=3.125$, $p<0.034$						
	Fimbria	$\chi^2(3)=3.591$, $p<0.309$						
	Fornix	$\chi^2(3)=1.503$, $p<0.682$						
	Hippocampus	$F(3,48)=2.914$, $p<0.044$			$p<0.027$			
	Internal capsule	$\chi^2(3)=2.717$, $p<0.437$						
	Motor cortex	$F(3,48)=1.594$, $p<0.203$						
	Optic tract	$\chi^2(3)=1.335$, $p<0.721$						
	Somatosensory cortex	$F(3,48)=0.805$, $p<0.497$						
Retardance	Anterior commissure	$F(3,43)=3.172$, $p<0.034$		$p<0.027$				
	Basal ganglia	$F(3,43)=0.570$, $p<0.148$						
	Corpus callosum	$\chi^2(3)=10.654$, $p<0.014$	$p<0.017$					
	Cortex	$\chi^2(3)=2.673$, $p<0.445$						
	Cerebral peduncle	$\chi^2(3)=4.068$, $p<0.254$						
	External capsule	$F(3,43)=1.163$, $p<0.335$						
	Fimbria	$\chi^2(3)=14.355$, $p<0.002$	$p<0.017$	$p<0.023$				
	Fornix	$F(3,43)=2.536$, $p<0.069$						
	Hippocampus	$\chi^2(3)=7.455$, $p<0.059$						
	Internal capsule	$F(3,43)=0.951$, $p<0.424$						
	Motor cortex	$\chi^2(3)=5.612$, $p<0.132$						
	Optic tract	$\chi^2(3)=10.888$, $p<0.012$				$p<0.043$	$p<0.079$	
	Somatosensory cortex	$F(3,43)=1.439$, $p<0.245$						

Supplementary Table S17. Summary statistics of hippocampal volume and cortical thickness analysis.

Parameter	Effects	Baseline → 3.5 months		3.5 months → 6 months	Baseline → 6 months	
		p-value	relative change (%)	p-value	p-value	relative change (%)
Cortical thickness	Time effect all groups	F(1,38)=15.188, p<0.001	95.9		F(1,38)=13.317, p<0.001	96.4
	Time effect HFD group			F(1,14)=5.648, p<0.032		
Hippocampal volume	Time effect all groups					

Supplementary Table S18. Summary statistics of immunohistochemical analysis of ionized calcium-binding adapter molecule (IBA-1). Abbreviations: high-fat diet (HFD), branched-chain amino acids (BCAA).

Parameters		Overall	HFD > Baseline (chow)	HFD+exercise > Baseline (chow)	HFD+BCAA+exercise > Baseline (chow)	HFD+exercise < HFD	HFD+BCAA+exercise > HFD	HFD+BCAA+exercise > HFD+exercise
IBA-1+ count/area	Anterior commissure	F(3,47)=4.049, p<0.012			p<0.057			p<0.072
	Basal ganglia	F(3,47)=11.561, p<0.001	p<0.001	p<0.001	p<0.001			p<0.068
	Corpus callosum	F(3,47)=4.893, p<0.005				p<0.062		p<0.001
	Cortex	F(3,47)=10.021, p<0.001	p<0.001		p<0.001	p<0.021		p<0.043
	External capsule	F(3,47)=2.391, p<0.081						
	Fimbria	F(3,47)=4.545, p<0.007			p<0.007			p<0.063
	Hippocampus	F(3,47)=9.737, p<0.001	p<0.001	p<0.019	p<0.001			p<0.052
	Internal capsule	F(3,47)=4.713, p<0.006			p<0.004			p<0.049
	Thalamus	F(3,47)=10.324, p<0.001	p<0.001	p<0.019	p<0.001			p<0.059
relative IBA-1+ area	Anterior commissure	F(3,47)=4.049, p<0.012			p<0.057			p<0.072
	Basal ganglia	F(3,47)=11.561, p<0.001	p<0.001	p<0.001	p<0.001			p<0.068
	Corpus callosum	F(3,47)=6.925, p<0.001			p<0.01	p<0.059		p<0.001
	Cortex	F(3,47)=9.315, p<0.001	p<0.001		p<0.001	p<0.024		p<0.032
	External capsule	F(3,47)=2.783, p<0.051						
	Fimbria	F(3,47)=5.290, p<0.003	p<0.027		p<0.003			p<0.08
	Hippocampus	F(3,47)=9.047, p<0.001	p<0.001	p<0.018	p<0.001			p<0.05
	Internal capsule	F(3,47)=5.258, p<0.003			p<0.002			p<0.045
	Thalamus	F(3,47)=11.655, p<0.001	p<0.001	p<0.006	p<0.001			p<0.069

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