## Supplementary materials

### Behavioral tests

**-Rotarod Test.** An accelerating rotarod apparatus (Ugo Basile, Comerio, Italy) was used to evaluate the motor coordination of rats. Two consecutive days before testing, each rat was placed on the rotating drum for 5 minutes with a constant speed of 6 revolutions per minute (RPM) twice a day for acclimatization. In the test, the rotarod speed increased from 4 to 40 RPM over 5 minutes. The time at which each rat fell off the rotarod was recorded in seconds with a maximum of 600 seconds [1, 2].

**-Beam Walking Test.** This test was used to evaluate the rats' motor coordination ability to pass through a narrow beam to reach a dark box [1]. A homemade wooden square beam (2 × 100 cm) was placed to a height of 0.6 m above the ground with a white light illuminating the beginning to encourage the rats to walk through the beam. In the test, the time to cross the beam and the forelimb and hindlimb foot faults numbers were manually recorded. The fault was defined as any foot slip off the beam top surface or any limb fall on the side of beam. For adaptive training to the beam and the surrounding condition, four trials were performed before recording the results, and the interval between trials was at least 5 minutes.

**-Motor Activity.** Rats were placed individually in an open-field activity chamber (20 cm high, 40 cm long, and 32 cm wide) with sawdust at the bottom. The crossovers through a line dividing the cages into two compartments were counted locomotor activity, and the number of rearings was measured as vertical activity. The motor activity was recorded for 15 minutes. Although the recording time was different from previous research [1-4], the result of this present study could reflect the motor activity alterations.

### Synthesis of $^{11}$C-PK11195 and $^{18}$F-DPA-714

$^{11}$C-PK11195 was synthesized as previously described [5, 6]. It used no-carrier-added $^{11}$C-methyl iodide as the methylation reagent to methylate the precursor PK11195 (Changshu Huayi Chemical Co.,Ltd, Jiangsu, China). No-carrier-added $^{11}$C-carbon dioxide was produced using a cyclotron (Sumitomo, Tokyo, Japan) by proton irradiation of $^{14}$N (p, α) $^{11}$C reaction on nitrogen gas. $^{11}$C-$CO_2$

was bubbled into $LiAlH_4$ solution, hydrogen iodide was added to the reactor to obtain $^{11}C$-$CH_3I$ after eliminating the solvent. $^{11}C$-$CH_3I$ was distilled under a stream of nitrogen into a reaction vessel containing precursor PK11195, dry potassium hydroxide, and dimethyl sulfoxide. During the process, the reaction vessel was sealed and heated to 90 ~ 180°C. Then, the crude product was purified by using 70% ethanol, 30% water as the semi-preparative reversed-phase high-performance liquid chromatography (HPLC) column. After evaporation of the HPLC solvent, the purified product was formulated in isotonic saline with 5% ethanol and filtered using sterile technique. And HPLC was used to analyze the concentration and radiochemical purity of $^{11}C$-PK11195 at the end of synthesis. Radiochemical purity was more than 98% and the specific activity ranged from 1.1 to 2.3 GBq/μmol.

The synthesis of $^{18}F$-DPA-714 was relatively complicated [7-9]. No-carrier-added aqueous $^{18}F$-fluoride ion radionuclide was obtained from a cyclotron (Sumitomo, Tokyo, Japan) by proton irradiation of 95% enriched $^{18}O$-$H_2O$ via the $^{18}O$ (p, n) $^{18}F$ nuclear reaction. The $^{18}F$-Fluoride, which was trapped and eluted from an anion-exchange resin of $^{18}O$-$H_2O$, was transferred to the reaction vessel with the solution containing $H_2O/CH_3CN$, $K_2CO_3$, and Kryptofix-222. Then, the reaction mixture was added to aliquots of acetonitrile and evaporated. The dry $^{18}F$-labeled K–F–Kryptofix-222 complex was added to the mixture of toluene-4-sulfonic acid 2-[4-(3-diethylcarbamoylmethyl-5, 7-dimethyl-pyrazolo-[1, 5-a] pyrimidin-2-yl)-phenoxy]-ethyl ester and acetonitrile, and heated to 80°C for about 10 min. After the $CH_3CN$ was evaporated off, the crude product was dissolved in $CH_3COONH_4$ and purified by semi-preparative reversed-phase HPLC column which was eluted with $CH_3COONH_4/CH_3CN$ (65/35% v/v). Then, the $^{18}F$-DPA-714 was washed out with isotonic saline containing 5% ethanol and filtered using sterile technique. The final product was analyzed by HPLC quality control of $^{18}F$-DPA-714. Radiochemical purity was more than 98% and the specific activity ranged from 96.7 to 144.5 GBq/μmol.

**Brain immunohistochemistry**

For brain immunohistochemistry, free-floating immunohistochemistry was performed as mentioned by previous studies [2, 3]. The brain specimens were dewaxed in xylene and rehydrated through graded ethanol solutions. Endogenous peroxidase activity was inactivated with 1% hydrogen peroxide for 15 min at 37 °C, and sections were

blocked with 5% newborn goat serum and 3% milk for 15 min at 37 °C. Then, sections were incubated with primary antibody overnight at 4 °C, followed by incubation with secondary antibody for 30 min at 37 °C. After each step, slices were washed gently with PBS for 5 min by 3 times. For staining of microglia, rabbit anti-mouse CD11b antibody (1:500; Abcam, Cambridge, UK) was used as primary antibody. The secondary antibody was a goat anti-rabbit immunoglobulin G (1:500; Vector, Burlingame, California, USA), which was detected using horseradish peroxidase (HRP) method. After reaction with diaminobenzidine (DAB, Sigma, Missouri, USA), sections were mounted on glass slides and dehydrated through graded ethanol solutions before coverslipping. Then tissues were observed by a photomicroscope and digital camera (Olympus IX71, Tokyo, Japan). Low magnification images presented were photographed at 40 × 10 for microglia. Higher magnification (100 × 10 images) was used for morphological analysis [2, 3].

## Reference


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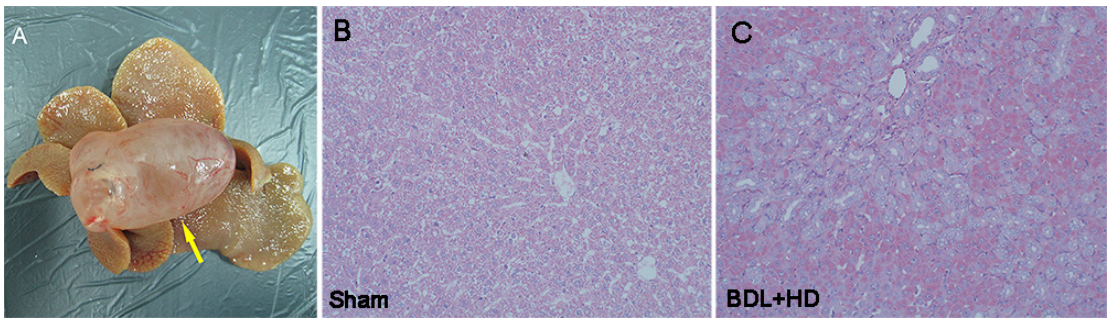
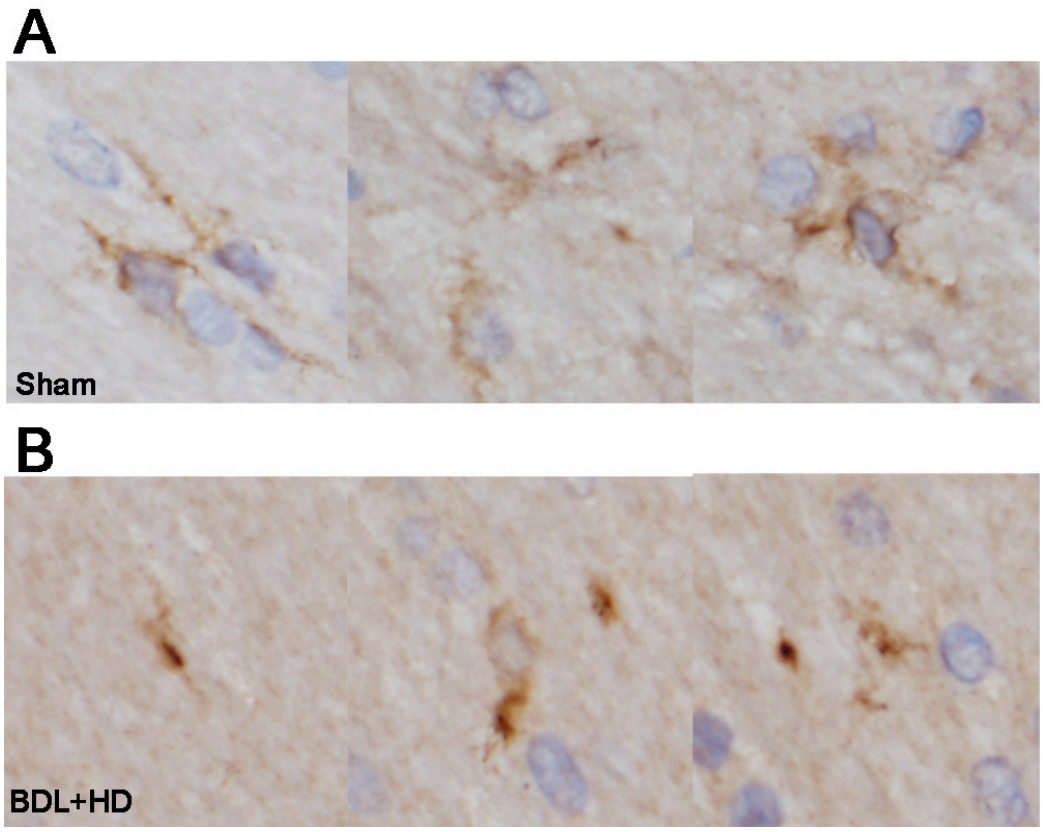
## Supplementary figures and figure legends




**Supplementary Figure S1. The liver gross specimen of a BDL+HD rat (A), and the H&E staining hepatic histologic findings of Sham group (B) and BDL+HD group (C) (original magnification × 200).**

The general observation of BDL liver showed that the bile duct proximal to the ligation site was markedly dilated, the volume of liver had increased, and liver's surface was nodular. The H&E staining found that hepatic cords were neatly arranged in the Sham group, and evidence of biliary cirrhosis in BDL+HD group was verified by pronounced destroyed hepatic cords, bile duct expansion and proliferation with inflammatory infiltration.

BDL=bile duct ligation; HD=hyperammonemic diet; H&E=hematoxylin-eosin.




**Supplementary Figure S2. The representative micrographs showing the microglia by CD11b immunohistochemistry in Sham group (A) and BDL+HD group (B) in sections from the basal ganglia.**

The microglial cells of Sham rats show ramified, indicating the microglia is inactive. BDL+HD rats show activated microglia with ameboid shape.

BDL=bile duct ligation; HD=hyperammonemic diet.

**Supplementary Table S1. Comparison of $^{11}$C-PK11195 Uptake Values of Global Brain between Sham and BDL+HD Groups (%ID/g)**

| Time points | Sham (n=5) | BDL+HD (n=8) | *T* | *P* |
|---|---|---|---|---|
| 150 s | 0.402±0.056 | 0.368±0.072 | 0.887 | 0.394 |
| 450 s | 0.270±0.037 | 0.249±0.049 | 0.824 | 0.428 |
| 750 s | 0.210±0.042 | 0.198±0.039 | 0.513 | 0.618 |
| 1050 s | 0.192±0.042 | 0.167±0.029 | 1.289 | 0.224 |
| 1350 s | 0.164±0.030 | 0.154±0.029 | 0.590 | 0.567 |
| 1650 s | 0.140±0.030 | 0.145±0.025 | -0.336 | 0.743 |
| 3600 s | 0.104±0.018 | 0.120±0.063 | -0.531 | 0.606 |

Note: Values are the mean ± standard deviation from the indicated number rats.

BDL=bile duct ligation; HD=hyperammonemic diet.

**Supplementary Table S2. Comparison of $^{18}$F-DPA-714 Uptake Values of Global Brain between Sham and BDL+HD Groups (%ID/g)**

| Time points | Sham (n=5) | BDL+HD (n=6) | *T* | *P* |
|---|---|---|---|---|
| 300 s | 0.226±0.013 | 0.250±0.049 | -1.158 | 0.292 |
| 900 s | 0.152±0.016 | 0.190±0.033 | -2.339 | 0.044* |
| 1500 s | 0.122±0.018 | 0.167±0.023 | -3.493 | 0.007** |
| 2100 s | 0.110±0.016 | 0.143±0.023 | -2.778 | 0.021* |
| 2700 s | 0.100±0.007 | 0.140±0.019 | -4.472 | 0.002** |
| 3300 s | 0.098±0.018 | 0.136±0.009 | -4.249 | 0.003** |
| 7200 s | 0.078±0.008 | 0.090±0.019 | -1.309 | 0.227 |

Note: Values are the mean ± standard deviation from the indicated number rats.

BDL=bile duct ligation; HD=hyperammonemic diet.

* $P<0.05$ and ** $P<0.01$ were regarded as statistically significant.

**Supplementary Table S3. Comparison of $^{18}$F-DPA-714 Uptake Values in Brain Regions between Sham and BDL+HD Groups at 2700 s and 3300 s Time Points (%ID/g)**

| Brain regions | Time points | Sham (n=5) | BDL+HD (n=6) | *T* | *P* |
|---|---|---|---|---|---|
| Acb Core Shell_L | 2700 s | 0.102±0.039 | 0.106±0.020 | -0.218 | 0.832 |
| | 3300 s | 0.084±0.032 | 0.099±0.027 | -0.858 | 0.411 |
| Acb Core Shell_R | 2700 s | 0.305±0.064 | 0.288±0.114 | 0.309 | 0.764 |
| | 3300 s | 0.355±0.110 | 0.292±0.107 | 0.991 | 0.345 |
| Amygdala_L | 2700 s | 0.108±0.008 | 0.130±0.042 | -1.129 | 0.285 |
| | 3300 s | 0.104±0.011 | 0.136±0.038 | -1.777 | 0.106 |
| Amygdala_R | 2700 s | 0.108±0.016 | 0.120±0.015 | -1.301 | 0.222 |
| | 3300 s | 0.094±0.015 | 0.127±0.024 | -2.679 | 0.023* |
| Caudate Putamen_L | 2700 s | 0.068±0.008 | 0.110±0.027 | -3.316 | 0.008** |
| | 3300 s | 0.070±0.012 | 0.103±0.023 | -2.900 | 0.016* |
| Caudate Putamen_R | 2700 s | 0.074±0.011 | 0.109±0.029 | -2.494 | 0.032* |
| | 3300 s | 0.074±0.015 | 0.111±0.030 | -2.566 | 0.028* |
| Cortex Auditory_L | 2700 s | 0.112±0.030 | 0.144±0.040 | -1.503 | 0.164 |
| | 3300 s | 0.108±0.024 | 0.144±0.038 | -1.881 | 0.089 |
| Cortex Auditory_R | 2700 s | 0.106±0.013 | 0.126±0.017 | -2.133 | 0.059 |
| | 3300 s | 0.110±0.023 | 0.126±0.021 | -1.229 | 0.247 |
| Cortex Cingulate_L | 2700 s | 0.096±0.025 | 0.139±0.032 | -2.478 | 0.033* |
| | 3300 s | 0.096±0.026 | 0.136±0.018 | -3.131 | 0.011* |
| Cortex Cingulate_R | 2700 s | 0.096±0.023 | 0.119±0.029 | -1.436 | 0.182 |
| | 3300 s | 0.088±0.025 | 0.133±0.028 | -2.850 | 0.017* |
| Cortex Entorhinal_L | 2700 s | 0.130±0.022 | 0.153±0.039 | -1.169 | 0.269 |
| | 3300 s | 0.130±0.025 | 0.150±0.041 | -0.955 | 0.362 |
| Cortex Entorhinal_R | 2700 s | 0.134±0.011 | 0.156±0.025 | -1.790 | 0.104 |
| | 3300 s | 0.126±0.009 | 0.149±0.031 | -1.573 | 0.147 |
| Cortex Frontal Association | 2700 s | 0.130±0.060 | 0.180±0.037 | -1.781 | 0.105 |
| | 3300 s | 0.156±0.105 | 0.189±0.067 | -0.658 | 0.525 |
| Cortex Frontal | 2700 s | 0.134±0.066 | 0.177±0.041 | -1.411 | 0.189 |
| | 3300 s | 0.160±0.058 | 0.180±0.065 | -0.550 | 0.595 |
| Cortex Insular_L | 2700 s | 0.118±0.029 | 0.124±0.044 | -0.280 | 0.785 |
| | 3300 s | 0.104±0.034 | 0.127±0.045 | -0.962 | 0.359 |
| Cortex Insular_R | 2700 s | 0.106±0.022 | 0.141±0.020 | -2.883 | 0.016* |

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|---|---|---|---|---|---|
| | 3300 s | 0.102±0.013 | 0.117±0.024 | -1.289 | 0.226 |
| Cortex Medial | 2700 s | 0.098±0.036 | 0.137±0.029 | -2.091 | 0.063 |
| Prefrontal_L | 3300 s | 0.084±0.030 | 0.100±0.018 | -1.163 | 0.272 |
| Cortex Medial | 2700 s | 0.116±0.036 | 0.117±0.046 | -0.046 | 0.964 |
| Prefrontal_R | 3300 s | 0.082±0.018 | 0.100±0.019 | -1.648 | 0.130 |
| Cortex Motor_L | 2700 s | 0.122±0.036 | 0.154±0.032 | -1.659 | 0.128 |
| | 3300 s | 0.110±0.043 | 0.159±0.038 | -2.068 | 0.065 |
| Cortex Motor_R | 2700 s | 0.116±0.042 | 0.153±0.031 | -1.755 | 0.110 |
| | 3300 s | 0.114±0.038 | 0.166±0.028 | -2.727 | 0.021* |
| Cortex Orbitofrontal_L | 2700 s | 0.120±0.040 | 0.136±0.019 | -0.917 | 0.381 |
| | 3300 s | 0.116±0.047 | 0.141±0.033 | -1.106 | 0.294 |
| Cortex Orbitofrontal_R | 2700 s | 0.120±0.039 | 0.137±0.040 | -0.733 | 0.480 |
| | 3300 s | 0.122±0.039 | 0.140±0.023 | -1.009 | 0.337 |
| Cortex Para_L | 2700 s | 0.084±0.030 | 0.109±0.020 | -1.712 | 0.118 |
| | 3300 s | 0.092±0.028 | 0.114±0.020 | -1.630 | 0.134 |
| Cortex Para_R | 2700 s | 0.082±0.023 | 0.107±0.019 | -2.090 | 0.063 |
| | 3300 s | 0.082±0.026 | 0.120±0.017 | -3.066 | 0.012* |
| Cortex Retrosplenial_L | 2700 s | 0.124±0.032 | 0.177±0.035 | -2.704 | 0.022* |
| | 3300 s | 0.112±0.029 | 0.173±0.039 | -2.973 | 0.014* |
| Cortex Retrosplenial_R | 2700 s | 0.124±0.025 | 0.173±0.042 | -2.326 | 0.042* |
| | 3300 s | 0.118±0.030 | 0.163±0.042 | -2.031 | 0.070 |
| Cortex | 2700 s | 0.108±0.028 | 0.124±0.024 | -1.078 | 0.306 |
| Somatosensory_L | 3300 s | 0.086±0.021 | 0.130±0.017 | -4.005 | 0.002** |
| Cortex | 2700 s | 0.094±0.019 | 0.121±0.011 | -3.154 | 0.010* |
| Somatosensory_R | 3300 s | 0.094±0.023 | 0.113±0.005 | -1.803 | 0.141 |
| Cortex Visual_L | 2700 s | 0.122±0.037 | 0.136±0.033 | -0.680 | 0.512 |
| | 3300 s | 0.114±0.038 | 0.137±0.031 | -1.157 | 0.274 |
| Cortex Visual_R | 2700 s | 0.110±0.034 | 0.137±0.018 | -1.812 | 0.100 |
| | 3300 s | 0.114±0.033 | 0.129±0.031 | -0.787 | 0.450 |
| Hippocampus Antero | 2700 s | 0.088±0.008 | 0.121±0.022 | -3.209 | 0.009** |
| Dorsal_L | 3300 s | 0.072±0.013 | 0.116±0.030 | -2.986 | 0.014* |
| Hippocampus Antero | 2700 s | 0.084±0.013 | 0.129±0.029 | -3.159 | 0.010* |
| Dorsal_R | 3300 s | 0.078±0.013 | 0.117±0.024 | -3.253 | 0.009** |
| Hippocampus | 2700 s | 0.098±0.031 | 0.143±0.019 | -3.122 | 0.011* |
| Posterior_L | 3300 s | 0.086±0.018 | 0.134±0.026 | -3.585 | 0.005** |
| Hippocampus | 2700 s | 0.104±0.027 | 0.136±0.026 | -2.034 | 0.069 |

| | | | | | |
|---|---|---|---|---|---|
| Posterior_R | 3300 s | 0.080±0.023 | 0.133±0.030 | -3.287 | 0.008** |
| Hypothalamus_L | 2700 s | 0.096±0.017 | 0.129±0.024 | -2.592 | 0.027* |
| | 3300 s | 0.106±0.019 | 0.114±0.030 | -0.539 | 0.602 |
| Hypothalamus_R | 2700 s | 0.102±0.018 | 0.123±0.021 | -1.776 | 0.106 |
| | 3300 s | 0.100±0.023 | 0.117±0.018 | -1.438 | 0.181 |
| Olfactory_L | 2700 s | 0.170±0.046 | 0.164±0.025 | 0.251 | 0.811 |
| | 3300 s | 0.170±0.033 | 0.159±0.021 | 0.733 | 0.480 |
| Olfactory_R | 2700 s | 0.168±0.024 | 0.154±0.033 | 0.796 | 0.444 |
| | 3300 s | 0.156±0.021 | 0.160±0.039 | -0.209 | 0.839 |
| Superior Colliculus_L | 2700 s | 0.082±0.028 | 0.157±0.026 | -4.843 | 0.001** |
| | 3300 s | 0.068±0.019 | 0.156±0.048 | -3.861 | 0.003** |
| Superior Colliculus_R | 2700 s | 0.084±0.026 | 0.160±0.041 | -3.611 | 0.005** |
| | 3300 s | 0.092±0.036 | 0.143±0.039 | -2.287 | 0.045* |
| Midbrain_L | 2700 s | 0.076±0.017 | 0.111±0.034 | -2.138 | 0.058 |
| | 3300 s | 0.076±0.017 | 0.101±0.024 | -2.024 | 0.071 |
| Midbrain_R | 2700 s | 0.068±0.008 | 0.117±0.025 | -4.184 | 0.002** |
| | 3300 s | 0.072±0.013 | 0.113±0.031 | -2.753 | 0.020* |
| Ventral Tegmental Area _L | 2700 s | 0.090±0.020 | 0.126±0.028 | -2.455 | 0.034* |
| | 3300 s | 0.090±0.023 | 0.106±0.034 | -0.896 | 0.391 |
| Ventral Tegmental Area _R | 2700 s | 0.078±0.019 | 0.139±0.037 | -3.345 | 0.007** |
| | 3300 s | 0.074±0.009 | 0.114±0.026 | -3.246 | 0.009** |
| Cerebellum-Grey_L | 2700 s | 0.118±0.011 | 0.186±0.023 | -6.052 | <0.001*** |
| | 3300 s | 0.110±0.007 | 0.177±0.026 | -6.588 | <0.001*** |
| Cerebellum-Grey_R | 2700 s | 0.120±0.012 | 0.186±0.024 | -5.632 | <0.001*** |
| | 3300 s | 0.116±0.009 | 0.177±0.030 | -5.026 | 0.001** |
| Cerebellum-White_L | 2700 s | 0.118±0.011 | 0.201±0.036 | -4.926 | 0.001** |
| | 3300 s | 0.110±0.014 | 0.187±0.047 | -4.079 | 0.004** |
| Cerebellum-White_R | 2700 s | 0.118±0.008 | 0.206±0.034 | -5.563 | <0.001*** |
| | 3300 s | 0.116±0.005 | 0.180±0.044 | -3.778 | 0.009** |
| Inferior Colliculus_L | 2700 s | 0.084±0.030 | 0.177±0.036 | -4.698 | 0.001** |
| | 3300 s | 0.076±0.018 | 0.150±0.030 | -4.875 | 0.001** |
| Inferior Colliculus_R | 2700 s | 0.084±0.013 | 0.167±0.044 | -4.680 | 0.002** |
| | 3300 s | 0.090±0.027 | 0.133±0.043 | -1.933 | 0.082 |
| Thalamus Whole_L | 2700 s | 0.082±0.033 | 0.124±0.028 | -2.400 | 0.037* |
| | 3300 s | 0.090±0.032 | 0.120±0.014 | -1.942 | 0.109 |
| Thalamus Whole_R | 2700 s | 0.078±0.024 | 0.126±0.035 | -2.651 | 0.024* |

| | | | | | |
|---|---|---|---|---|---|
| Pituitary | 3300 s | 0.082±0.029 | 0.116±0.034 | -1.781 | 0.105 |
| | 2700 s | 0.446±0.053 | 0.457±0.091 | -0.243 | 0.813 |
| | 3300 s | 0.406±0.050 | 0.457±0.087 | -1.171 | 0.269 |
| Cerebellum-Bloodflow | 2700 s | 0.202±0.022 | 0.271±0.080 | -2.179 | 0.065 |
| | 3300 s | 0.186±0.029 | 0.247±0.085 | -1.760 | 0.118 |
| Central Canal-Periaqueductal Gray | 2700 s | 0.060±0.016 | 0.110±0.019 | -4.774 | 0.001** |
| | 3300 s | 0.058±0.016 | 0.089±0.032 | -1.924 | 0.083 |
| Pons | 2700 s | 0.114±0.026 | 0.169±0.047 | -2.315 | 0.043* |
| | 3300 s | 0.098±0.019 | 0.157±0.045 | -2.737 | 0.021* |
| Septum | 2700 s | 0.110±0.012 | 0.141±0.038 | -2.063 | 0.075 |
| | 3300 s | 0.086±0.013 | 0.134±0.037 | -3.180 | 0.013* |
| Medulla | 2700 s | 0.120±0.016 | 0.170±0.017 | -5.103 | <0.001*** |
| | 3300 s | 0.112±0.008 | 0.157±0.023 | -4.790 | 0.001** |

Note: Values are the mean ± standard deviation from the indicated number rats.

BDL=bile duct ligation; HD=hyperammonemic diet; L=left; R=right.

* $P<0.05$, ** $P<0.01$, and *** $P<0.001$ were regarded as statistically significant.

**Supplementary Table S4. Comparison of $^{18}$F-DPA-714 Uptake Values in Global and Regional Brain among Six Groups (%ID/g)**

| Brain regions | Sham+NS (n=5) | Sham+IBU (n=5) | BDL+NS (n=6) | BDL+HD+NS (n=6) | BDL+IBU (n=6) | BDL+HD+IBU (n=5) | *F* | *P* |
|---|---|---|---|---|---|---|---|---|
| **Global brain** | 0.096±0.089 | 0.104±0.022[c] | 0.137±0.029[aa b cc d] | 0.140±0.022[aa bb cc d] | 0.075±0.022[b d] | 0.108±0.016[c] | 8.047 | <0.001[***] |
| **Regional brain** | | | | | | | | |
| Amygdala_L | 0.108±0.013 | 0.106±0.025 | 0.147±0.025[a b cc] | 0.155±0.034[aa bb cc d] | 0.087±0.030[d] | 0.120±0.021[c] | 5.845 | 0.001[**] |
| Amygdala_R | 0.112±0.013 | 0.114±0.021 | 0.143±0.043[cc] | 0.170±0.045[aa bb cc d] | 0.083±0.029 | 0.104±0.030 | 5.139 | 0.002[**] |
| Caudate Putamen_L | 0.082±0.013 | 0.086±0.019[c] | 0.110±0.024[a cc] | 0.130±0.013[a bb cc dd] | 0.058±0.024[b d] | 0.090±0.023[c] | 8.956 | <0.001[***] |
| Caudate Putamen_R | 0.088±0.016 | 0.088±0.022 | 0.108±0.019[bb cc] | 0.128±0.018[aa cc dd] | 0.065±0.022 | 0.088±0.019 | 7.231 | <0.001[***] |
| Cortex Auditory_R | 0.112±0.022 | 0.132±0.031 | 0.162±0.026[a cc d] | 0.170±0.045[aa b cc d] | 0.100±0.024 | 0.120±0.027 | 4.899 | 0.003[**] |
| Cortex Cingulate_L | 0.104±0.038 | 0.116±0.029[c] | 0.143±0.031[a cc] | 0.158±0.026[aa b cc d] | 0.077±0.022[b d] | 0.122±0.026[c] | 5.888 | 0.001[**] |
| Cortex Cingulate_R | 0.086±0.019[d] | 0.110±0.038 | 0.143±0.022[aa cc] | 0.151±0.019[aa b cc] | 0.092±0.025[d] | 0.130±0.044[a c] | 5.074 | 0.002[**] |
| Cortex Entorhinal_L | 0.150±0.021 | 0.160±0.046 | 0.192±0.032[cc] | 0.207±0.025[a b cc] | 0.118±0.038[d] | 0.164±0.043[c] | 4.712 | 0.003[**] |
| Cortex Entorhinal_ | 0.142±0.027 | 0.146±0.031 | 0.198±0.044[a b cc] | 0.205±0.067[a b cc] | 0.115±0.032 | 0.134±0.009 | 4.774 | 0.003[**] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| R | | | d | dd | | | | |
| Cortex Insular_R | 0.126±0.025 | 0.138±0.031 | 0.183±0.044[a cc] | 0.207±0.067[aa b cc d] | 0.100±0.022 | 0.140±0.042 | 5.017 | 0.002[**] |
| Cortex Motor_L | 0.132±0.030 | 0.142±0.037 | 0.171±0.038[c] | 0.205±0.027[aa b cc d] | 0.112±0.039 | 0.156±0.052 | 4.461 | 0.004[**] |
| Cortex Para_L | 0.098±0.037 | 0.118±0.018 | 0.127±0.020 | 0.170±0.018[aa bb cc] | 0.098±0.037 | 0.134±0.044 | 4.532 | 0.004[**] |
| Cortex Para_R | 0.096±0.025 | 0.116±0.041 | 0.138±0.046[c] | 0.173±0.041[aa b cc] | 0.082±0.034[d] | 0.132±0.022[c] | 4.669 | 0.003[**] |
| Cortex Somatosensory_L | 0.100±0.017 | 0.120±0.027 | 0.138±0.021[a cc] | 0.158±0.023[aa b cc] | 0.090±0.030[d] | 0.130±0.045[c] | 4.515 | 0.004[**] |
| Cortex Somatosensory_R | 0.112±0.024 | 0.120±0.030 | 0.148±0.034[cc] | 0.170±0.040[aa b cc d] | 0.085±0.021[d] | 0.126±0.024[c] | 5.839 | 0.001[**] |
| Cortex Visual_L | 0.108±0.013 | 0.120±0.023 | 0.162±0.032[a cc] | 0.175±0.021[aa b cc] | 0.098±0.025[d] | 0.105±0.028[c] | 3.988 | 0.008[**] |
| Cortex Visual_R | 0.108±0.015 | 0.112±0.030 | 0.162±0.039[aa b cc d] | 0.168±0.035[aa bb cc d] | 0.105±0.037 | 0.120±0.023 | 4.643 | 0.003[**] |
| Hippocampus Antero Dorsal_L | 0.102±0.023 | 0.110±0.029[c] | 0.135±0.031[a cc d] | 0.137±0.021[a cc d] | 0.070±0.023[b] | 0.100±0.028 | 5.478 | 0.001[**] |
| Hippocampus Antero Dorsal_R | 0.098±0.008 | 0.108±0.028[c] | 0.138±0.012[aa b cc] | 0.143±0.024[aa b cc d] | 0.078±0.022[b d] | 0.110±0.036[c] | 6.584 | <0.001[***] |
| Hippocampus Posterior_R | 0.108±0.019 | 0.124±0.036[c] | 0.138±0.034[cc] | 0.140±0.006[cc] | 0.077±0.027[b d] | 0.114±0.038[c] | 3.991 | 0.008[**] |
| Hypothala | 0.104± | 0.114± | 0.142±0 | 0.150±0 | 0.085± | 0.106±0 | 4.1 | 0.00 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| mus_L | 0.011 | 0.022 | .041[a cc] | .027[a cc d] | 0.034 | .029 | 12 | 7[**] |
| Hypothalamus_R | 0.102±0.016 | 0.112±0.033 | 0.155±0.040[aa b cc dd] | 0.140±0.033[a cc d] | 0.077±0.023 | 0.102±0.008 | 5.886 | 0.001[**] |
| Superior Colliculus_L | 0.078±0.016 | 0.086±0.040 | 0.125±0.038[a c] | 0.147±0.034[aa bb cc] | 0.073±0.023[d] | 0.118±0.049[c] | 4.124 | 0.007[**] |
| Midbrain_L | 0.078±0.016 | 0.082±0.019 | 0.108±0.025[a cc] | 0.137±0.026[aa bb cc d] | 0.065±0.024[d] | 0.098±0.025[c] | 7.201 | <0.001[***] |
| Ventral Tegmental Area _R | 0.082±0.013 | 0.076±0.013 | 0.127±0.038[aa bb cc] | 0.132±0.025[aa bb cc d] | 0.077±0.013 | 0.100±0.022 | 5.819 | 0.001[**] |
| Cerebellum-Grey_L | 0.116±0.011 | 0.142±0.034 | 0.165±0.026[aa cc] | 0.170±0.024[aa cc] | 0.110±0.025[d] | 0.152±0.040[c] | 4.545 | 0.004[**] |
| Cerebellum-Grey_R | 0.122±0.016 | 0.146±0.034[c] | 0.167±0.026[a cc] | 0.167±0.023[a cc] | 0.110±0.035[b] | 0.136±0.034 | 3.857 | 0.009[**] |
| Inferior Colliculus_L | 0.070±0.012[b d] | 0.122±0.038[a] | 0.157±0.033[aa cc] | 0.142±0.012[aa cc] | 0.083±0.039 | 0.124±0.053[a] | 5.392 | 0.001[**] |
| Thalamus Whole_L | 0.084±0.018 | 0.090±0.024 | 0.113±0.020[a cc] | 0.128±0.024[aa bb cc d] | 0.075±0.019 | 0.100±0.021 | 5.087 | 0.002[**] |
| Central Canal-Periaqueductal Gray | 0.074±0.027 | 0.076±0.029 | 0.107±0.020[a c] | 0.125±0.024[aa bb cc d] | 0.070±0.028 | 0.090±0.020 | 4.454 | 0.004[**] |
| Pons | 0.098±0.013 | 0.118±0.043 | 0.150±0.021[aa cc] | 0.162±0.031[aa b cc] | 0.097±0.031 | 0.120±0.016 | 5.292 | 0.002[**] |
| Medulla | 0.104±0.009[d] | 0.130±0.037 | 0.157±0.019[aa cc] | 0.155±0.019[aa cc] | 0.107±0.033[d] | 0.122±0.036[a c] | 4.151 | 0.006[**] |

Note: Values are the mean ± standard deviation from the indicated number rats.

BDL, bile duct ligation; HD, hyperammonemic diet; NS, normal saline; IBU, ibuprofen; L, left; R, right.

[**] $P<0.01$, and [***] $P<0.001$ were regarded as statistically significant. Values significantly

different from Sham+NS rats are indicated by ‘a’, from Sham+IBU rats by ‘b’, from BDL+IBU rats by ‘c’, and from BDL+HD+IBU rats by ‘d’. $^{a}$ $P$<0.05; $^{aa}$ $P$<0.01; $^{b}$ $P$<0.05; $^{bb}$ $P$<0.01; $^{c}$ $P$<0.05; $^{cc}$ $P$<0.01; $^{d}$ $P$<0.05; $^{dd}$ $P$<0.01.

## Graphical abstract