

# Functional Analysis of Brain Imaging Suggests Changes in the Availability of mGluR5 and Altered Connectivity in the Cerebral Cortex of Long-Term Abstaining Males with Alcohol Dependence: A Preliminary Study

**Table S1.** Voxel-based correlation analysis between [ $^{11}\text{C}$ ]ABP688 BP<sub>ND</sub> values and age/number of cigarettes smoked per day in whole subjects ( $n = 22$ ).

Variables	MNI Coordinates	Regions	T-Value	p-Value	FDR <sub>p</sub>
Number of cigarettes smoked per day					
Negative correlation	32;-81;-23	Right inferior temporal cortex, middle temporal cortex, inferior occipital cortex, and fusiform gyrus	5.773		0.030
	18;11;-21	Right parahippocampal gyrus and olfactory cortex	4.583		0.030
	42;0;-47	Right inferior temporal cortex	5.238		0.030
	5;8;59	Right supplementary motor area and superior frontal cortex (medial part)	5.253		0.030
	17;21;63	Right supplementary motor area	4.676		0.030
	56;-47;48	Right inferior parietal cortex	4.461		0.030
	41;14;35	Right inferior frontal cortex (opercular part)	4.486		0.030
	62;9;27	Right precentral gyrus and postcentral gyrus	4.296		0.030
	57;2;-5	Right superior temporal cortex and superior temporal pole	4.578		0.030
	53;41;11	Right inferior frontal cortex (triangular part)	4.888		0.030
	59;9;-23	Right middle temporal pole	4.130	<0.0005	0.030
	62;-5;-26	Right middle temporal cortex	4.567		0.030
	47;29;-12	Right inferior frontal cortex (orbital part)	4.230		0.030
	12;-98;8	Right cuneus	4.417		0.030
	3;-12;33	Right middle cingulate gyrus	4.205		0.030
	2;-57;38	Left precuneus and right precuneus	4.690		0.030
	0;56;11	Left superior frontal cortex (medial part) and right superior frontal cortex (medial part)	4.216		0.030
	3;45;45	Left superior frontal cortex (medial part) and right superior frontal cortex (medial part)	5.073		0.030
	0;2;38	Right middle cingulate gyrus and left middle cingulate gyrus	5.644		0.030
	-3;66;17	Left superior frontal cortex (medial part)	4.684		0.030
	2;38;17	Left anterior cingulate cortex	4.345		0.030
	-12;-65;39	Left precuneus and cuneus	5.343		0.030
	-5;35;50	Left superior frontal cortex (medial part)	5.001		0.030
	-2;-27;44	Left middle cingulate cortex	4.547		0.030

	-14;8;14	Left caudate	4.657	0.030
	-17;5;-29	Left parahippocampal gyrus	4.390	0.030
	-20;-42;-14	Left fusiform gyrus	4.286	0.030
	-38;-83;-6	Left inferior occipital cortex	4.343	0.030
	-30;-90;3	Left middle occipital cortex	4.342	0.030
	-6;9;72	Left supplementary motor area	5.203	0.030
	6;-92;-6	Left calcarine fissure and surrounding cortex	4.175	0.030
	-3;62;-6	Left medial orbitofrontal cortex	4.368	0.030
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Age				
Negative correlation	59;-11;47	Right precentral gyrus	4.025	0.503
	27;18;65	Right superior frontal cortex	3.746	0.503
	35;-39;-8	Right parahippocampal gyrus	4.411	0.503
	44;-33;11	Right superior temporal cortex	3.367	0.503
	-2;-84;32	Left cuneus	3.496	0.503
	-2;46;36	Left superior frontal cortex (medial part)	3.120	0.503
	-2;-59;11	Left precuneus and calcarine fissure and surrounding cortex	4.016	0.503
	-36;20;29	Left inferior frontal cortex (triangular part)	3.821	<0.005 0.503
	-53;-24;26	Left supramarginal gyrus and postcentral gyrus	3.533	0.503
	-24;15;-30	Left superior temporal pole	4.137	0.503
	-45;21;-18	Left superior temporal pole	3.305	0.503
	3;14;-2	Left olfactory cortex	3.342	0.503
	-48;15;-11	Left superior temporal pole	3.275	0.503
	-14;-32;6	Left thalamus	3.749	0.503
	-27;-14;-15	Left hippocampus	4.156	0.503

BP<sub>ND</sub>, binding potential with respect to nondisplaceable compartment; MNI, Montreal Neurological Institute; FDR<sub>p</sub>, false discovery rate—corrected *p*-value.

**Table S2.** ROI-based correlation analyses between [<sup>11</sup>C]ABP688 BP<sub>ND</sub> values and age/number of cigarettes smoked per day in whole subjects (*n* = 22).

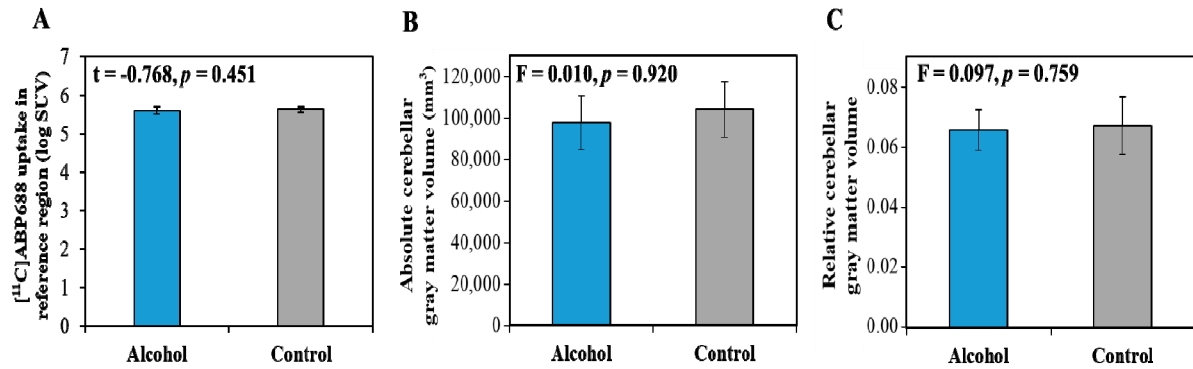
Regions of Interest	Number of Cigarettes Smoked		Age	
	Per Day			
	Pearson Correlation	<i>p</i> -Value	Pearson Correlation	<i>p</i> -Value
Anterior cingulate gyrus	−0.567	0.006*	−0.221	0.322
Superior frontal cortex	−0.416	0.054	−0.172	0.443
Middle frontal cortex	−0.472	0.027*	−0.154	0.495
Inferior frontal cortex (triangular part)	−0.465	0.029*	−0.207	0.356
Superior temporal cortex	−0.537	0.010*	−0.253	0.256
Middle temporal cortex	−0.535	0.010*	−0.164	0.466
Superior parietal cortex	−0.472	0.026*	−0.307	0.164
Inferior parietal cortex	−0.536	0.010*	−0.194	0.387
Hippocampus	−0.420	0.052	−0.383	0.078
Amygdala	−0.459	0.032*	−0.237	0.289
Thalamus	−0.460	0.031*	−0.306	0.166
Caudate	−0.539	0.010*	−0.297	0.179
Putamen	−0.477	0.025*	−0.117	0.605
Ventral striatum	−0.572	0.005*	−0.308	0.163
Globus pallidus	−0.251	0.259	0.138	0.541

\*The asterisk indicates a significant correlation (*p* < 0.05). ROI, region of interest; BP<sub>ND</sub>, binding potential with respect to nondisplaceable compartment.

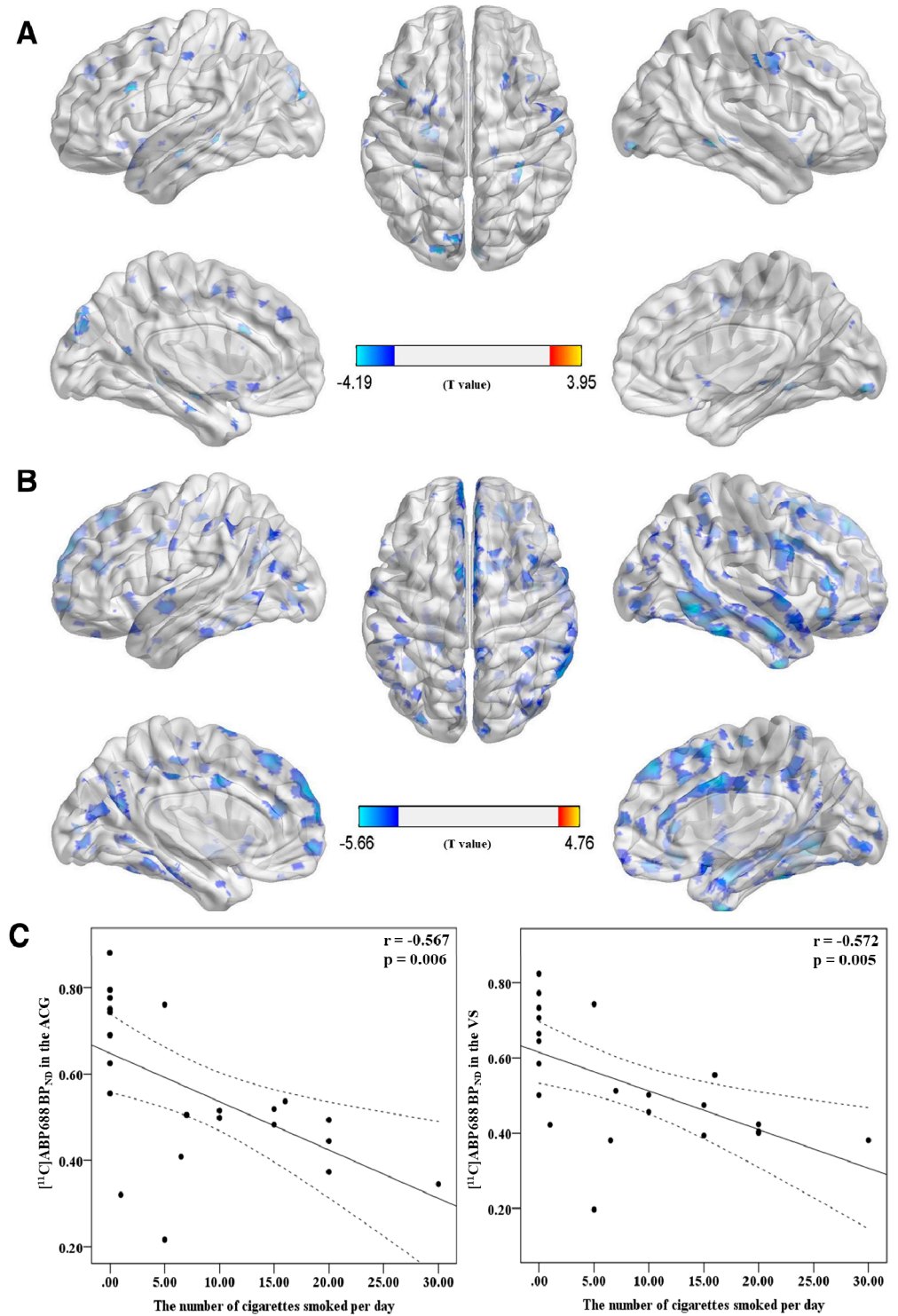
**Table S3.** ROI-based correlation analysis between [<sup>11</sup>C]ABP688 BP<sub>ND</sub> values and clinical characteristics in the alcohol dependence group ( $n = 12$ ).

ROIs	Duration of Illness			Duration of Alcohol Abstinence			OCDS			MAST		
	$r$	$p$	$p'$	$r$	$p$	$p'$	$r$	$p$	$p'$	$r$	$p$	$p'$
ACG	-0.177	0.582	0.240	0.606	0.037*	0.164	-0.113	0.727	0.312	0.055	0.865	0.815
SFC	-0.402	0.195	0.094	0.466	0.127	0.268	-0.178	0.581	0.369	0.133	0.681	0.664
MFC	-0.341	0.278	0.121	0.513	0.088	0.233	-0.176	0.584	0.322	0.102	0.753	0.725
IFC	-0.350	0.265	0.150	0.471	0.122	0.246	-0.227	0.477	0.295	0.108	0.738	0.724
STC	-0.243	0.447	0.232	0.498	0.100	0.270	-0.152	0.636	0.353	0.081	0.803	0.773
MTC	-0.220	0.492	0.247	0.557	0.060	0.189	-0.171	0.595	0.295	0.004	0.990	0.965
SPC	-0.270	0.396	0.183	0.565	0.056	0.173	-0.095	0.770	0.453	0.042	0.897	0.868
IPC	-0.212	0.507	0.233	0.637	0.026*	0.103	-0.151	0.639	0.299	0.013	0.968	0.938
Hip	-0.248	0.437	0.301	0.534	0.073	0.142	-0.170	0.597	0.415	-0.038	0.907	0.923
Amy	-0.275	0.387	0.241	0.578	0.049*	0.109	-0.199	0.535	0.338	-0.168	0.601	0.617
Tha	-0.057	0.860	0.597	0.514	0.088	0.238	-0.287	0.366	0.154	0.143	0.657	0.625
Cau	-0.217	0.499	0.224	0.532	0.075	0.254	-0.131	0.686	0.335	-0.012	0.970	0.995
Put	-0.329	0.297	0.162	0.560	0.058	0.136	-0.200	0.534	0.324	0.010	0.975	0.957
VS	-0.217	0.497	0.225	0.496	0.101	0.324	-0.131	0.685	0.336	0.174	0.588	0.534
GP	-0.336	0.286	0.197	0.511	0.089	0.148	-0.282	0.375	0.253	0.116	0.719	0.714

\*The asterisk indicates a significant correlation ( $p < 0.05$ ). The  $p'$  indicates the  $p$ -value of partial correlation analysis after controlling for the number of cigarettes smoked per day. ROI, region of interest; BP<sub>ND</sub>, binding potential with respect to nondisplaceable compartment; OCDS, Obsessive Compulsive Drinking Scale; MAST, Michigan Alcoholism Screening Test; ACG, anterior cingulate gyrus; SFC, superior frontal cortex; MFC, middle frontal cortex; IFCT, inferior frontal cortex (triangular part); STC, superior temporal cortex; MTC, middle temporal cortex; SPC, superior parietal cortex; IPC, inferior parietal cortex; Hip, hippocampus; Amy, amygdala; Tha, thalamus; Cau, caudate; Put, putamen; VS, ventral striatum; GP, globus pallidus.



**Figure S1.** Comparisons of the cerebellar standard uptake value (SUV) and cerebellar gray matter (GM) volume between the alcohol dependence and control groups. The  $[^{11}\text{C}]\text{ABP688}$  SUV in the cerebellar GM (reference region) did not differ significantly between the groups (log SUV: alcohol group:  $5.598 \pm 0.087$ , control group:  $5.624 \pm 0.069$ ;  $t = -0.768, p = 0.451$ ) (A). The cerebellar GM volume was compared between the groups using analysis of covariance (ANCOVA) with age as a covariate. There was no significant between-group difference in absolute cerebellar GM volume (alcohol group:  $97513.8 \pm 12996.6 \text{ mm}^3$ , control group:  $103881.2 \pm 13631.8 \text{ mm}^3$ ,  $F = 0.010, p = 0.920$ ) (B). No significant group difference was observed in relative cerebellar GM volume, which was calculated by dividing the absolute cerebellar GM volume by the intracranial volume (alcohol group:  $0.066 \pm 0.007$ , control group:  $0.067 \pm 0.009$ ,  $F = 0.097, p = 0.759$ ) (C).



**Figure S2.** Voxel-based analysis showing negative correlations of  $[^{11}\text{C}]\text{ABP688 BP}_{\text{ND}}$  with age ( $p < 0.005$ ,  $k = 20$ ) (A) and the number of cigarettes smoked per day ( $p < 0.0005$ ,  $k = 20$ ) (B) in whole subjects ( $n = 22$ ). Images were visualized with the BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>). Representative scatter plots of the results of region-of-interest (ROI)-based correlation analysis between  $[^{11}\text{C}]\text{ABP688 BP}_{\text{ND}}$  and the number of cigarettes smoked per day for the anterior cingulate gyrus (ACG) and ventral striatum (VS) ( $p < 0.01$ ) (C).