Measuring specific receptor binding of a PET radioligand in human brain without pharmacological blockade: the genomic plot

Mattia Veronese, Paolo Zanotti-Fregonara, Gaia Rizzo,
Alessandra Bertoldo, Robert B. Innis and Federico E. Turkheimer

Supplementary Material

Supplementary Table 1 – [^{11}C]WAY100635 data

ROIs	V_T (ml/cm^3)			mRNA (unitless)		
Frontal lobe	1.50	±	0.85	53.9	±	8.7
Parietal lobe	1.42	±	0.77	43.4	±	12.4
Temporal lobe	1.88	±	0.85	78.7	±	7.2
Occipital lobe	1.21	±	0.58	36.5	±	53.3
Cingulate gyrus	1.88	±	0.77	57.6	±	3.0
Hippocampus	1.81	±	1.05	n.a.	±	n.a.
Insula	1.95	±	1.12	83.6	±	9.0
Striatum	0.59	±	0.39	5.6	±	0.6
Globus pallidus	0.48	±	0.46	10.5	±	3.3
Basal forebrain	0.63	±	0.27	28.8	±	35.2
Claustrum	n.a.	±	n.a	n.a.	±	n.a.
Amygdala	1.45	±	0.77	45.2	±	66.4
Thalamus	0.58	±	0.35	16.0	±	3.4
Cerebellum	0.53	±	0.58	3.8	±	0.2
Brainstem	0.52	±	0.39	n.a.	±	n.a.

Distribution volume estimates (V_T) refer to a population of 15 healthy subjects (Bose et al., 2011). Genomic data (mRNA) are derived from the Allen human brain atlas (query: HTR1A). For each region the average values and the standard deviations across subjects are reported.

References

Bose, S.K., Mehta, M.A., Selvaraj, S., Howes, O.D., Hinz, R., Rabiner, E.A., Grasby, P.M., Turkheimer, F.E., Murthy, V., 2011. Presynaptic 5-HT1A is related to 5-HTT receptor density in the human brain. Neuropsychopharmacology 36, 2258-2265.

Supplementary Table 2 – [^{11}C]Ro15-4513 data

ROIs	V_T (ml/cm^3)			mRNA (unitless)		
Frontal lobe	4.07	±	0.44	285	±	71
Parietal lobe	3.70	±	0.51	208	±	57
Temporal lobe	4.96	±	0.53	317	±	81
Occipital lobe	3.90	±	0.48	165	±	51
Cingulate gyrus	5.89	±	0.52	349	±	104
Hippocampus	7.82	±	0.85	852	±	76
Insula	5.11	±	0.54	436	±	182
Striatum	4.18	±	0.51	293	±	95
Globus pallidus	n.a.	±	n.a.	27	±	49
Basal forebrain	n.a.	±	n.a.	204	±	9
Claustrum	n.a.	±	n.a.	818	±	84
Amygdala	7.61	±	0.87	n.a.	±	n.a.
Thalamus	2.73	±	0.2	148	±	36
Cerebellum	n.a.	±	n.a.	7	±	30
Brainstem	n.a.	±	n.a.	n.a.	±	n.a.

Distribution volume estimates (V_T) refer to a population of 4 healthy subjects (Stokes et al., 2014). Genomic data (mRNA) are derived from the Allen human brain atlas (query: GABRA5). For each region the average values and the standard deviations across subjects are reported.

References

Stokes, P.R., Myers, J.F., Kalk, N.J., Watson, B.J., Erritzoe, D., Wilson, S.J., Cunningham, V.J., Barros, D.R., Hammers, A., Turkheimer, F.E., 2014. Acute increases in synaptic GABA detectable in the living human brain: A [11 C] Ro15-4513 PET study. Neuroimage 99, 158-165.

Supplementary Table 3 – [^{11}C]LY2795050 data

ROIs	V_T (ml/cm^3)			mRNA (unitless)		
Frontal lobe	2.66	±	0.29	16.8	±	3.1
Parietal lobe	n.a.	±	n.a.	13.7	±	2.7
Temporal lobe	2.74	±	0.30	16.9	±	1.9
Occipital lobe	2.58	±	0.26	11.5	±	2.5
Cingulate gyrus	2.74	±	0.38	18.8	±	3.1
Hippocampus	2.31	±	0.28	16.2	±	5.5
Insula	3.41	±	0.34	24.4	±	5.2
Striatum	2.60	±	0.36	22.9	±	3.9
Globus pallidus	3.11	±	0.37	6.1	±	2.0
Basal forebrain	n.a.	±	n.a.	20.6	±	8.0
Claustrum	n.a.	±	n.a.	76.6	±	19.0
Amygdala	3.95	±	0.51	35.8	±	15.3
Thalamus	2.14	±	0.21	27.8	±	10.2
Cerebellum	1.96	±	0.18	8.8	±	4.0
Brainstem	n.a.	±	n.a.	17.8	±	5.0

Distribution volume estimates (V_T) refer to a population of 16 healthy subjects (Naganawa et al., 2014). Genomic data (mRNA) are derived from the Allen human brain atlas (query: OPRK1). For each region the average values and the standard deviations across subjects are reported.

References

Naganawa, M., Zheng, M.-Q., Nabulsi, N., Tomasi, G., Henry, S., Lin, S.-F., Ropchan, J., Labaree, D., Tauscher, J., Neumeister, A., 2014. Kinetic modeling of 11C-LY2795050, a novel antagonist radiotracer for PET imaging of the kappa opioid receptor in humans. Journal of Cerebral Blood Flow & Metabolism 34, 1818-1825.

Supplementary Table 4 – [^{11}C]FIMX data

ROIs	V_T (ml/cm^3)			mRNA (unitless)		
Frontal lobe	2.4	±	0.31	22.3	±	3.1
Parietal lobe	2.3	±	0.28	21.4	±	3.3
Temporal lobe	3.1	±	0.37	28.3	±	3.2
Occipital lobe	2.7	±	0.46	19.3	±	3.4
Cingulate gyrus	2.8	±	0.41	23.5	±	3.5
Hippocampus	2.9	±	0.39	32.6	±	3.7
Insula	3.0	±	0.41	29.1	±	4.8
Striatum	1.8	±	0.21	17.4	±	3.4
Globus pallidus	n.a.	±	n.a.	22.0	±	5.3
Basal forebrain	n.a.	±	n.a.	21.5	±	3.5
Claustrum	n.a.	±	n.a.	17.9	±	9.1
Amygdala	2.7	±	0.37	20.4	±	4.7
Thalamus	3.3	±	0.50	34.3	±	5.2
Cerebellum	13.4	±	1.90	144.1	±	24.0
Brainstem	n.a.	±	n.a.	14.2	±	2.4

Distribution volume estimates (V_T) refer to a population of 12 healthy subjects (Zanotti-Fregonara et al., 2015). Genomic data (mRNA) are derived from the Allen human brain atlas (query: GMR1). For each region the average values and the standard deviations across subjects are reported.

References

Zanotti-Fregonara, P., Rong, X., Zoghbi, S.S., Liow, J.S., Fujita, M., Veronese, M., Gladding, R.L., Rallis-Frutos, D., Hong, J., Pike, V.W., Innis, R.B., 2015. The positron emission tomographic radioligand 18F-FIMX images and quantifies metabotropic glutamate receptor 1 in proportion to the regional density of its gene transcript in human brain. Journal of Nuclear Medicine (in press).

Supplementary Table 5 – [^{11}C]NOP-1A data

ROIs	**V_T (ml/cm^3)**			**mRNA (unitless)**		
Frontal lobe	9.0	±	0.83	32.4	±	3.3
Parietal lobe	9.1	±	0.87	35.0	±	2.2
Temporal lobe	9.6	±	0.85	34.0	±	3.7
Occipital lobe	9.3	±	0.89	40.4	±	3.7
Cingulate gyrus	8.9	±	0.88	32.5	±	4.1
Hippocampus	n.a.	±	n.a.	47.9	±	11.4
Insula	n.a.	±	n.a.	30.1	±	5.8
Striatum	8.7	±	0.94	40.7	±	6.6
Globus pallidus	n.a.	±	n.a.	21.4	±	3.8
Basal forebrain	n.a.	±	n.a.	41.3	±	5.6
Claustrum	n.a.	±	n.a.	53.9	±	14.4
Amygdala	n.a.	±	n.a.	54.6	±	9.1
Thalamus	5.5	±	0.57	55.5	±	10.9
Cerebellum	5.5	±	0.57	15.1	±	3.9
Brainstem	6.7	±	0.67	46.2	±	4.6

Distribution volume estimates (V_T) refer to a population of 11 healthy subjects (Lohith et al., 2014). Genomic data (mRNA) are derived from the Allen human brain atlas (query: OPRL1). For each region the average values and the standard deviations across subjects are reported.

References

Lohith, T.G., Zoghbi, S.S., Morse, C.L., Araneta, M.D.F., Barth, V.N., Goebl, N.A., Tauscher, J.T., Pike, V.W., Innis, R.B., Fujita, M., 2014. Retest imaging of [11 C] NOP-1A binding to nociceptin/orphanin FQ peptide (NOP) receptors in the brain of healthy humans. Neuroimage 87, 89-95.

Supplementary Table 6 – [^{11}C](R)rolipram data

ROIs	V_T (ml/cm^3)			mRNA (unitless)		
Frontal lobe	0.53	±	0.13	71.7	±	75.6
Parietal lobe	0.56	±	0.14	42.1	±	7.7
Temporal lobe	0.56	±	0.13	41.7	±	5.0
Occipital lobe	0.45	±	0.13	45.2	±	9.5
Cingulate gyrus	0.57	±	0.14	38.5	±	6.4
Hippocampus	0.55	±	0.15	n.a.	±	n.a.
Insula	0.63	±	0.15	37.1	±	5.1
Striatum	0.63	±	0.16	57.5	±	10.2
Globus pallidus	0.57	±	0.13	94.1	±	23.2
Basal forebrain	0.59	±	0.17	60.0	±	16.5
Claustrum	n.a.	±	n.a.	54.5	±	15.2
Amygdala	0.56	±	0.14	48.7	±	16.0
Thalamus	0.57	±	0.14	54.3	±	12.9
Cerebellum	0.45	±	0.11	24.2	±	7.8
Brainstem	0.38	±	0.08	n.a.	±	n.a.

Distribution volume estimates (V_T) refer to a population of 12 healthy subjects (Zanotti-Fregonara et al., 2011). Genomic data (mRNA) are derived from the Allen human brain atlas (query: PDE4). For each region the average values and the standard deviations across subjects are reported.

References

Zanotti-Fregonara, P., Zoghbi, S.S., Liow, J.-S., Luong, E., Boellaard, R., Gladding, R.L., Pike, V.W., Innis, R.B., Fujita, M., 2011. Kinetic analysis in human brain of [11 C](R)-rolipram, a positron emission tomographic radioligand to image phosphodiesterase 4: a retest study and use of an image-derived input function. Neuroimage 54, 1903-1909.

Supplementary Table 7 – [^{11}C]Raclopride

ROIs	BP_{ND} (untiless)			mRNA (unitless)		
Frontal lobe	0.26	±	0.03	4.7	±	0.6
Parietal lobe	0.23	±	0.02	5.0	±	0.5
Temporal lobe	0.27	±	0.02	5.5	±	0.6
Occipital lobe	0.23	±	0.02	5.6	±	1.0
Cingulate gyrus	0.26	±	0.03	6.0	±	2.4
Hippocampus	0.21	±	0.05	9.2	±	4.6
Insula	0.34	±	0.06	5.3	±	1.0
Striatum	1.60	±	0.30	41.3	±	9.2
Globus pallidus	n.a.	±	n.a.	n.a.	±	n.a.
Basal forebrain	0.72	±	0.13	12.4	±	2.3
Claustrum	n.a.	±	n.a.	11.3	±	3.1
Amygdala	n.a.	±	n.a.	9.5	±	2.1
Thalamus	0.37	±	0.07	13.7	±	2.6
Cerebellum	Reference region – discarded from the analysis					
Brainstem	n.a.	±	n.a.	15.3	±	2.5.

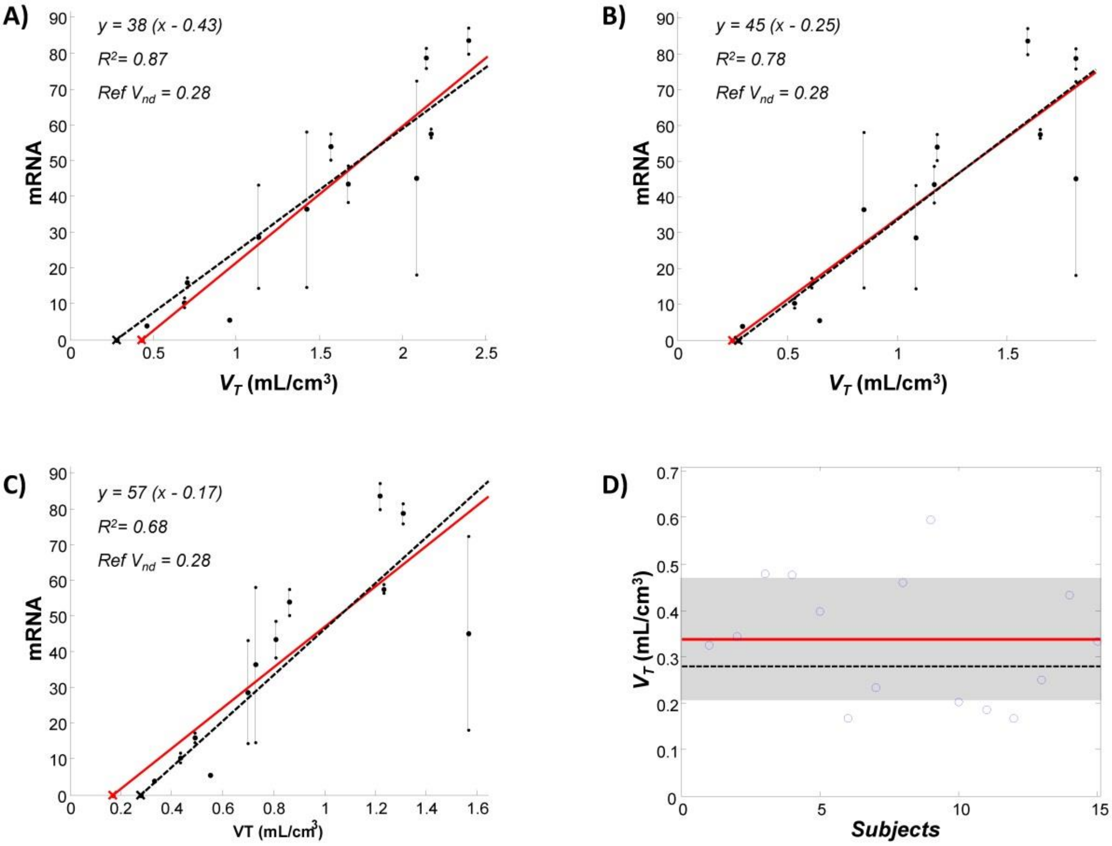
Binding potential (BP_{ND}) refer to a population of 10 healthy subjects (Pavese et al., 2006). Genomic data (mRNA) are derived from the Allen human brain atlas (query: DRD2). For each region the average values and the standard deviations across subjects are reported.

References

Pavese, N., Gerhard, A., Tai, Y., Ho, A., Turkheimer, F., Barker, R., Brooks, D., Piccini, P., 2006. Microglial activation correlates with severity in Huntington disease A clinical and PET study. Neurology 66, 1638-1643.

Supplementary Figure 1 – Single subject analysis with [^{11}C]WAY100635 PET data

Panels A-C show some representative single-subject genomic plot applications. Both $\mathrm{V_T}$ (x-axis) and mRNA (y-axis) standard errors are reported. Red lines refer to genomic plot regressions. Black dashed lines refer to the data regression with x-intercepts forced to the population $\mathrm{V_{ND}}$ reference value. Panel D shows the distribution of $\mathrm{V_{ND}}$ estimates obtained with the single subject analysis. Population $\mathrm{V_{ND}}$ reference estimate (red line) and its standard deviation (grey area) are compared with single subject $\mathrm{V_{ND}}$ estimates (blue circles). Population average of $\mathrm{V_{ND}}$ individual estimates (dashed black line) is also reported.



Supplementary Figure 2 – Single subject analysis with [^{11}C]Raclopride PET data

Panels A-C show some representative single-subject genomic plot applications. Both BP_{ND} (x-axis) and mRNA (y-axis) standard errors are reported. Red lines refer to genomic plot regressions. Black dashed lines refer to the data regression with x-intercepts forced to the origin. Panel D shows the V_{ND} absolute biases, defined as the relative difference between the individual genomic plot estimates and the single-subject reference values (as defined by the reference region).