Partial-volume correction increases estimated dopamine D2-like receptor binding potential and reduces adult age differences

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SUPPLEMENTARY INFORMATION

Number of Supplementary Tables: 7

Supplementary Table 1. Sample characteristics for each study

	Dataset		
	Yale FLB PET (n=37)	Vanderbilt Fallypride PET (n=64)	T (99), p
Age (SD)	47.81 (16.93)	51.67 (17.21)	1.09, 0.28
Age Range	26 - 79	26 - 83	
% Female	54.1	53.1	0.008, 0.93^
MTL Vol (cm^3) (SD)	13.44 (1.73)	13.73 (1.39)	1.01, 0.32
Thalamus Vol (cm^3) (SD)	12.32 (1.54)	12.80 (1.44)	1.60, 0.11
Temporal Cortex Vol (cm^3) (SD)	96.19 (11.90)	99.26 (12.10)	1.23, 0.22
Striatum Vol (cm^3) (SD)	16.01 (1.91)	16.49 (2.02)	1.17, 0.25
Parietal Cortex Vol (cm^3) (SD)	93.95 (14.01)	105.69 (15.99)	3.72, <0.001
Frontal Cortex Vol (cm^3) (SD)	151.50 (22.21)	169.14 (23.27)	3.73, <0.001
ACC Vol (cm^3) (SD)	12.51 (1.88)	13.28 (2.18)	1.81, 0.07

^ Chi-square text (df=1)

Supplementary Table 2. Summary brain regions of interest used in analyses. Bilateral cortical and subcortical volumes from the parcellation of the T1 structural MRI data that were combined to form each summary region. All reported subregions reflect Hammers atlas VOIs available through PNEURO except the thalamus and striatum, which were derived from PNEURO's deep nuclei parcellation.

Summary Region of Interest (ROI)	Subregions of Interest (bilateral)	Reported BP_{ND} Dataset
Frontal Cortex	FL_inf_fr_G	FLB
	FL_mid_fr_G	FLB
	FL_OFC_AOG	FLB
	FL_OFC_LOG	FLB
	FL_OFC_MOG	FLB
	FL_OFC_POG	FLB
	FL_precen_G	FLB
	FL_strai_G	FLB
	FL_sup_fr_G	FLB
Anterior Cingulate Cortex	G_cing_ant	FLB, Fallypride
	Presubgen_antCing	FLB, Fallypride
	Subcall_area	FLB, Fallypride
	Subgen_antCing	FLB, Fallypride
Medial Temporal Lobe	Amygdala	FLB, Fallypride
	G_paraH_amb	FLB, Fallypride
	Hippocampus	FLB, Fallypride
	Ant_TL_inf_lat	FLB, Fallypride
	Ant_TL_med	FLB, Fallypride
Temporal Cortex	G_fus	FLB, Fallypride
	G_sup_temp_ant	FLB, Fallypride
	G_sup_temp_post	FLB, Fallypride
	G_tem_midin	FLB, Fallypride
	Post_TL	FLB, Fallypride
Parietal Cortex	PL_postce_G	FLB
	PL_rest	FLB
	PL_sup_pa_G	FLB
Thalamus	Thalamus	FLB, Fallypride
Striatum	CaudateNucl	Fallypride
	Putamen	Fallypride
	Ventral_striatum	Fallypride

Supplementary Table 3. Correlations between uncorrected BP_{ND} and PVC BP_{ND} for each region of interest in each study.

Region	Fallypride	FLB
Thalamus	0.987 [0.975, 0.993]	0.998 [0.997, 0.999]
ACC	0.842 [0.774, 0.902]	0.971 [0.907, 0.995]
MTL	0.939 [0.891, 0.967]	0.930 [0.832, 0.988]
Temporal Cortex	0.950 [0.927, 0.973]	0.969 [0.912, 0.993]
Frontal Cortex		0.992 [0.983, 0.997]
Parietal Cortex		0.939 [0.790, 0.993]
Striatum	0.989 [0.983, 0.993]	

Supplementary Methods and Results

Effects of PVC on binding potential estimation error

We tested for effects of PVC on BP_{ND} estimation error across our anatomical ROIs by calculating a volume-weighted measure of standard error (SE) of the SRTM BP_{ND} estimation before and after PVC from PKIN in each Hammer's atlas or deep nuclei parcellation VOI that made up the summary anatomical ROIs (Supplementary Table 2). The volume-weighted BP_{ND} from each ROI was divided by the volume-weighted SE measure for each subject to obtain a measure of BP_{ND} signal relative to error, BP_{ND}/SE (see Supplementary Table 4), that indicated the relative BP_{ND} precision for uncorrected and PVC data. We compared uncorrected and PVC BP_{ND}/SE from each ROI in our data using Wilcoxon matched-pairs signed-ranks tests. For the FLB data, PVC increased BP_{ND}/SE in thalamus ($Z=5.3$, $p<0.001$), parietal cortex ($Z=4.52$, $p<0.001$), and frontal cortex ($Z=3.21$, $p<0.002$). Conversely, FLB BP_{ND}/SE was reduced in temporal cortex ($Z=–4.55$, $p<0.001$), MTL ($Z=–4.23$, $p<0.001$), and ACC ($Z=–4.07$, $p<0.001$) after PVC. For the Fallypride data, BP_{ND}/SE was increased after PVC in striatum ($Z=6.96$, $p<0.001$), thalamus ($Z=6.94$, $p<0.001$), and temporal cortex ($Z=2.17$, $p=0.030$). Conversely, Fallypride BP_{ND}/SE was reduced in ACC ($Z=–4.08$, $p<0.001$) and not significantly different in MTL ($Z=–1.39$, $p=0.164$) after PVC.

Age effects on binding potential controlling for brain volume and sex

We ran additional linear regressions with mean-centered age, mean-centered regional grey matter volume in each ROI, and sex (female = 0, male = 1) as predictors of uncorrected and PVC BP_{ND} for each region and study (Supplementary Tables 5 and 6). To gain insight into how the covariates affected the age effect sizes, we estimated standardized estimates of the age effects (Pearson's correlations) on uncorrected and PVC BP_{ND} controlling for regional grey matter volume and sex (Supplementary Table 7). These analyses included sex as an explanatory variable as it has been suggested to affect brain

volume in a regionally specific way[1, 2], as well as having an impact on dopamine signaling in some studies.[3, 4] Furthermore, an early PET study demonstrating age differences in D2 receptor availability found differential age effects in men and women.[5] The tables also display estimates of the PVC effects controlling for volume and sex, but we note that the inclusion of these variables may be somewhat redundant given that regional volume differences will already be accounted for in the PVC corrected data, albeit in a more geometrically sophisticated manner.

References

1. Gur RC, Gunning-Dixon FM, Turetsky BI, et al. Brain region and sex differences in age association with brain volume: a quantitative MRI study of healthy young adults. *Am J Geriatr Psychiatry* 2002; 10: 72-80.
2. Gur RC, Mozley PD, Resnick SM, et al. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America* 1991; 88: 2845-2849.
3. Kaasinen V, Nagren K, Hietala J, et al. Sex differences in extrastriatal dopamine d(2)-like receptors in the human brain. *The American journal of psychiatry* 2001; 158: 308-311.
4. Pohjalainen T, Rinne JO, Nagren K, et al. Sex differences in the striatal dopamine D2 receptor binding characteristics in vivo. *The American journal of psychiatry* 1998; 155: 768-773.
5. Wong DF, Wagner HN, Jr., Dannals RF, et al. Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. *Science* 1984; 226: 1393-1396.

Supplementary Table 4. Volume-adjusted (see Methods) mean BP_{ND}, standard error (SE), and BP_{ND}/SE from anatomical regions of interest (see Supplementary Table 2) pre-PVC (unc = uncorrected) and post-PVC are indicated along with their standard deviation for both data sets. BP_{ND} relative to standard error varies across anatomical regions of interest.

Region	Fallypride DSTE					
	unc BP_{ND}	PVC BP_{ND}	unc BP_{ND} SE	PVC BP_{ND} SE	unc BP_{ND}/SE	PVC BP_{ND}/SE
Thalamus	1.95 ± 0.33	2.40 ± 0.38	2.16 ± 0.44	2.18 ± 0.45	0.95 ± 0.28	1.16 ± 0.34
ACC	0.57 ± 0.17	0.70 ± 0.22	13.57 ± 4.76	21.99 ± 10.72	0.05 ± 0.03	0.04 ± 0.02
MTL	1.10 ± 0.19	1.50 ± 0.27	7.25 ± 1.59	11.77 ± 7.54	0.16 ± 0.05	0.15 ± 0.05
Temporal Cortex	0.70 ± 0.22	1.13 ± 0.29	4.69 ± 2.05	9.71 ± 14.65	0.18 ± 0.09	0.19 ± 0.09
Striatum	19.11 ± 3.08	29.77 ± 4.59	2.77 ± 0.42	2.83 ± 0.48	7.04 ± 1.48	10.79 ± 2.39

Region	FLB HRRT					
	unc BP_{ND}	PVC BP_{ND}	unc BP_{ND} SE	PVC BP_{ND} SE	unc BP_{ND}/SE	PVC BP_{ND}/SE
Thalamus	3.15 ± 0.55	3.51 ± 0.61	5.05 ± 1.53	5.26 ± 1.59	0.68 ± 0.24	0.73 ± 0.25
ACC	1.01 ± 0.32	1.19 ± 0.37	11.43 ± 12.56	18.29 ± 26.55	0.12 ± 0.07	0.11 ± 0.06
MTL	1.26 ± 0.29	1.45 ± 0.36	16.35 ± 9.50	23.96 ± 17.06	0.09 ± 0.04	0.08 ± 0.04
Temporal Cortex	1.35 ± 0.43	1.68 ± 0.51	4.92 ± 2.01	9.31 ± 9.39	0.33 ± 0.19	0.26 ± 0.17
Frontal Cortex	0.77 ± 0.27	0.93 ± 0.31	5.70 ± 2.49	7.88 ± 7.54	0.18 ± 0.13	0.19 ± 0.15
Parietal Cortex	0.83 ± 0.32	0.98 ± 0.39	7.03 ± 9.15	5.81 ± 5.09	0.23 ± 0.21	0.28 ± 0.24

Supplementary Table 5. Multiple regression results for effects of age, volume, and sex on D2-like receptor availability (BP_{ND}) from study using [18F]Fallypride. Age and volume were mean-centered and sex was 0 for female and 1 for male. Intercept is average BP_{ND} for average age, average volume, female subjects. Unstandardized effects reported with 95% CIs.

Region		Fallypride DSTE			
		Intercept	Age	Volume (cm^3)	Sex (male)
Thalamus	unc	2.00 [1.90, 2.12]	–0.010 [–0.015, –0.005]	–0.020 [–0.090, 0.051]	–0.120 [–0.291, 0.050]
	PVC	2.45 [2.32, 2.58]	–0.010 [–0.016, –0.003]	–0.034 [–0.119, 0.051]	–0.114 [–0.319, 0.091]
ACC	unc	0.59 [0.54, 0.64]	–0.005 [–0.008, –0.003]	–0.003 [–0.024, 0.018]	–0.042 [–0.124, 0.041]
	PVC	0.69 [0.61, 0.77]	–0.003 [–0.007, 0.001]	–0.002 [–0.033, 0.030]	0.021 [–0.103, 0.145]
MTL	unc	1.09 [1.02, 1.15]	–0.004 [–0.007, –0.001]	–0.007 [–0.372, 0.712]	0.034 [–0.070, 0.138]
	PVC	1.45 [1.36, 1.55]	–0.003 [–0.007, 0.001]	–0.020 [–0.076, 0.036]	0.093 [–0.058, 0.244]
Temporal Cortex	unc	0.71 [0.64, 0.78]	–0.004 [–0.008, 0.000]	0.004 [–0.002, 0.009]	–0.032 [–0.138, 0.074]
	PVC	1.13 [1.03, 1.23]	–0.004 [–0.009, 0.001]	0.003 [–0.004, 0.010]	–0.013 [–0.163, 0.137]
Striatum	unc	19.44 [18.45, 20.43]	–0.100 [–0.140, –0.059]	0.105 [–0.318, 0.528]	–0.707 [–2.311, 0.897]
	PVC	30.19 [28.65, 31.73]	–0.141 [–0.204, –0.078]	–0.064 [–0.723, 0.596]	–0.909 [–3.409, 1.590]

Supplementary Table 6. Multiple regression results for effects of age, volume, and sex on D2-like receptor availability (BP_{ND}) from study using [11C]FLB457. Age and volume were mean-centered and sex was 0 for female and 1 for male. Intercept is average BP_{ND} for average age, average volume, female subjects. Unstandardized effects reported with 95% CIs.

Region		FLB HRRT			
		Intercept	Age	Volume (cm^3)	Sex (male)
Thalamus	unc	3.12 [2.87, 3.38]	–0.015 [–0.026, –0.003]	–0.169 [–0.321, –0.017]	0.053 [–0.366, 0.473]
	PVC	3.49 [3.20, 3.77]	–0.016 [–0.028, –0.003]	–0.199 [–0.369, –0.030]	0.049 [–0.417, 0.516]
ACC	unc	0.98 [0.84, 1.11]	–0.011 [–0.017, –0.004]	–0.033 [–0.095, 0.030]	0.071 [–0.136, 0.279]
	PVC	1.18 [1.02, 1.34]	–0.012 [–0.020, –0.004]	–0.036 [–0.109, 0.038]	0.037 [–0.209, 0.283]
MTL	unc	1.21 [1.06, 1.36]	–0.006 [–0.011, 0.000]	–0.031 [–0.103, 0.041]	0.103 [–0.146, 0.352]
	PVC	1.40 [1.22, 1.59]	–0.007 [–0.014, 0.001]	–0.038 [–0.128, 0.052]	0.117 [–0.194, 0.427]
Temporal Cortex	unc	1.33 [1.15, 1.51]	–0.014 [–0.022, –0.006]	–0.006 [–0.018, 0.007]	0.041 [–0.233, 0.315]
	PVC	1.69 [1.47, 1.92]	–0.014 [–0.024, –0.004]	–0.002 [–0.018, 0.013]	–0.042 [–0.383, 0.299]
Frontal Cortex	unc	0.73 [0.62, 0.84]	-0.011 [-0.017, -0.006]	–0.006 [–0.010, –0.001]	0.094 [–0.079, 0.267]
	PVC	0.88 [0.75, 1.01]	-0.012 [-0.018, -0.005]	–0.007 [–0.013, –0.002]	0.101 [–0.103, 0.305]
Parietal Cortex	unc	0.74 [0.61, 0.87]	-0.014 [-0.021, -0.007]	–0.011 [–0.021, –0.002]	0.190 [–0.016, 0.395]
	PVC	0.92 [0.75, 1.09]	-0.014 [-0.023, -0.005]	–0.009 [–0.022, 0.003]	0.131 [–0.137, 0.399]

Supplementary Table 7. Standardized correlation coefficients (with 95% CIs) for the effects of age (reported in Table 2 but repeated here for ease of comparison), effects of age controlling for volume, and effects of age controlling for volume and sex on D2-like receptor availability (BP_{ND}).

Region		Fallypride DSTE Study			FLB HRRT Study		
		Age	Age (vol)	Age (vol, sex)	Age	Age (vol)	Age (vol, sex)
Thalamus	unc	–0.448 [–0.675, –0.221]	–0.554 [–0.821, –0.288]	–0.508 [–0.780, –0.235]	–0.250 [–0.582, 0.082]	–0.445 [–0.787, –0.103]	–0.453 [–0.806, –0.100]
	PVC	–0.361 [–0.597, –0.124]	–0.480 [–0.757, –0.202]	–0.441 [–0.726, –0.156]	–0.215 [–0.550, 0.120]	–0.423 [–0.764, –0.083]	–0.430 [–0.782, –0.078]
ACC	unc	–0.509 [–0.727, –0.290]	–0.551 [–0.793, –0.308]	–0.535 [–0.780, –0.291]	–0.494 [–0.792, –0.196]	–0.561 [–0.899, –0.224]	–0.569 [–0.911, –0.228]
	PVC	–0.230 [–0.476, 0.018]	–0.226 [–0.502, 0.049]	–0.232 [–0.512, 0.047]	–0.472 [–0.774, –0.169]	–0.545 [–0.887, –0.203]	–0.549 [–0.896, –0.201]
MTL	unc	–0.370 [–0.605, –0.134]	–0.372 [–0.617, –0.127]	–0.376 [–0.622, –0.129]	–0.338 [–0.660, –0.015]	–0.342 [–0.669, –0.014]	–0.327 [–0.658, 0.005]
	PVC	–0.152 [–0.403, 0.098]	–0.158 [–0.418, 0.103]	–0.165 [–0.425, 0.095]	–0.317 [–0.643, –0.008]	–0.322 [–0.651, 0.008]	–0.308 [–0.642, 0.027]
Temporal Cortex	unc	–0.416 [–0.647, –0.185]	–0.320 [–0.594, –0.046]	–0.312 [–0.589, –0.036]	–0.513 [–0.808, –0.219]	–0.565 [–0.882, –0.249]	–0.566 [–0.888, –0.245]
	PVC	–0.293 [–0.536, –0.051]	–0.230 [–0.520, 0.060]	–0.227 [–0.521, 0.066]	–0.452 [–0.758, –0.146]	–0.479 [–0.811, –0.147]	–0.478 [–0.816, –0.141]
Striatum	unc	–0.572 [–0.780, –0.364]	–0.573 [–0.796, –0.350]	–0.557 [–0.783, –0.331]			
	PVC	–0.511 [–0.729, –0.292]	–0.541 [–0.773, –0.308]	–0.527 [–0.763, –0.290]			
Frontal Cortex	unc				–0.471 [–0.773, –0.168]	–0.676 [–1.011, –0.340]	–0.702 [–1.040, –0.363]
	PVC				–0.394 [–0.709, –0.078]	–0.620 [–0.966, –0.274]	–0.645 [–0.995, –0.295]
Parietal Cortex	unc				–0.455 [–0.761, –0.149]	–0.660 [–1.041, –0.279]	–0.733 [–1.109, –0.356]
	PVC				–0.427 [-0.737, –0.117]	–0.576 [–0.971, –0.181]	–0.617 [-1.022, –0.213]