Dopamine D1 and D2 receptors are distinctly associated with rest-activity rhythms and drug reward

Supporting information

Table S1 PET and diurnal measures between participants using different scanners

Mean (SD)	HRRT scanner (n=16)	PET/CT scanner (n=16)	p-value
Age	47.93 (9.70)	36.87 (12.23)	.008
BMI	26.74 (4.89)	28.64 (2.79)	.188
Sex (f/m)	7/9	5/11	.465
PET measures			
D1R_caudate	1.30 (.20)	1.34 (.25)	.620
D1R_putamen	1.58 (.16)	1.64 (.21)	.380
D1R_NAc	1.36 (.14)	1.39 (.24)	.593
D2R_caudate	2.63 (.30)	2.59 (.24)	.703
D2R_putamen	3.27 (.31)	3.21(.29)	.568
D2R_NAc	2.61 (.26)	2.57 (.31)	.693
Parametric diurnal measures (Actigraphy)			
Log_amplitude	1.29 (.44)	1.35 (.55)	.761
Log_mesor	4.86 (.34)	5.03 (.52)	.314
Acrophase (24-h decimal time)	15.37 (1.88)	14.98 (1.40)	.551
Up-mesor (24-h decimal time)	7.34 (1.98)	7.27 (2.05)	.926
Down-mesor (24-h decimal time)	23.40 (2.57)	22.70 (1.43)	.395
F-statistic	801.63 (398.28)	867.65 (544.69)	.715

Non-parametric diurnal measures (Actigraphy)			
L5 (mg)	5.09 (1.67)	5.11 (1.71)	.980
M10 (mg)	46.65 (19.74)	56.65 (43.44)	.569
Daily mean activity (mg)	29.82 (9.73)	33.12 (21.17)	.582
Sleep onset (24-h decimal time)	24.07 (1.47)	24.24 (1.27)	.750
Wakeup time (24-h decimal time)	6.97 (1.67)	7.31 (1.54)	.578
Sleep midpoint (24-h decimal time)	3.52 (1.47)	3.77 (1.24)	.626
L5 starting time (24-h decimal time)	8.79 (6.47)	7.66 (6.14)	.634
M10 starting time (24-h decimal time)	10.02 (2.08)	9.62 (1.73)	.586
Intra-daily variability	.44 (.12)	.44 (.19)	.929
Inter-daily stability	.15 (.07)	.15 (.09)	.961
Questionnaires			
Self-reported bedtime (24-h decimal time)	23.50 (1.15)	23.09 (1.25)	.348
Self-reported wakeup time	6.94 (1.14)	6.48 (1.39)	.320

Self-reported exercise frequency (per week)	6.43 (2.54)	8.01 (5.28)	.310
Self-reported exercise duration[a]	3.20 (1.86)	3.93 (2.23)	.498
Self-reported exercise intensity[b]	1.83 (.56)	1.70 (.46)	.347
MEQ	56.06 (9.67)	58.19 (10.81)	.562

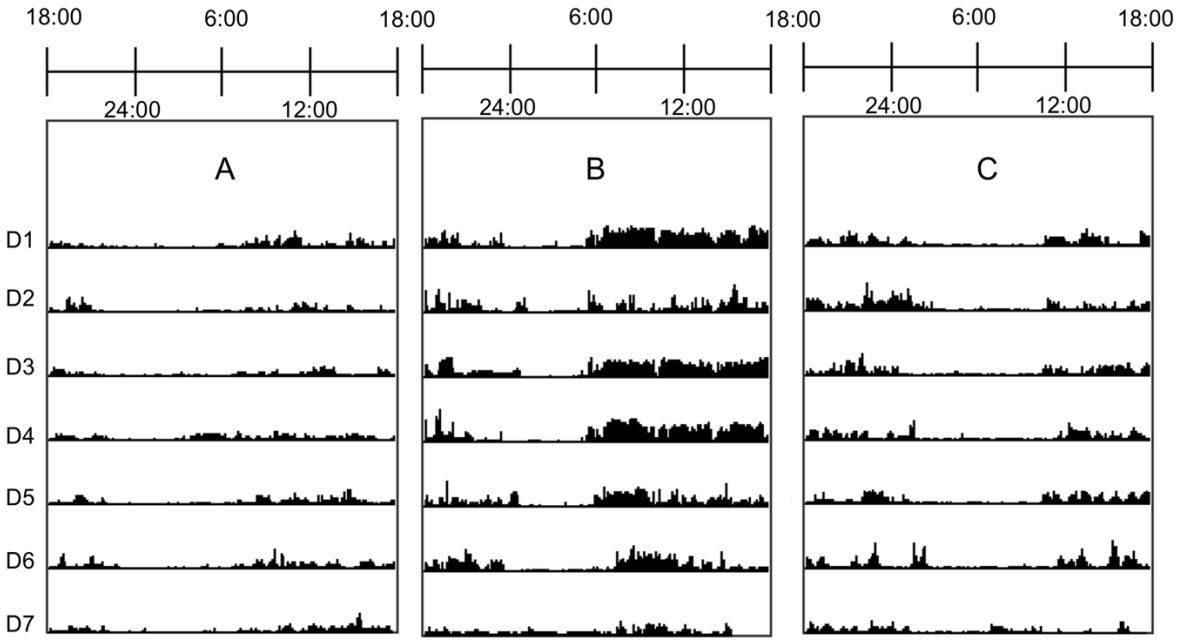
[a] Exercise duration: 1= Less than 30 min; 2= 30-60 min; 3= greater than 60 min

[b] Exercise intensity: 1= Low; 2= Moderate; 3= High

Table S2 Striatal subregions associated with diurnal measures—including PET scanner as a covariate

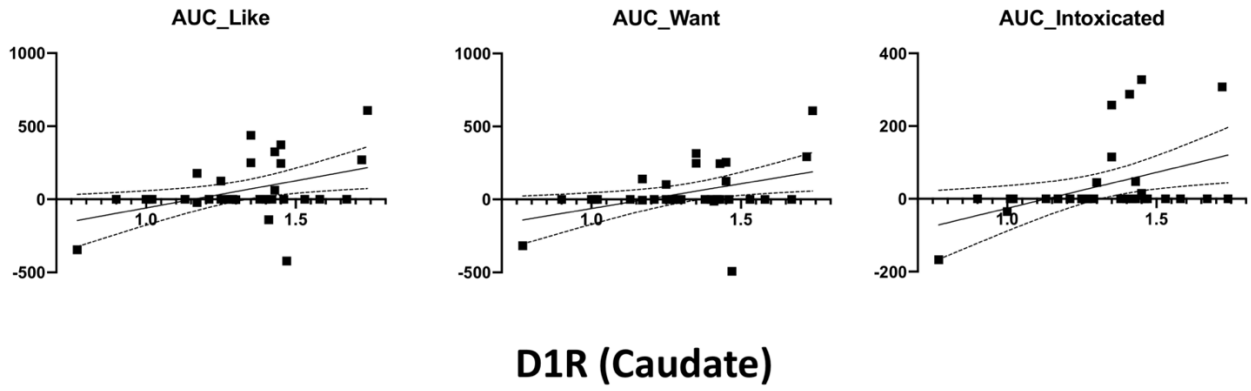
Diurnal measures	Striatal regions (structural/functional)	peak x y z (MNI)			K	t Value
Rhythm timing and D1R (positive correlation)						
Acrophase	Caudate_L/Executive	-17	10	17	25	4.20
Rhythm height and D2/3R (negative correlation)						
M10	Putamen_L/limbic	-17	12	-7	24	4.75
Daily mean activity	Putamen_L/limbic	-15	10	-7	33	5.08
	Putamen_R/limbic	15	12	-7	19	4.71
M10-L5	Putamen_L/limbic	-17	12	-7	24	4.68

Figure S1 Representative actograms of one-week rest-activity patterns



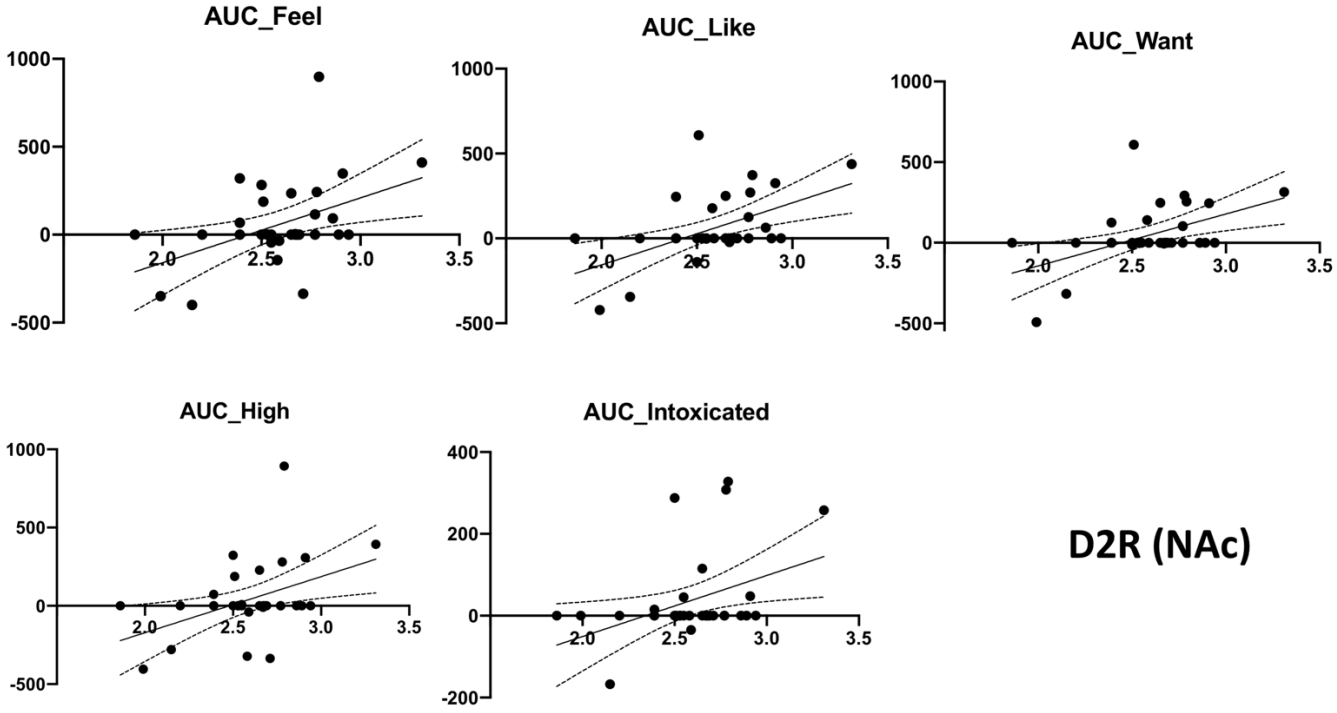
Subject A had lower 24-h mean activity (19.5 mg) than subject B (58.95 mg) and C (28.56 mg). Subject C had later acrophase (18.30) and onset of M10 (12.67) than subject A (acrophase: 14.62, M10 onset: 8.60) and subject B (acrophase: 14.11, M10 onset: 7.44).

Figure S2 D1R in the caudate and subjective drug effects (AUC)



The area under the curve (AUC) for the changes in subjective drug effects from baseline was used as outcome measures. Y axis: We subtracted placebo from MP ratings to estimate MP-induced subjective drug effects. X axis: D1R in the caudate. The solid lines indicate the lines of best fit, and the dashed lines indicate the 95% confidence intervals.

Figure S3 D2R in the nucleus accumbens and subjective drug effects (AUC)



The area under the curve (AUC) for the changes in subjective drug effects from baseline was used as outcome measures. Y axis: We subtracted placebo from MP ratings to estimate MP-induced subjective drug effects. X axis: D2R in the nucleus accumbens (NAc). The solid lines indicate the lines of best fit, and the dashed lines indicate the 95% confidence intervals.

Figure S4: MP vs PO-induced drug effects

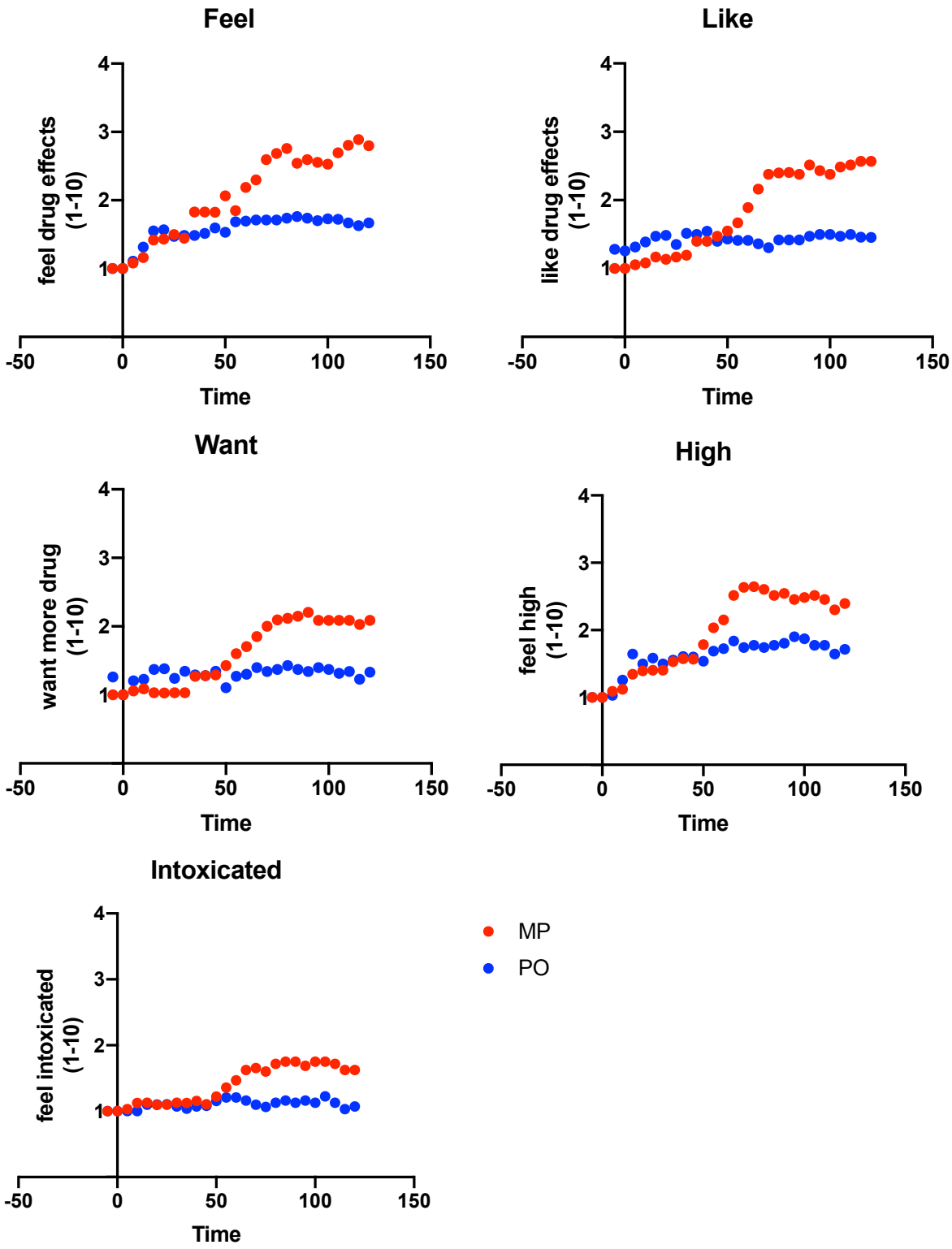
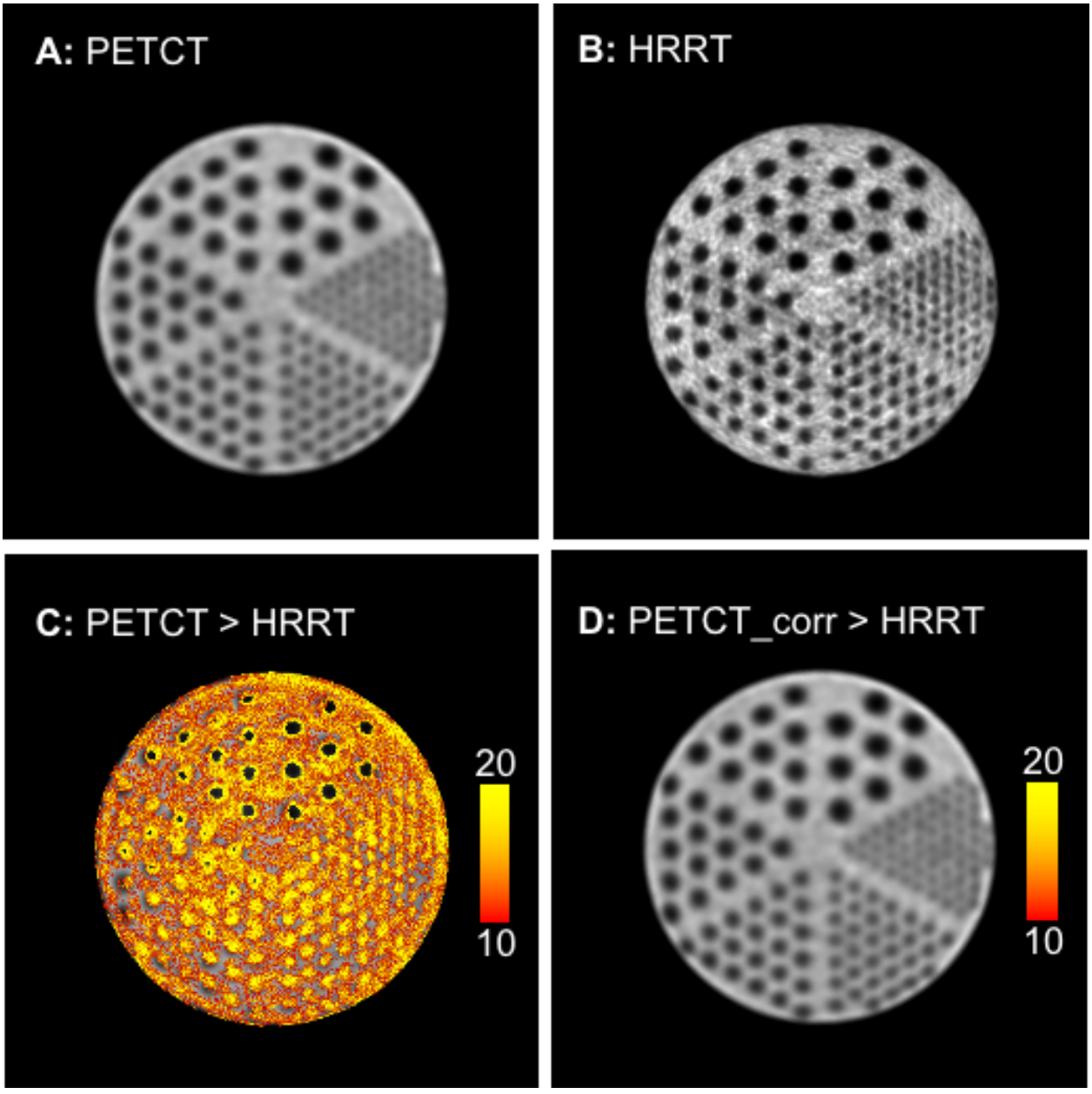


Figure S5 Accuracy of corrections for scanner differences



PETCT (A) and HRRT (B) images of a 20-cm cylindrical Jaszczak phantom filled with 1 mCi of 18F-FDG (scan duration 1 hour), each of which was used to simulate 10 different images by adding normally-distributed random noise to the voxel signal to achieve a noise to signal ratio (NSR) of 10%. The statistical overlaid on the PETCT image (C and D) reflect the difference in

relative signal intensity between simulated HRRT images and uncorrected (C) or corrected (D) PETCT images. Color bars indicate voxelwise scores (paired t-test)

Age modulates associations between physical activity and D2/3R availability

As the reference paper *"Reduced effects of age on dopamine D2 receptor levels in physically active adults"* (1) indicates different associations of physical activity with NAc D2/3R availability in younger vs. older participants, we further explored whether this can be observed in our data.

We divided our subjects into two groups: i.e., younger half (n=16, age 31.8± 5.86) and older half (n=16, age 53.0 ± 5.88). There were no significant age differences between our current study and the reference paper* in younger half (t=1.27, p=.21), while the older half in the reference paper (60.9 ± 10.46) was older than in our study (t=2.72, p=.01).

In the current study, negative associations between physical activity and D2/3R were significant in the young subjects (Self-reported exercise history r=-.705, p=.023; M10: r=-.645, p=.044) but not in the older subjects (Self-reported exercise history r=-.494, p=.147; M10: r=-.612, p=.060) while controlling for sex and BMI. Similar to the reference paper, we found that age modulated the relationship between physical activity and NAc D2/3R availability such that more physical activity was correlated with lower D2/3R availability in young but not older subjects.

However, the limited sample size restricts our ability to draw solid conclusions from these results. Of note, for the reported results in the manuscript, we controlled for age in all analyses.

**We thank authors of this paper for openly sharing their data*

References

1. Dang J, et al. Individual differences in dopamine level modulate the ego depletion effect. *International Journal of Psychophysiology* 2016;99:121–124.