Striatal Dopamine Release in Response to Morphine: A [^{11}C]-raclopride Positron Emission Tomography Study in Healthy Men

Supplemental Information

Participants

Fifteen healthy male participants who had previously received oral prescription opioid analgesics were enrolled in the current study. Subjects were included if they were healthy, based on clinical laboratory results and medical history reviewed by a physician, between the ages of 21–55 years, non-smokers or light smokers (< 15 cigarettes/week). Potential participants were excluded if they had a history of psychiatric disorders or alcohol or substance use disorders assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (1). Other exclusion criteria were: neurological disorders, medical conditions that could alter cerebral function (i.e., cardiovascular, endocrine, oncological, or autoimmune disease), current use of prescribed or over-the-counter opioid analgesics (per self-report and urine drug screen) and/or other medications known to interfere with DA transmission, and/or head trauma with loss of consciousness for more than 30 min, as assessed during the medical examination. In addition, participants were excluded if they had used opioid analgesics for > 6 weeks (lifetime), or within the 3 months prior to study enrollment. All participants completed the self-report version of the Comprehensive Psychopathology Rating Scales (CPRS-SA) (2). All the procedures were approved by the NIH Addiction Institutional Review Board and the NIH Radiation Safety Committee.

PET ScanProtocol

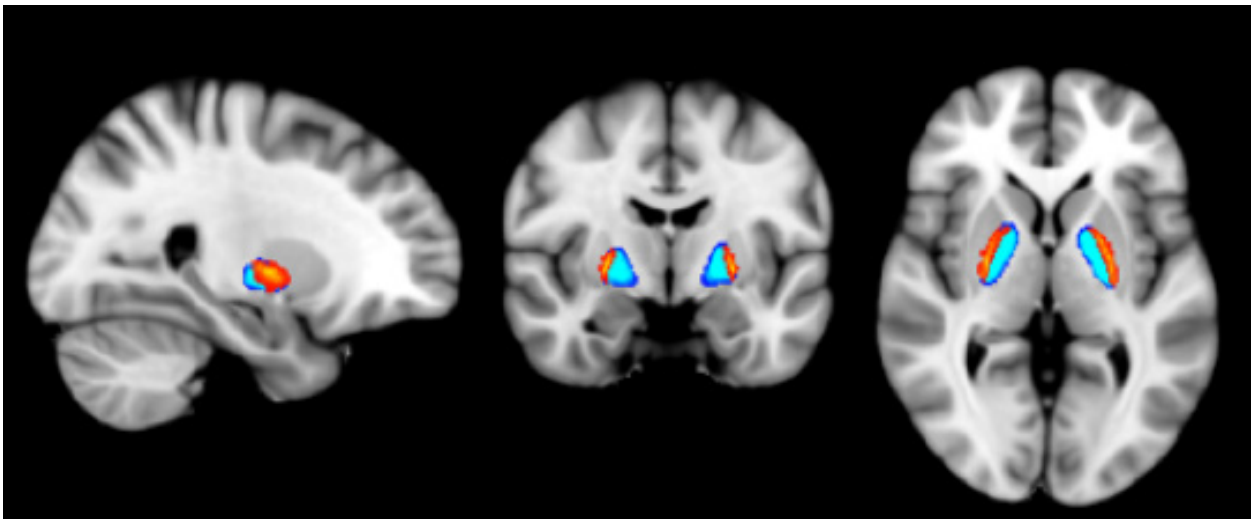
[^{11}C]-raclopride PET scans were acquired using a GE Advance Tomograph (GE, Waukesha, WI), with full-width at half-maximum [FWHM] resolution 6–7 mm, scanning 35 simultaneous slices

with 4.25-mm slice separation. An 8-min transmission scan was first acquired with 2 rotating rod sources for the purpose of attenuation correction. Then, the infusion (morphine or placebo) was initiated. At 5 min after the start of the infusion, a 12 mCi dose of [^{11}C]-raclopride was administered over 1 min into the intravenous line placed in an antecubital vein.

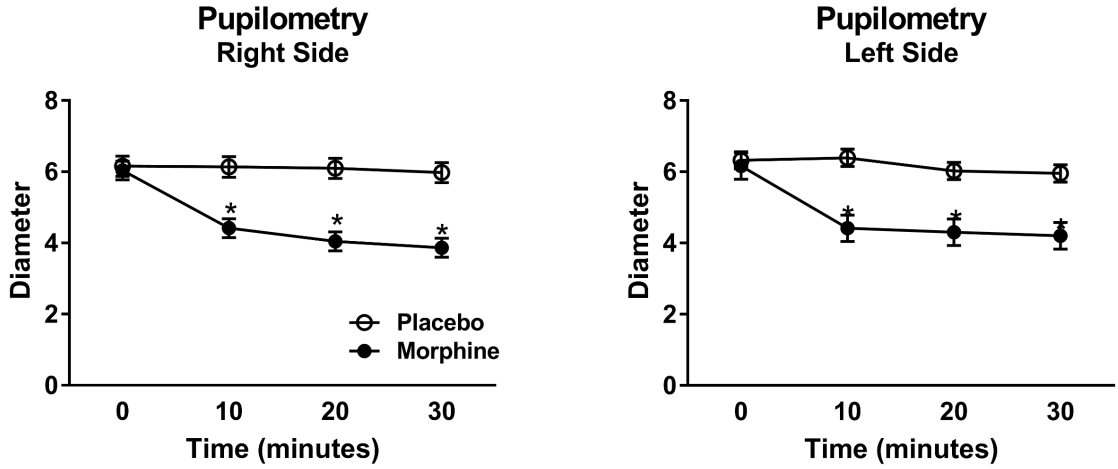
Dynamic PET scans began with the start of the [^{11}C]-raclopride injection and continued for 90 min. During the PET imaging procedures, the participants rested quietly under dim illumination and minimal acoustic noise. To ensure that participants did not fall asleep, they were monitored throughout the procedure and were asked to keep their eyes open. The PET data were PVE-corrected using the statistical parametric mapping (SPM) toolbox PETPVE12 (3) and the Müller-Gärtner approach (4).

Supplementary Table S1. Subject Characteristics (n=15)

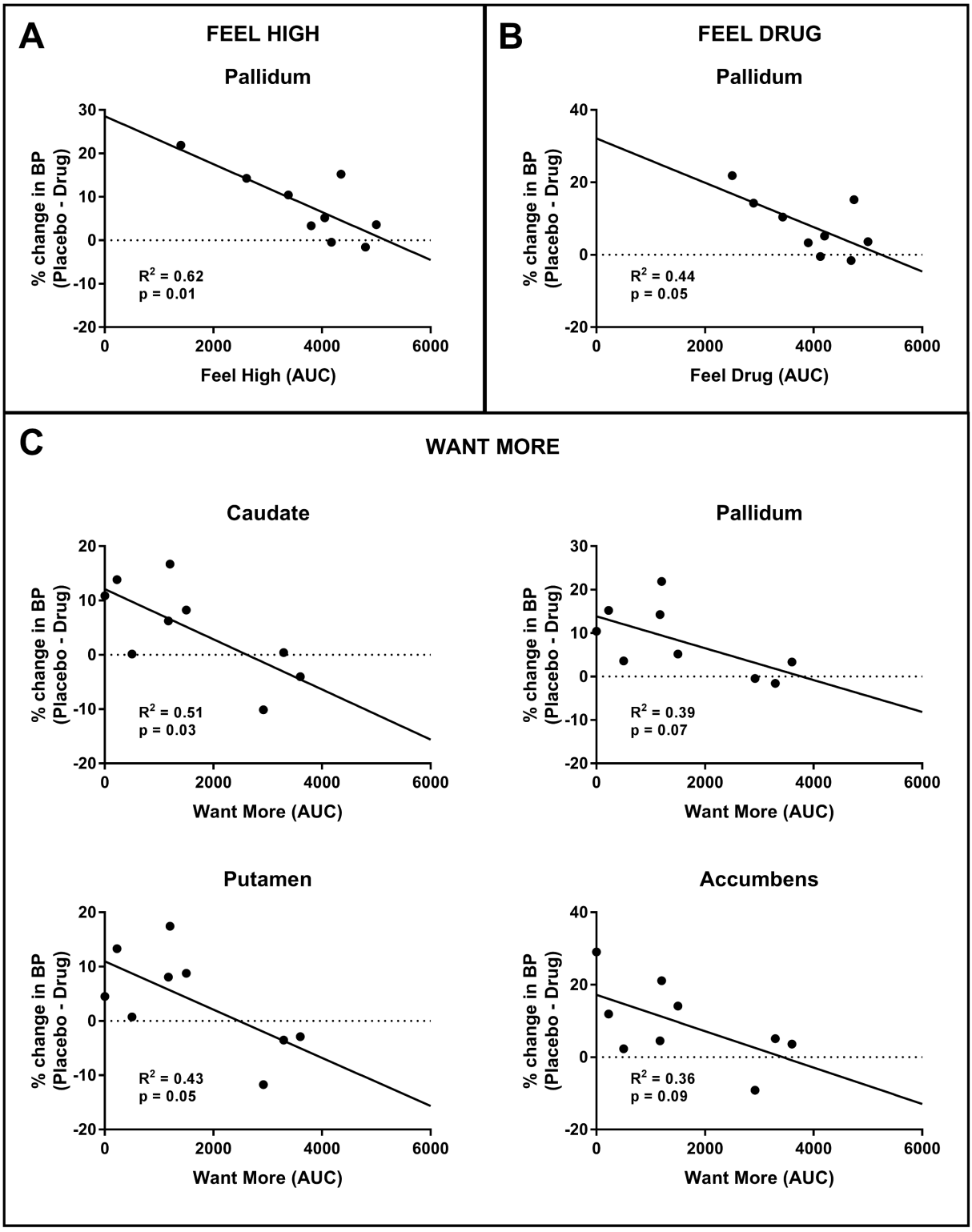
Characteristic	Mean (±SD)
Age (years)	30.2±9.4
Body Mass Index (BMI)	25.9±3.4
Ethnicity (% Caucasian)	73%
Education	13.1 (2.7)



Supplementary Figure S1. Average map of the top 10% voxels (yellow-red) overlaid on the globus pallidus ROI (blue). The voxels showing the highest BP_{ND} are localized in the external segment of the Globus Pallidus.



Supplementary Figure S2. Pupil diameter changes in response to morphine and placebo (Visit 1). Injection of morphine produced a significant decrease in pupil diameters, in both the right ($F[3,35] = 16.18$, $p<0.0001$) and the left eye ($F[3,35] = 17.98$, $p<0.0001$). Sample size: 10 healthy, non-smoking men.



Supplementary Figure S3. Correlations between the DEQ scores collected inside the scanner environment (Visit 2 and 3) and [^{11}C]-raclopride ΔBP_{ND}. A) Correlations between the DEQ 'want more' rating score and percent changes in [^{11}C]raclopride BP_{ND}. ΔBP_{ND} was negatively correlated

with self-reported drug wanting in Caudate (r^2 = 0.51; p= 0.03) and Putamen (r^2 = 0.43; p= 0.05); B) [^{11}C]-raclopride ΔBP_{ND} within the GP was inversely correlated with subjective ratings of 'high' (r^2 = 0.62; p= 0.01); C) Percent change in [^{11}C]-raclopride BP_{ND} within the GP was also negatively correlated with self-reported 'feel drug' measures (r^2 = 0.44; p= 0.05). Sample size: 9 healthy, non-smoking, right-handed men.

Supplemental References

1. First MB SR, Gibbon M (2002): *Structured Clinical Interview for DSM-IV-TR Axis I Disorders*. New York: New York: Biometrics Research, New York State Psychiatric Institute.

2. Svanborg P, Asberg M (1994): A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *Acta Psychiatr Scand*. 89:21-28.

3. Gonzalez-Escamilla G, Lange C, Teipel S, Buchert R, Grothe M, Initiative AsDN (2017): PETPVE12: an SPM toolbox for Partial Volume Effects correction in brain PET - Application to amyloid imaging with AV45-PET. *Neuroimage*. 147:669-677.

4. Müller-Gärtner HW, Links JM, Prince JL, Bryan RN, McVeigh E, Leal JP, et al. (1992): Measurement of radiotracer concentration in brain gray matter using positron emission tomography: MRI-based correction for partial volume Effects. *J Cereb Blood Flow Metab*. 12:571-583.