

Reproducibility of Repeated Measures of Endogenous Dopamine Competition with [¹¹C]Raclopride in the Human Brain in Response to Methylphenidate

Gene-Jack Wang, Nora D. Volkow, Joanna S. Fowler, Jean Logan, Naomi R. Pappas, Christopher T. Wong, Robert J. Hitzemann and Noelwah Netusil

Medical and Chemistry Departments, Brookhaven National Laboratory, Upton; Departments of Radiology and Psychiatry, State University of New York, Stony Brook; and Psychiatry Service, Veterans Affairs Medical Center, Northport, New York

The measure of changes in synaptic dopamine (DA) concentration in response to the psychostimulant drug methylphenidate (MP) has been used as an indicator of responsiveness of the DA system. The purpose of this study was to assess the reproducibility of these measures. **Methods:** Seven healthy subjects were scanned with PET and [¹¹C]raclopride twice in the same day: 7 min after placebo or methylphenidate (0.5 mg/kg) administration. In parallel we also measured the physiologic and behavioral responses to placebo and to methylphenidate. The same procedures were repeated 1–2 wk later to assess test-retest reproducibility. **Results:** Measures of plasma to brain transfer constant (K₁), striatal distribution volume (DV_{str}) and DA D₂ receptor availability (Bmax/Kd), for the placebo condition were similar for the first (E1) and second (E2) evaluations (Bmax/Kd, E1: 2.77 ± 0.44; E2: 2.97 ± 0.44). MP administration did not change K₁, but it significantly decreased DV_{str} (E1: -25.9% ± 8.7%, *P* ≤ 0.0002; E2: -20.7% ± 11.7%, *P* ≤ 0.007) and Bmax/Kd (E1: -18.4% ± 8.7%, *P* ≤ 0.002; E2: -13.4% ± 9.2%, *P* ≤ 0.008), and the magnitude of these changes, though lower for E2, did not differ significantly. MP increased pulse rate (E1: +64% ± 43%, *P* ≤ 0.002; E2: +69% ± 33%, *P* ≤ 0.001), systolic pressure (E1: +37% ± 19%, *P* ≤ 0.0006; E2: +29% ± 15%, *P* ≤ 0.0009), self reports for drug effects (0: nothing to 10: extreme) of "rush" (E1: +8 ± 3, *P* ≤ 0.0004; E2: +6 ± 4, *P* ≤ 0.01) and "high" (E1: +8 ± 3, *P* ≤ 0.0001, E2: +8 ± 3, *P* ≤ 0.0003), anxiety (E1: +5 ± 4, *P* ≤ 0.02; E2: +4 ± 4, *P* = 0.1) and restlessness (E1: +4 ± 4, *P* ≤ 0.04; E2: +4 ± 5, *P* = 0.1). The magnitude of the cardiovascular and behavioral effects did not differ between E1 and E2. **Conclusion:** MP-induced changes in striatal DV and in Bmax/Kd, as well as the behavioral and cardiovascular effects, were reproducible with repeated administration.

Key Words: [¹¹C]raclopride; methylphenidate; pharmacologic challenge; PET; reproducibility

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Measures of dopamine (DA) D₂ receptors using PET and [¹¹C]raclopride have been used to assess neuropsychiatric disorders such as schizophrenia (1–4), Parkinson's disease (5–11), Huntington's disease (12), Wilson's disease (13), manganese intoxication (14,15), cocaine abuse (16), alcoholism (17,18) and opiate dependence (19), as well as during aging (20–23). These measures have also been performed to assess the progress of disease (24,25), which is feasible because repeated measures of [¹¹C]raclopride binding in the human brain are highly reproducible (26–29).

[¹¹C]raclopride-PET has also been used to assess levels of DA D₂ receptor occupancies by different doses of typical and atypical antipsychotics and to assess the relation between levels of occupancy and therapeutic effectiveness and side effects (30). Because raclopride is sensitive to competition with endogenous DA (31), due to its relatively low affinity for DA D₂ receptor, [¹¹C]raclopride has also been used to assess relative changes in synaptic DA induced by psychostimulant drugs. Drug-induced changes in [¹¹C]raclopride striatal binding are interpreted as reflecting changes induced by DA occupancy of D₂ receptors secondary to the changes in DA synaptic concentration (32–34). This measure has been used as an indication of the responsiveness of the DA system to pharmacologic challenge. With this strategy, a recent study showed decreased DA responsivity in cocaine abusers when compared with controls, consistent with decreased DA release during cocaine detoxification (16). In contrast, studies in schizophrenic patients have documented an enhanced DA response to psychostimulants when compared with healthy controls (4,35). Furthermore, in these studies the magnitude of the increase in DA concentration induced by the psychostimulant was significantly correlated with the increase in positive psychotic symptoms; corroborating the importance of DA in this disorder. Because this strategy may be useful in monitoring disease progression and/or response to treatment, it is important to evaluate the

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For correspondence or reprints contact: Gene-Jack Wang, MD, Medical Department, Brookhaven National Laboratory, Upton, NY 11973.

reproducibility of this measurement under test-retest conditions.

This study assesses the reproducibility of measurement of endogenous DA competition in human brain with [¹¹C]raclopride using methylphenidate (MP) as the pharmacological agent in seven subjects who were tested twice, 1–2 wk apart. MP is a psychostimulant drug that raises synaptic DA concentration by blocking DA transporters and is used for the treatment of attention deficit hyperactivity disorder (36–38).

MATERIALS AND METHODS

Subjects

Seven healthy subjects (two women, five men; mean age 31.4 ± 7.9 y, age range 24–42 y) without medical or neuropsychiatric illnesses were selected for the study. Subjects with past and present usage of alcohol or drugs (except for caffeine and cigarettes) were excluded from the studies. Prescan urinalysis ensured absence of psychoactive drug use. Subjects were instructed to discontinue any over-the-counter medication 1 wk before the scan. Informed consent was obtained from each participant after the nature of the experiment was fully explained. Studies were approved by the Investigational Review Board at Brookhaven National Laboratory.

Experimental Design

Two sets of identical studies were performed 1–2 wk apart in each subject. Each set consisted of two PET scans performed on the same day with [¹¹C]raclopride. In the first scan, subjects were injected with a placebo (3 mL saline solution) given 7 min before [¹¹C]raclopride. In the second scan, subjects were injected with MP (0.5 mg/kg) given 7 min before [¹¹C]raclopride. The subjects were unaware of the drug received. MP concentration in plasma was measured before and 27 and 67 min after MP administration with high-performance liquid chromatography (HPLC) performed at the National Psychopharmacology Laboratory.

PET Scanning

For five of the subjects (subjects 1–5), PET scans were performed with a CTI-931 (Computer Technologies, Inc., Knoxville, TN) tomograph (resolution 6 × 6 × 6.5 mm full width at half maximum [FWHM], 15 slices). Procedures for subjects' positioning, scanning protocol and arterial blood sampling for the CTI-931 were described previously (27). For two of the subjects (subjects 6 and 7), PET scans were performed with a Siemens HR⁺ tomograph (resolution 3 × 3 × 3 mm FWHM, 63 slices). To ensure accurate repositioning of subjects for the repeated scans, an individually molded headholder was made for each subject. The head of the subject was then positioned in the gantry with the aid of two orthogonal laser lines, one placed at the corner of the canthus and the other parallel to the sagittal plane. Scanning protocol and arterial blood sampling procedures were the same for the scans performed with the Siemens HR⁺ PET and with the CTI-931 PET. Briefly, a series of 20 emission scans (scans were taken every minute for the first 10 min and then ten 5-min scans were taken for the next 50 min) were obtained from the time of injection up to 60 min after intravenous injection of 148–296 MBq (4–8 mCi) [¹¹C]raclopride. Quantitation of [¹¹C]raclopride in plasma was performed as described previously (27).

Cardiovascular Assessment

Electrocardiographic recording, blood pressure and pulse rate were obtained every 15 min for 30 min before injection of saline or MP and then at 2, 4, 6, 8, 10, 15, 20, 30, 40 and 67 min after administration.

Behavioral and Cognitive Evaluation

Before placebo or MP and at 27 and 67 min after placebo or MP administration, subjects were asked to evaluate on an analog scale rated from 0 (felt nothing) to 10 (felt extremely) their subjective perception of alertness, annoyance, depression, distrustful thought (perception that others are trying to cause harm), happiness, hunger, mood (defined as a contrast between being depressed and being happy), sexual desire, stimulation, talkativeness, tiredness, desire to use MP and loss of control over MP use. The subjective experiences of rush, high (defined as euphoria), anxiety and restlessness (defined as the need to move) were also recorded every minute for 20 min, as well as 25, 30, 45 and 67 min after drug injection.

Image Analysis

For images obtained with the CTI-931 PET scanner, regions of interest (ROIs) in striatum and cerebellum were drawn directly on an averaged emission image (summation of images obtained between 10–60 min) as described previously (19). ROIs for striatum were obtained bilaterally from the planes where they were best identified (two slices). Right and left cerebellar regions (two slices) were obtained in the two planes 1.0 and 1.7 cm above the canthomeatal line. Images obtained with the Siemens HR⁺ scanner were resliced parallel to the line between the anterior and the posterior commissures (AC-PC line). To increase the signal on each plane, we summed contiguous planes, which gave images with a 4.8 mm FWHM rather than the 2.4 mm FWHM from the original planes. ROIs in striatum and cerebellum were drawn directly on the averaged emission images (summation of images obtained between 10–60 min). ROIs for striatum (three slices) were obtained bilaterally from the planes where they were best identified. Right and left cerebellar regions (three slices) were obtained in the three planes 1.0 and 1.7 cm below the AC-PC lines. These regions were then projected into the dynamic images to generate time-activity curves for striatum and cerebellum. Values for the striatal and cerebellar regions were computed by using the weighted average from the different slices where the regions were obtained. The time-activity curves for tissue concentration, along with the time-activity curves for unchanged tracer in plasma, were used to calculate the distribution volume (DV) and the blood-to-tissue transport constant (K1) in striatum and cerebellum using a graphical analyses technique for reversible systems (39). The D₂ receptor availability was quantified with the ratio of the DV in striatum to that in cerebellum, which corresponds to $B_{max}/K_d' + 1$ (39).

Statistical Analysis

Comparison for measures of K1, DV and B_{max}/K_d at placebo between the first and the second evaluation and between the placebo and the MP condition were evaluated with repeated analysis of variance (ANOVA). Comparisons of MP-induced changes in B_{max}/K_d (placebo-MP) between the first and the second evaluation were tested with repeated ANOVA. Comparison between the plasma MP concentration, the cardiovascular and the behavioral effects were tested with repeated ANOVA. For the behavioral measures for which we obtained a complete time response (high, rush, anxiety and restlessness), we compared MP-induced changes (placebo-MP) in peak effects as well as in the

TABLE 1
Subject Data, K1, DV in Cerebellum and Striatum, Striatal [¹¹C]Raclopride Binding (Bmax/Kd) After Placebo in First and Second Evaluations as Well as Percentage Change of Bmax/Kd

Subject no.	Age (y)	Sex	Evaluation	Cerebellum		Striatum		Striatal Bmax/Kd	Percentage change Bmax/Kd
				K1	DV	K1	DV		
1	25	M	1	0.060	0.686	0.144	2.521	2.677	-6.6%
			2	0.077	0.666	0.152	2.566		
2	31	M	1	0.075	0.534	0.113	1.791	2.354	-15.7%
			2	0.055	0.493	0.118	1.835		
3	24	M	1	0.071	0.517	0.116	2.006	2.878	+6.9%
			2	0.075	0.531	0.135	1.954		
4	32	M	1	0.053	0.486	0.111	2.080	3.280	-10.5%
			2	0.071	0.380	0.107	1.755		
5	42	M	1	0.058	0.607	0.128	2.088	2.442	-13.7%
			2	0.061	0.466	0.113	1.761		
6	42	F	1	0.053	0.682	0.102	2.281	2.344	-9.4%
			2	0.056	0.479	0.101	1.708		
7	24	F	1	0.065	0.421	0.115	1.855	3.404	-5.5%
			2	0.069	0.454	0.111	2.085		

K1 = plasma to brain transfer constant (mL/min/g); DV = distribution volume (mL/g).
Percentage change of Bmax/Kd is (first evaluation minus second evaluation) minus first evaluation times 100.

area under the curve (AUC) for the time points between 0 and 20 min after drug administration between the first and the second evaluations. For the measures for which we obtained only three time points (baseline, MP 27 and MP 67 min), we compared the three measurements between the first and the second evaluations using a 2 within (experiment and drug) repeated ANOVA design. For the cardiovascular effects, we averaged the measurements obtained between baseline and 20 min after MP administration, which was the period when we observed peak effects, and then compared MP-induced changes in these measurements (placebo-MP) between the first and the second evaluations.

RESULTS

Measurements of Bmax/Kd after placebo did not differ between the first (E1) and second (E2) evaluations (E1:

2.77 ± 0.44; E2: 2.97 ± 0.44; Table 1). Administration of MP did not change the plasma-to-brain transfer constant (K1) in striatum or cerebellum; however, MP significantly decreased the DV in cerebellum (DV_{cb}; E1: -14.3% ± 7%, P ≤ 0.005; E2: -12% ± 9.8%, P ≤ 0.03), in striatum (DV_{sr}; E1: -25.9% ± 8.7%, P ≤ 0.0002; E2: -20.7% ± 11.7%, P ≤ 0.007) and Bmax/Kd estimates in striatum (E1: -18.4% ± 8.7%, P ≤ 0.002; E2: -13.4% ± 9.2%; P ≤ 0.008) in the first and in the second evaluations (Table 2). The magnitude of MP-induced decrements in striatal DV and in Bmax/Kd did not differ between the first and second evaluations (DV_{cb}: P = 0.7; DV_{sr}: P = 0.41; Bmax/Kd: P = 0.11; Fig. 1).

The concentration of MP in plasma did not differ significantly for both evaluations and corresponded to 122 ± 23.4

TABLE 2
Percentage Change After Methylphenidate Injection (Methylphenidate-Placebo/Placebo) of K1, DV of Striatum and Cerebellum as Well as Striatal [¹¹C]Raclopride Binding (Bmax/Kd) in First and Second Evaluations

Subject no.	First evaluation					Second evaluation				
	Cerebellum		Striatum		Striatal Bmax/Kd	Cerebellum		Striatum		Striatal Bmax/Kd
	K1	DV	K1	DV		K1	DV	K1	DV	
1	-35.0	-12.0	-44.8	-14.9	-4.7	-18.2	-26.7	-15.8	-32.7	-11.0
2	+8.0	-9.0	+25.0	-28.8	-31.1	+27.3	-19.1	-18.7	-36.7	-29.8
3	-12.7	-3.9	-33.8	-13.4	-13.4	+1.3	-13.2	-7.8	-13.7	-1.0
4	+32.1	-19.3	-13.1	-34.9	-25.3	-25.4	-4.5	-22.5	-15.1	-14.3
5	+20.7	-12.2	-12.1	-24.4	-19.7	+9.8	-5.8	-16.9	-10.5	-6.6
6	+69.8	-26.3	+20.7	-33.4	-13.9	+30.4	+1.7	+4.0	-7.4	-12.4
7	+7.7	-17.8	-10.0	-31.3	-21.0	+29.0	-16.5	+5.0	-28.7	-18.6
Mean	+12.9	-14.3	-9.7	-25.9	-18.4	+7.8	-12.0	-10.4	-20.7	-13.4
SD	33.3	7.4	25.7	8.7	8.7	22.9	9.8	11.1	11.7	9.2

K1 = plasma to brain transfer constant (mL/min/g); DV = distribution volume (mL/g).

FIGURE 1. Distribution volume images of [¹¹C]raclopride PET studies in healthy subject at level of basal ganglia (right images) and cerebellum (left images) for first evaluation (study 1) with placebo (baseline), first evaluation with methylphenidate, second evaluation (study 2) with placebo and second evaluation with methylphenidate. Images for both evaluations are scaled with respect to maximum value obtained on placebo condition of first evaluation and presented using rainbow scale in which red represents highest value (2 mL/g) and dark violet represents lowest value.

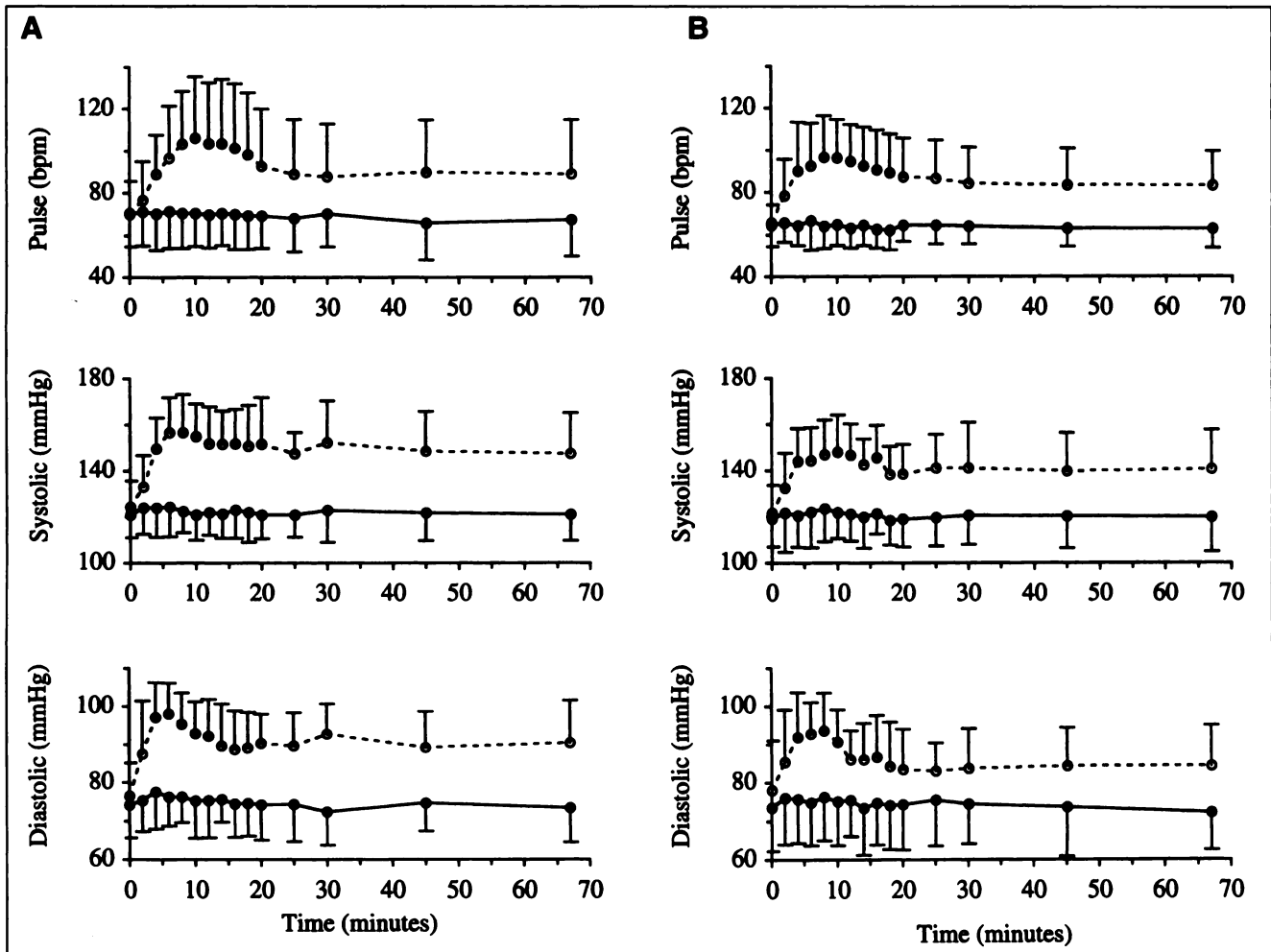
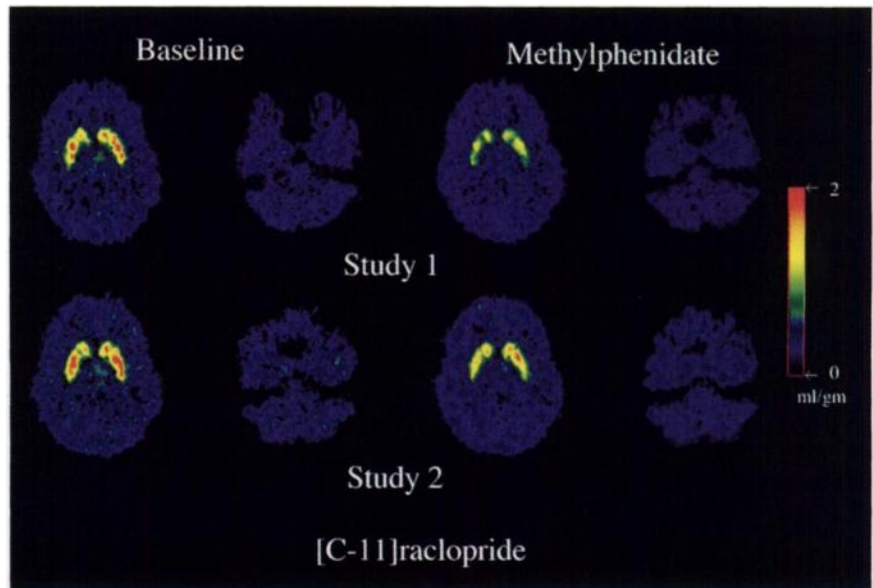


FIGURE 2. Averaged measures of blood pressure and pulse rate before and after intravenous injection of placebo (●) and methylphenidate (○) in first (A) and second (B) evaluations.

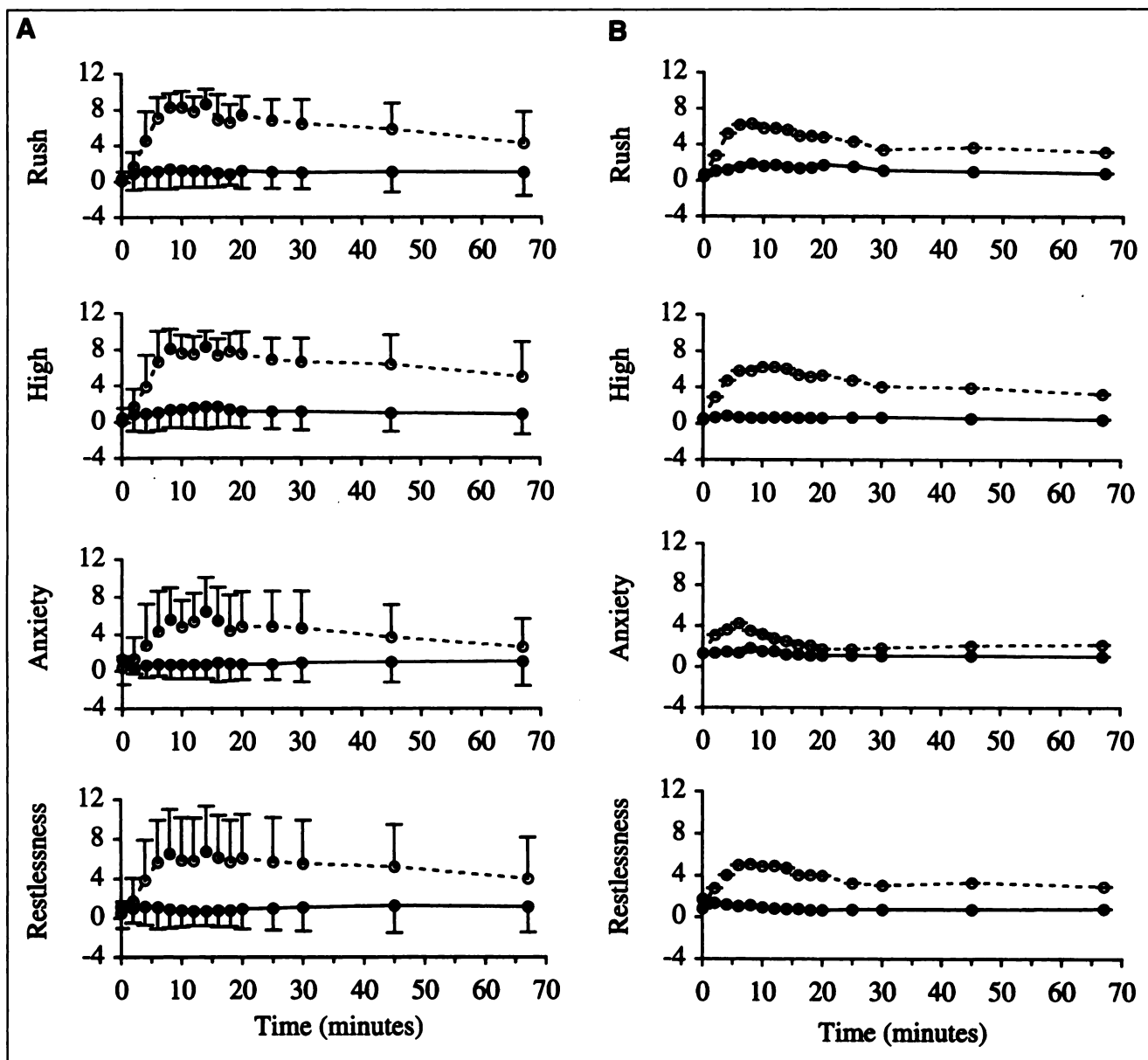


FIGURE 3. Self-reports of drug effects (0 = nothing to 10 = extreme) for rush, high, anxiety and restlessness before and after intravenous injection of placebo (●) and methylphenidate (○) in the first (A) and second (B) evaluations.

and 135.9 ± 23.1 ng/mL at 27 min and to 71.6 ± 14.6 and 79.9 ± 19.3 ng/mL at 67 min after MP administration.

MP significantly increased pulse rate ([PR] E1: $+64\% \pm 43\%$, $P \leq 0.002$; E2: $+69\% \pm 33\%$, $P \leq 0.001$), systolic

pressure ([SP] E1: $+37\% \pm 19\%$, $P \leq 0.0006$; E2: $+29\% \pm 15\%$, $P \leq 0.0009$) and diastolic blood pressure ([DP] E1: $+38\% \pm 17\%$, $P \leq 0.0002$; E2: $+34\% \pm 21\%$, $P \leq 0.0008$) (Fig. 2). The magnitude of the cardiovascular effects did not

TABLE 3
Published Reports of Percentage Change of Striatum-to-Cerebellum Ratio for [^{11}C]Raclopride Uptake for Test-Retest Studies

Reference	Age (mean y)	Age (range y)	Sex	Percentage changes (mean)	Percentage change (range)
Nordstrom et al. (26)	27.3	19–36	6M, 4F	1.2%	–10.8% to +12.0%
Volkow et al. (27)	—	21–46	5M	0.4%	–8.1% to +6.7%
Schlosser et al. (28)	48.1	24–75	5M, 3F	–0.3%	–12.7% to +12.2%
Breier et al. (29)	32.5	—	5M, 1F	1.9%	–4% to +6%
Wang et al. (reported here)	31.4	24–42	5M, 2F	–5.6%	–11.0% to +5.2%

differ between the first and second evaluations (PR: $P = 0.95$; SP: $P = 0.1$; DP: $P = 0.2$).

MP increased the subjective perception of rush (E1: $+7 \pm 3$, $P \leq 0.0004$; E2: $+5 \pm 4$, $P \leq 0.01$) and high (E1: $+7 \pm 2$, $P \leq 0.0001$; E2: $+7 \pm 3$, $P \leq 0.0003$), anxiety (E1: $+5 \pm 4$, $P \leq 0.02$; E2: $+4 \pm 4$, $P = 0.1$) and restlessness (E1: $+4 \pm 4$, $P \leq 0.04$; E2: $+4 \pm 5$, $P = 0.1$) (Fig. 3). The peak effects for these behavioral changes did not differ between evaluations. However, a comparison of the AUC revealed that, although MP-induced effects in high and restlessness were comparable for both evaluations, they were significantly lower for the second than for the first evaluation for self-reports of rush (E1: 112 ± 27 ; E2: 75 ± 34 ; $F = 6$; $df 1.13$; $P < 0.05$) and of anxiety (E1: 75 ± 55 ; E2: 30 ± 51 ; $F = 16$; $df 1.13$; $P < 0.007$).

In addition, MP decreased tiredness (drug effect $F = 5.3$; $df 2.12$; $P \leq 0.02$), increased talkativeness (drug effect $F = 13$; $df 2.12$; $P \leq 0.001$) and made subjects feel more stimulated ($F = 15$; $df 2.12$; $P \leq 0.0005$) (data not shown). None of the drug by experiment effects were significant, indicating that these behavioral effects did not differ between the first and the second evaluations.

DISCUSSION

This study shows that decreases in striatal [^{11}C]raclopride binding induced by acute MP administration are reproducible in a given subject when tested at a 1- to 2-wk interval. They also show that the behavioral and cardiovascular effects induced by MP (except for rush and anxiety) were also highly reproducible.

After initial MP administration, the subjects reported significant increase in rush, high, anxiety and restlessness. They also reported feeling stimulated, talkative and less tired. These behavioral effects are compatible with those previously reported after intravenous administration of MP (33).

The only behavioral effects that differed between evaluations were the changes in anxiety and rush, which were lower in the second than in the first evaluation. The decrease in anxiety could reflect the fact that the anxiety associated with the novelty of the experimental procedure differed between the first and second evaluations. The reason for the lower rush in the second evaluation is unclear, but could reflect a decrease in sympathetic tone, which could also have contributed to the decrease in anxiety during the second evaluation.

For this study, the average change in B_{max}/K_d corresponded to $-18.4\% \pm 8.7\%$ for the first evaluation and to $-13.4\% \pm 9.2\%$ for the second evaluation. These values are similar to those obtained in a separate group of subjects in whom we reported an average of $-23\% \pm 15\%$ change (33). In that study we also showed that the magnitude of the changes decreased as a function of age. The similar values obtained in both studies, which were performed in control subjects of equivalent ages, indicate that MP-induced changes in DA are also reproducible across groups of control

subjects. Although this study included men and women, the sample size was too small to assess gender differences in DA responses to psychostimulants. Further studies are required to assess whether there are differences in DA responses to psychostimulants throughout the menstrual cycle.

Although not significant, the changes in DA responsivity in the second evaluation tended to be smaller than those during the first evaluation. A possible explanation could be that the novelty component, which has been shown to affect drug responses (40,41), accounts for the differences between the first and second evaluations. Further studies are required to evaluate the effects of novelty in psychostimulant induced DA changes.

Finally, this study also replicates previous studies (Table 3) that have shown that measures of DA D_2 receptor availability under baseline conditions as assessed with [^{11}C]raclopride are highly reproducible (26–29).

CONCLUSION

This study demonstrates that measures of striatal DA changes induced by MP with [^{11}C]raclopride and PET are reproducible. It also showed high reproducibility for most of the behavioral and cardiovascular effects of MP under the PET experimental conditions.

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