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Reliability of Striatal [^{11}C]Raclopride Binding in Smokers Wearing Transdermal Nicotine Patches

Karmen K. Yoder[1,2,3], **Daniel S. Albrecht**[1,2,3], **David A. Kareken**[1,2,3,4,5], **Lauren M. Federici**[1,2,3], **Kevin M. Perry**[1,2], **Elizabeth A. Patton**[1,2], **Qi-Huang Zheng**[1,2], **Bruce H. Mock**[1,2], **Sean J. O'Connor**[5], and **Christine M. Herring**[1,2]

[1]Indiana University Center for Neuroimaging, Indiana University School of Medicine, Indianapolis, IN USA

[2]Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN USA

[3]Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN USA

[4]Department of Neurology, Indiana University School of Medicine, Indianapolis, IN USA

[5]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN USA

Abstract

Purpose—In studies where [^{11}C]raclopride (RAC) PET is used to assess changes in striatal dopamine, it is important to control for cognitive states, such as drug craving, that could alter dopamine levels. In cigarette-smokers, transdermal nicotine patches (TNP) can control nicotine craving, but the effects of nicotine patches on RAC binding are unknown. Thus, we sought to determine the test-retest reliability of RAC binding in the presence of nicotine patches.

Methods—Eleven male smokers were scanned twice with RAC on separate days while wearing transdermal nicotine patches.

Results—Across the striatum, test-retest variability was 7.63 ± 5.88; percent change in binding potential was 1.11 ± 9.83; and the intraclass correlation coefficient was 0.91 ($p < 0.0001$).

Conclusions—Baseline RAC binding is highly reproducible in smokers wearing nicotine patches. This suggests that transdermal nicotine patches are an acceptable method for controlling cigarette craving during studies that utilize RAC to examine changes in dopamine.

Keywords

transdermal nicotine patch; dopamine; D_2 receptor; [^{11}C]raclopride; positron emission tomography; test-retest variability

First/Corresponding Author: Karmen K. Yoder, Ph.D., Assistant Professor of Radiology & Imaging Sciences, R2, E124, 950 W. Walnut St., Indianapolis, IN 46202, p: 317.278.9840, f: 317.274.1067, kkyoder@iupui.edu.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Introduction

It is possible to assess *in vivo* changes in relative dopamine levels with PET and dopaminergic radioligands that are sensitive to alterations in endogenous dopamine concentration [1–4] (e.g., [^{11}C]raclopride, [^{18}F]fallypride, and [^{11}C]FLB). The goal of such studies is the comparison of dopamine D_2 receptor availability during a test condition relative to a baseline or resting condition, with the difference in D_2 signal between these two states attributed to changes in dopamine levels. There are many types of challenge paradigms (cognitive, motor, pharmacologic), methods of PET acquisition (single-bolus, bolus-plus-infusion) and study designs (one or two scans). Regardless of the scientific question being asked, or the particulars of the methodological approach, all experiments share a critical assumption: *within* subjects, the baseline state represents a stable comparator for the challenge condition [2, 5]. Unfortunately, this assumption can be easily violated by transient changes in cognitive states that may alter dopamine [1–2, 5]. When possible, it would be desirable to control internal states that may contribute to confounding measurements of D_2 availability.

Several studies indicate that the internal state of drug craving is related to striatal dopamine levels [6–10]. For example, both Volkow et al. [6] and Wong et al. [7] presented cocaine users with cocaine-related cues, and found that cue-induced striatal dopamine release correlated with self-reported cue-induced craving. This evidence strongly supports the concept that increases in striatal dopamine levels are related to drug craving. In 2004, Heinz and colleagues [10] reported decreased D_2 availability in the ventral striatum was negatively correlated with alcohol craving severity. It is reasonable to view lower D_2 availability as a function of higher dopamine levels, and therefore this report is consistent with the idea that higher dopamine concentration may be associated with drug craving. On the other hand, Brody et al. [8–9] reported that smoking-induced reductions in BP_{ND} were associated with *decreased* craving for cigarettes, and proposed that increases in dopamine alleviate cigarette craving. In this case, however, the presence of chemosensory sensations and habitual motor routines of cigarette smoking may have increased DA independently of craving. Thus, in studies of populations with high rates of cigarette smoking, differences in nicotine withdrawal, and hence, craving between scan states present a serious challenge for data interpretation. Although transdermal nicotine patches could be used to control nicotine craving in smokers, it is not known whether stable baseline measurements of D_2 availability are possible with nicotine patches. Therefore, the purpose of this study was to determine the reliability of striatal [^{11}C]raclopride binding in the presence of transdermal nicotine patches in nicotine-dependent cigarette smokers.

Materials and Methods

All procedures were approved by the Indiana University Institutional Review Board, and performed in accordance with the ethical standards of the Belmont Report (United States Department of Health and Human Services, 1979). All subjects signed informed consent statements agreeing to participate in the study. Subjects were right-handed, social drinking male smokers who were in otherwise good physical and mental health. The absence of either alcohol abuse or dependence was confirmed by the Semi-Structured Assessment for the

Genetics of Alcoholism [11]. Subjects were excluded from participation if they endorsed recreational use of legal or illicit stimulants, painkillers, or sedatives, and/or consumption of > 1 marijuana cigarette (or equivalent) per week. Subject demographics are presented in Table 1. Nicotine dependence was assessed with the Fagerstrom Test for Nicotine Dependence [12].

Study Procedures

Procedures in this study are similar to those described previously [13]. Subjects underwent identical procedures on two separate days. Figure 1 illustrates the general timeline. Briefly, subjects presented to the Indiana Clinical Research Center at approximately 8 a.m. Shortly after arrival, an IV catheter was placed in an antecubital vein, and a transdermal nicotine patch was placed on the upper arm of each subject. Patch dose was based on subjects' self-report of cigarettes smoked per day (14 mg dose with 10 < 20 cigarettes per day; 21 mg dose with > 20 cigarettes). Two subjects were given a 14 mg patch; all others received a 21 mg patch. Subjects were given a full breakfast. As part of another study protocol, the morning of each study day, subjects received an IV alcohol infusion to a target breath alcohol concentration (BrAC) of 60 mg% using the Alcohol Clamp. The rationale and implementation of the alcohol clamping technique have been described in detail elsewhere [14–15]. The BrAC of all subjects returned to 0mg% prior to scanning. The Cigarette Withdrawal Scale (CWS) [16], a self-report Likert rating scale, was given periodically throughout each study day. Nicotine craving was measured with the second dimension on the CWS, which specifically captures the individual's current subjective state of cigarette craving. There are 4 questions on this dimension, each with a 5-point scale; possible scores for cigarette craving range from 4 – 20. Ratings were taken upon arrival for the study (Time 1), and before and after the resting (baseline) scan (Times 2 and 3). Eleven subjects completed both baseline RAC scans; a twelfth subject voluntarily withdrew from the study after the first RAC scan.

Scanning and Reconstruction Procedures

A magnetization prepared rapid gradient echo (MP-RAGE) magnetic resonance image (MRI) was acquired on all subjects using a Siemens 3T Trio for anatomic co-registration of PET data (see "Image Processing Procedures").

Subjects received two baseline [^{11}C]raclopride (RAC) scans in the early afternoon on two separate days. Time of injection was typically between 14:00 and 15:00. Breath alcohol concentration was 0mg% prior to scanning. The time between the end of the morning alcohol infusion and the baseline RAC scan was typically ~ 4 hours. RAC synthesis was completed as described previously [17]. RAC PET scans were acquired on a Siemens EXACT HR+ (3D mode; septa retracted). Prior to each PET scan, a 10-min transmission scan using three internal rod sources was acquired for attenuation correction. RAC PET scans were initiated with the IV infusion of 535 ± 45.4 MBq [^{11}C]RAC (mass dose: 0.13 ± 0.06 nmol/kg) over 1.5 min. Dynamic acquisition occurred for 50 min (time frames: 10 × 30s, 45 × 60s). Dynamic PET images were generated using Siemens Fourier Rebinning (FORE) and filtered backprojection algorithms including corrections for attenuation, randoms, scatter, and deadtime.

Image Processing Procedures

Image processing is similar to that described previously [13, 18]. MRI DICOM and RAC PET images were converted to Neuroimaging Informatics Technology Initiative (NIfTI) format (http://nifti.nimh.nih.gov/) using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). For each subject, dynamic PET data were co-registered to an early-time mean image to facilitate motion correction. The early mean PET image was co-registered to the MRI scan using the normalized mutual information algorithm in SPM5, with the transformation matrix from this co-registration subsequently applied to the motion-corrected dynamic PET data. Each subject's MRI was spatially normalized to Montreal Neurological Institute (MNI) space. The transformation matrix obtained from the spatial normalization step was then applied to the motion-corrected, MRI-registered PET data from each subject.

All regions of interest (ROIs) were drawn on an average normalized MRI from all subjects, using MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/). Striatal regions of interest (ROIs) consisted of the left and right ventral striatum, pre-commissural dorsal caudate, pre-commissural dorsal putamen, post-commissural caudate, and post-commissural putamen, and were drawn according to specific anatomic landmarks [19–20]. For the reference region (tissue that contains little to no D_2/D_3 receptor density), an ROI was created that contained all cerebellar gray matter except for the vermis. Time-activity curves for each ROI were generated from the dynamic RAC data using the MarsBaR toolbox for SPM5 (http://marsbar.sourceforge.net/). For each striatal ROI, D_2/D_3 receptor availability was indexed with BP_{ND}, the binding potential of [^{11}C]raclopride calculated as bound tracer concentration relative to nondisplaceable tracer concentration [21]. Estimations of BP_{ND} were conducted using the multilinear reference tissue model (MRTM) [22].

Metrics of Test-Retest Reproducibility of Baseline RAC binding

The relative reproducibility of striatal BP_{ND} between Day 1 and Day 2 was examined with three calculations, test-retest variability (TRV) to assess relative variation in BP_{ND} between days as a function of the overall average BP_{ND} across days, percent change in BP_{ND} (ΔBP_{ND}) as a qualitative descriptor of differences in BP_{ND} between Day 1 and Day 2, and the intraclass correlation coefficient (ICC, one-way random effects model; as implemented in the PASW statistical package [23–24]), a metric of similarity between measurements on each day. TRV was calculated as: $|BP_{day1} - BP_{day2}|/[(BP_{day1} + BP_{day2})/2]$ [25–26]. ΔBP between Day 1 and Day 2 was calculated as: $[(BP_{day1} - BP_{day2})/BP_{day1}] \times 100$. Paired *t*-tests were used to determine if striatal BP_{ND} was significantly different between scan days.

Other Statistical Tests

Independent *t*-tests were used to test for differences in injected radioactivity and injected mass dose between scan days. To examine the stability of cigarette craving (CWS dimension 2 score), repeated-measures ANOVA (2 days × 3 time points) was used to test for effects of scan day, time point, and day*time point.

Results

RAC Scan Parameters

Average number of days between scans was 11.7 ± 25.2 (range: 1 – 83 days). Injected radioactivity of RAC on Day 1 and Day 2 was 537 ± 54.7 and 533 ± 36.5 MBq, respectively. Corresponding mass doses were 0.13 ± 0.05 and 0.13 ± 0.06 nmol/kg. Injected radioactivity and mass doses were not significantly different between scan days.

Subject Data

The demographic characteristics of the subjects are shown in Table 1. Eight subjects reported smoking a full pack of cigarettes per day; two reported a half-pack, and one reported two packs per day. Three subjects tested positive for marijuana on both scan days; these subjects endorsed sporadic recreational use of marijuana within the previous month. One subject tested positive for opiates on Day 2 (subject had undergone a dental procedure, and reported taking a single tablet of acetaminophen and No. 3 codeine phosphate two days prior). Two of these subjects had test-retest variability for striatal RAC binding well within 1 s.d. of the sample average (7.6 ± 5.9%; Table 2); the other was within 1.5 s.d. of the mean TRV.

Exact timing of patch placement was not available for one subject on Day 1. Across the remaining data points (n = 21), the interval between patch placement and resting scan was 5.9 ± 0.9 hours. Ratings for the CWS were unavailable for one subject at both Day 1-Time 2 and Day 2-Time 3; for one subject at Day 2- Time 2; and for one subject at Day 2-Time 3. Cigarette craving scores are presented in Figure 1. Repeated-measures ANOVA indicated that the CWS rating was stable within subjects, i.e., there were no main effects of day or timepoint, and no day*timepoint interaction.

Test-Retest Reproducibility of Resting RAC Signal

BP_{ND} values for both scan days, percent change of BP_{ND} between days (%Δ), the test-retest variability (TRV), and intra-class correlation coefficients (ICC) are presented in Table 2.

Discussion

In the current sample of 11 otherwise healthy cigarette smokers, there was good reproducibility of striatal [^{11}C]raclopride RAC binding in the presence of transdermal nicotine patches. Overall, our test-retest metrics (Table 2) comport well with literature values for single-bolus RAC studies in healthy control subjects ([25, 27–29]). The average striatal data were exceptionally stable, with slight variations in reliability between subregions. We chose to demonstrate test-retest reliability with three methods. The percent change in BP_{ND} between scans is the most commonly used parameter of effect size, and corresponds to the calculation most commonly used to describe relative changes in dopamine levels between conditions. Test-retest variability (TRV) quantifies the size of absolute variability across measurements. Both indices provide useful estimates of the effect sizes needed to achieve statistical significance with a two-scan dopamine challenge paradigm (although statistical significance is possible with smaller effect sizes). In this

study, these assessments of RAC test-retest reliability suggest a range of variability consistent with what others have reported when scanning the same individuals across days. Overall, the intra-class correlation (ICC) coefficient *r*-values in this study were also quite good, and indicate that estimations of BP_{ND} on Day 1 correlated well with measurements on Day 2. Lower ICC values were found in small regions that tend to have slightly noisier time-activity curves, and hence more variable estimates of BP_{ND}.

One potential concern about the use of nicotine patches is the possibility that nicotine itself might cause measurable dopamine release [30–31]. Two human RAC studies by Brody et al. support this view [8–9]. However, those designs included the actual physical act of smoking cigarettes. When nicotine is delivered intranasally to humans, or intravenously to unanesthetized monkeys, there is no evidence of significant decreases in RAC binding [32–33]. Taken together, these latter studies strongly suggest that nicotine itself does not release dopamine to levels measurable by RAC PET. It is also possible that the physical and sensory properties associated with cigarette smoking are the key components of the smoking-induced dopamine release reported by Brody et al.

In this study, the administration of IV alcohol to subjects the morning of the RAC PET study may be an unintended source of variance in baseline RAC BP_{ND}. In our previous work, we found no evidence of alcohol-induced dopamine release in social drinkers [34–35]. However, healthy social drinkers do not typically expose themselves to alcohol shortly after breakfast. We cannot exclude the possibility that alcohol exposure early in the morning may have caused unpredictable changes in the dopamine tone of healthy social drinkers.

Another limitation of this study was the absence of test-retest values for striatal RAC binding in smokers without nicotine patches, which could have assessed any variability in baseline striatal BP_{ND} attributable to nicotine withdrawal. However, the most important assumption in a typical dopaminergic RAC PET challenge paradigm is that the *within-subject state of basal dopamine is stable.* The present data demonstrate that it is possible to control nicotine craving (which is highly likely to alter endogenous dopamine) while keeping estimates of baseline D_2 availability stable.

Conclusion

The presence of transdermal nicotine patches does not appear to affect the stability of baseline [^{11}C]raclopride binding potential. We suggest that, in RAC challenge studies, the use of nicotine patches in smoking subjects is feasible to eliminate unwanted variance in D_2 availability caused by nicotine craving and concomitant alterations in striatal dopamine levels.

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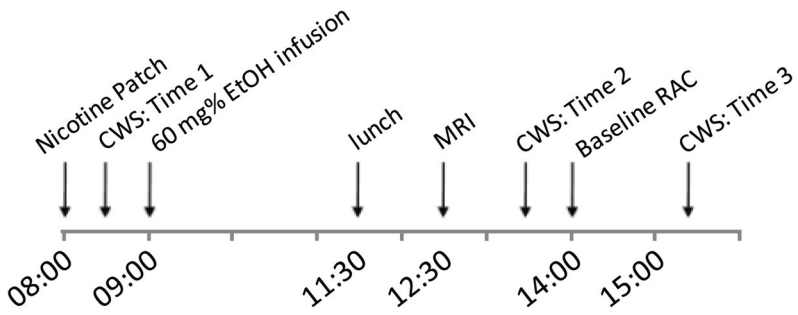

Fig. 1.

General outline of study day, starting with subject arrival at ~ 8:00 a.m. All times are approximate. CWS: Cigarette Withdrawal Scale; EtOH: alcohol; MRI: magnetic resonance imaging; RAC: [^{11}C]raclopride. Additional details are given in the text.

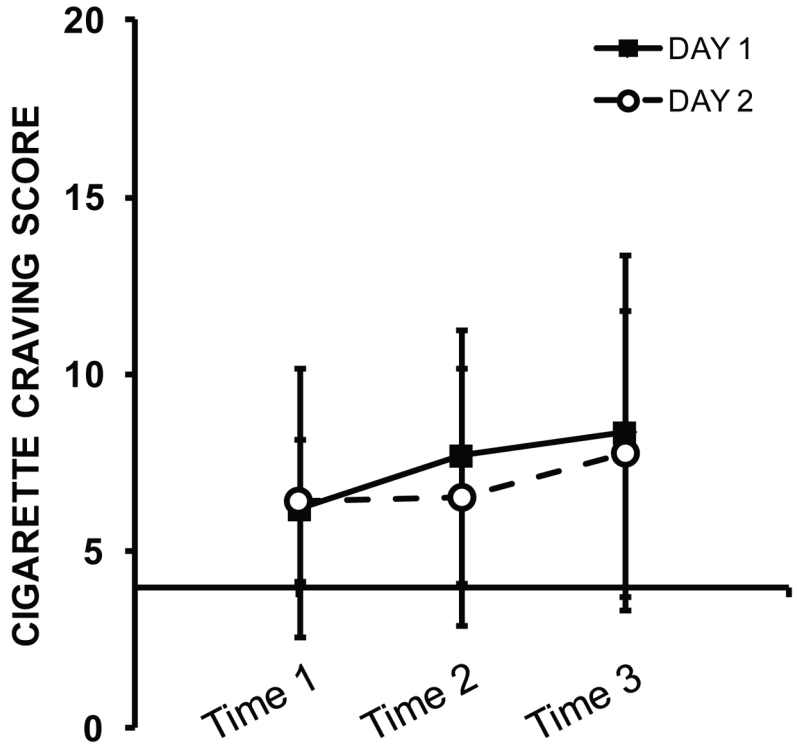

Fig. 2.

Mean ± s.d. cigarette craving ratings from Day 1 (filled circles) and Day 2 (open triangles), and Times 1, 2, and 3 (please see Figure 1 for approximate timing of ratings). The *x*-axis crosses the *y*-axis at the value of 4 to denote that 4 is the lowest possible score on the index; for reference, 20 is the highest possible score. Craving ratings did not vary within subjects across either day or time point (see text for details).

Table 1

Subject demographic, smoking, and drinking characteristics. Top row is mean ± s.d.; bottom row is data range. C: caucasian. AA: African-American. H/L: Hispanic/Latino. D/DDay: drinks per drinking day. D/Wk: drinks per week. The average Fagerstrom score indicates moderate nicotine dependence in this sample.

n	Age	Race	Ethnicity	Education (years)	Fagerstrom Score	D/DDay	D/wk
11	35.0 ± 10 *(25 – 55)*	3 AA *8 C*	0 H/L	12.6 ± 1.92 *(9 – 15)*	4.55 ± 1.51 *(3 – 8)*	3.27 ± 0.99 *(1.23 – 4.31)*	5.01 ± 3.02 *(0.39– 10.9)*

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Table 2

Test-retest data from resting [^{11}C]raclopride (RAC) scans in 11 cigarette smokers wearing transdermal nicotine patches. Data are mean ± standard deviation.

	BP_{ND} Day 1	BP_{ND} Day 2	%Δ	%TRV	ICC	ICC *p*-value[a]
LpreDCA	2.21 ± 0.22	2.08 ± 0.16*	−5.51 ± 4.85	8.43 ± 5.67	0.41	0.09
RpreDCA	2.06 ± 0.17	2.16 ± 0.20	5.22 ± 4.96	8.40 ± 6.68	0.35	n.s.[b]
LpreDPU	2.68 ± 0.28	2.70 ± 0.29	0.82 ± 1.62	5.41 ± 3.50	0.83	< 0.0005
RpreDPU	2.62 ± 0.26	2.62 ± 0.23	0.34 ± 1.33	7.89 ± 5.41	0.47	0.06
LVST	2.37 ± 0.30	2.34 ± 0.39	−0.94 ± 0.01	11.2 ± 6.57	0.67	< 0.01
RVST	2.25 ± 0.26	2.35 ± 0.33	4.30 ± 4.70	6.75 ± 5.84	0.77	< 0.005
LpostCA	1.70 ± 0.19	1.64 ± 0.22	−3.54 ± 3.80	7.43 ± 6.86	0.70	< 0.005
RpostCA	1.52 ± 0.26	1.65 ± 0.23**	9.50 ± 9.65	9.50 ± 7.40	0.74	< 0.005
LpostPU	2.81 ± 0.21	2.90 ± 0.24	3.31 ± 3.09	5.50 ± 4.69	0.59	< 0.05
RpostPU	2.80 ± 0.20	2.73 ± 0.26	−2.42 ± 2.16	5.83 ± 4.80	0.62	< 0.05
Striatum[c]	2.30 ± 0.48	2.32 ± 0.49	1.11 ± 9.83	7.63 ± 5.88	0.91	< 0.0001

[a] Trend-level significance is defined as $0.05 < p < 0.1$

[b] n.s.: not significant.

[c] Average of all regions across all subjects ($n = 110$)

* Significantly different from Day 1, paired *t*-test, $p < 0.05$

** Significantly different from Day 1, paired *t*-test, $p < 0.01$

Abbreviations: BP_{ND}: binding potential; %Δ : percent change in BP_{ND} from Day 1 to Day 2; %TRV: percent test-retest variability; ICC: intraclass correlation coefficient; L: left; R; right; pre: pre-commissural; post: post-commissural; DCA: dorsal caudate; DPU: dorsal putamen; VST: ventral striatum; CA: caudate; PU: putamen.