Neuropharmacology 64 (2013) 479–488

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Effects of nicotinic acetylcholine receptor agonists on cognition in rhesus monkeys with a chronic cocaine self-administration history

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ARTICLE INFO

Article history:
Received 30 April 2012
Received in revised form
9 July 2012
Accepted 9 August 2012

Keywords:
Cocaine
nAChR
PET
PNU-282987
Varenicline
Nonhuman primates

ABSTRACT

Cocaine use is associated with impaired cognitive function, which may negatively impact treatment outcomes. One pharmacological strategy to improve cognition involves nicotinic acetylcholine receptor (nAChR) stimulation. However, the effects of chronic cocaine exposure on nAChR distribution and function have not been characterized. Thus, one goal of this study was to examine nAChR availability in rhesus monkeys with an extensive cocaine self-administration history ($n = 4$; ~6 years, mean intake, 1463 mg/kg) compared to age-matched cocaine-naive control monkeys ($n = 5$). Using [^{11}C]-nicotine and positron emission tomography (PET) imaging, cocaine-experienced monkeys showed significantly higher receptor availability in the hippocampus compared to cocaine-naive monkeys. A second goal was to examine the effects of nAChR agonists on multiple domains of cognitive performance in these same monkeys. For these studies, working memory was assessed using a delayed match-to-sample (DMS) task, associative learning and behavioral flexibility using stimulus discrimination and reversal learning tasks. When administered acutely, the nonselective high-efficacy agonist nicotine, the low-efficacy α4β2* subtype-selective agonist varenicline and the high-efficacy α7 subtype-selective agonist, PNU-282987 significantly improved DMS performance in both cocaine-naive and cocaine-experienced monkeys. Individual doses of nicotine and varenicline that engendered maximum cognitive enhancing effects on working memory did not affect discrimination or reversal learning, while PNU-282987 disrupted reversal learning in the cocaine-naive monkeys. These findings indicate that a cocaine self-administration history influenced nAChR distribution and the effects of nAChR agonists on cognitive performance, including a reduced sensitivity to the disrupting effects on reversal learning. The cognitive enhancing effects of nAChR agonists may be beneficial in combination with behavioral treatments for cocaine addiction.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

Chronic cocaine use continues to be a significant public health concern worldwide (SAMHSA, 2009). Cocaine binds to the dopamine (DA), serotonin (5-HT), and norepinephrine (NE) transporters (DAT, SERT, and NET, respectively; Ritz et al., 1987) and induces numerous neurobiological changes throughout mesocorticolimbic regions that disrupt executive function (Volkow et al., 1993; Tomasi et al., 2009; Moeller et al., 2010). For example, compared to control groups, chronic cocaine users showed lower brain function measured via fMRI or positron emission tomography (PET) in regions mediating cognition and showed impaired performance on tasks measuring response inhibition, behavioral flexibility, impulsivity, and working memory (Volkow et al., 1991, 1992; Fillmore and Rush, 2002; Bolla et al., 2004; Hester and Garavan, 2004; Tomasi et al., 2007a,b; Goldstein et al., 2007, 2010; Moeller et al., 2010).

Currently, there are no FDA-approved treatments for cocaine dependence (Karila et al., 2008). Behavioral treatment strategies have proven successful (see Vocci and Montoya, 2009 for review) and success rates have been shown to be directly correlated with neuropsychological measures upon treatment initiation (Teichner et al., 2001; Aharonovich et al., 2006; Turner et al., 2009; Schmitz et al., 2009; Moeller et al., 2010). Thus, cognitive enhancement

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http://dx.doi.org/10.1016/j.neuropharm.2012.08.004

may increase retention and success of behavioral treatments, resulting in improved overall abstinence from cocaine (e.g., Sofuoglu, 2010; Perry et al., 2011).

The acetylcholine (ACh) neurotransmitter system has been extensively studied as a mechanism to improve cognitive deficits associated with hypodopaminergic function such as depression and Parkinson's Disease (for reviews see Rezvani and Levin, 2001; Forgacs and Bodis-Wollner, 2004; Cincotta et al., 2008). Nicotine, a high-efficacy agonist that nonselectively binds at all nicotinic acetylcholine receptor (nAChR) subtypes indirectly stimulates dopamine release (e.g. Rollema et al., 2007, 2009) and has shown cognitive-enhancing effects on measures of attention and memory in rodent, monkey and human studies (see Rezvani and Levin, 2001 for review). However, the high abuse liability of nicotine may preclude its use clinically as a cognitive enhancer (e.g., Schorling et al., 1994; Roll et al., 1996).

The two primary nAChR subtypes distributed within the mammalian CNS are α7 and α4β2* receptors and subtype-selective agonists at each subtype have produced cognitive enhancing effects in animal models (e.g., Hahn et al., 2003; Bitner et al., 2007; Howe et al., 2010; Castner et al., 2011) and may have lower abuse liability than nicotine. Varenicline (Chantix©), an FDA-approved medication with success as a smoking cessation agent (Gonzalez et al., 2006; Jorenby et al., 2006), has high affinity and low-efficacy at α4β2* receptors and low affinity and high-efficacy at α7 receptors (Coe et al., 2005; Mihalak et al., 2006). Data from animal studies and limited clinical trials suggest that varenicline improves cognition across multiple domains (see Rollema et al., 2009 for review) and has limited abuse liability (Rollema et al., 2007; McColl et al., 2008; Gould et al., 2011).

Cognitive impairments have been described as one of the consequences of long-term cocaine use (e.g., Moeller et al., 2010; Hanlon et al., 2011). However, the direct effects of cocaine on nAChR distribution and function are not clear. Cocaine self-administration in animal models produces parallel neurobiological deficits including a hypodopaminergic state (e.g., Diana, 2011; Gould et al., 2012b) and cognitive deficits similar to those seen in human cocaine users (see Beveridge et al., 2008 for review) including impairments on attention, memory, impulsivity and behavioral flexibility in rodents (Dalley et al., 2005; George et al., 2008; Winstanley et al., 2007, 2009) and monkeys (Liu et al., 2008, 2009; Porter et al., 2011; Gould et al., 2012a). Thus, the first goal of this study was to extend the evaluation of cocaine-induced brain changes in rhesus monkeys with an extensive cocaine self-administration history from measures of glucose utilization (Gould et al., 2012a) to nAChR availability using [^{11}C]-nicotine and PET imaging. A second goal was to examine the effects of subtype-selective nAChR agonists of various efficacies including nicotine, varenicline, and PNU-282987, a novel high-efficacy α7-selective nAChR agonist (Bodnar et al., 2005) on cognitive function in these same monkeys and age-matched drug-naive control monkeys. These compounds were tested on three distinct cognitive domains, associative learning, reversal learning and working memory – the latter two domains were shown to be impaired by cocaine self-administration in these monkeys (Gould et al., 2012a) and are mediated in part by distinct neurobiological substrates (e.g., Chudasama and Robbins, 2006; Mehta and Riedel, 2006).

2. Materials and methods

2.1. Subjects

Nine singly housed adult male rhesus macaques (*Macaca mulatta*) of Indian origin served as subjects. Four monkeys (13–14 years old) had an extensive cocaine self-administration history (~6 yrs; mean 1463 mg/kg cumulative cocaine intake) at the initiation of this study (Czoty et al., 2007; Blaylock et al., 2011; Gould et al., 2012a). Intakes for the monkeys prior to Exp. 1 were: R-1374 (1995 mg/kg), R-1375 (976 mg/kg), R-1377 (1647 mg/kg) and R-1381 (1234 mg/kg). Five additional monkeys, age-matched (11–14 years old) and cocaine-naive, were studied. Each monkey was fitted with an aluminum collar (Primate Products, Redwood City, CA) and trained to sit in a primate chair (Primate Products) for use in operant sessions. All monkeys were surgically implanted with indwelling vascular access ports and intravenous catheters (Access Technologies, Skokie, IL) into a major vein (see Czoty et al., 2007). Monkeys were weighed weekly and fed enough food daily (Purina Monkey Chow and fresh fruit) to maintain ~95% free-feeding body weight; water was available *ad libitum* in their homecage, which measured 0.71 × 0.84 × 0.84 m (Allentown Caging Inc., Allentown, NJ). All experimental procedures were performed in accordance with the 2003 National Research Council *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* and were approved by the Wake Forest University Institutional Animal Care and Use Committee. Environmental enrichment was provided as outlined in the Institutional Animal Care and Use Committee's Nonhuman Primate Environmental Enrichment Plan.

2.2. Apparatus

During training, all animals underwent cognitive testing between 7:00 and 10:00 AM (5–7 days/week). Cognitive testing was conducted using the Cambridge Neuropsychological Test Automated Battery (CANTAB; Lafayette Instruments, Lafayette, IN) apparatus. CANTAB stations (0.38 × 0.56 × 0.31 m) were located in sound-attenuating, ventilated chambers (0.8 × 0.8 × 1.32 m) and included touch-sensitive computer screens (0.3 × 0.23 m) with a stimulus light, a non-retractable response lever, and a pellet receptacle located to the right side of each panel. In addition, monkeys responded in afternoon sessions (1:00–4:00 PM), in separate sound-attenuating chambers (1.5 × 0.74 × 0.76 m; Med Associates, East Fairfield, VT), under a fixed-ratio (FR) 30 schedule of reinforcement maintained by food presentation or cocaine infusions (see below). Each operant panel contained two photo-optic switches (Model 117-1007; Stewart Ergonomics, Inc., Furlong, PA). Illumination of a yellow light over the left photo-optic switch signaled the initiation of each trial. A response was registered by breaking the infrared beam within a circular recess of the switch. A minimum of 2 h elapsed between morning and afternoon sessions during which monkeys were returned to their home cages. A timeline of experimental events is shown in Fig. 1.

2.3. Morning cognition sessions

2.3.1. Delayed match-to-sample (DMS) task

At the start of each trial the house light was illuminated for 5 s followed by the appearance of a "target" stimulus in the center of the computer screen (sample phase). A response on this stimulus was followed by a delay (see below) and the presentation of a minimum of 3 shapes around the edges of the screen (match phase). Responding on the "target" image during the match phase resulted in delivery of 2, 190-mg sucrose pellets, whereas a response on any other distracter image resulted in trial termination. The house light remained illuminated during each delay and remained lit throughout post-trial timeouts (5 s) following correct trials but was extinguished following incorrect responses. If no response was emitted within 10 s during either phase, the house light was extinguished and the trial was terminated. Three delays were randomly distributed throughout a total of 60 trials per session (20 trials/delay). Delay values and the number of distracter images were individualized such that short, mid and long delays (0–150 s) produced

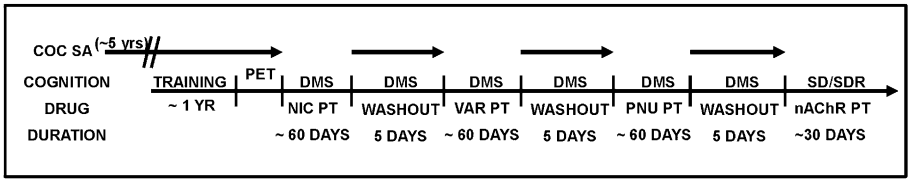

Fig. 1. Study Timeline. Rhesus monkeys performed cognitive tests in daily AM sessions and self-administered cocaine (cocaine-experienced) or food pellets (cocaine-naive) in PM sessions. PM self-administration sessions were discontinued during assessment of nAChR agonists on cognition. Arrows represent periods when cocaine (cocaine-experienced) or food (cocaine-naive) self-administration sessions occurred.

delay-dependent reductions in % accuracy (short delay, >80%; middle delay, 55–80%; long delay, 30–55%; see Table 2 for starting parameters). As learning continued to occur with daily repetition of the task, delays and the number of distracter images were periodically increased on an individual basis to maintain similar delay-dependent decreases in percent accuracy to maintain the above criteria.

2.3.2. Stimulus discrimination and reversal learning

Three distinct stimuli (e.g. A, B, and C) were displayed on the screen. In the first stage (simple discrimination; SD) one image was designated as "correct" (A+) and resulted in reinforcement when touched (delivery of 1, 190-mg pellet), followed by a 5 s timeout (TO), while responding on either of the other two stimuli (B− or C−) was not reinforced and resulted in trial termination and a 15 s TO. Within each trial the three shapes were distributed in a pseudo-random fashion on the left, middle and right side of the screen. Acquisition criterion for each stage was defined as 18 correct responses out of 20 consecutive trials. Upon acquisition, the contingencies associated with these stimuli were changed (reversal) such that responding on stimulus A was not reinforced (A−) and responding on stimulus B was now reinforced (B+). Stimulus C was never associated with reinforcement (always C−) and allowed for an assessment of perseverative responding during the reversal stage (responses allocated on the previously reinforced stimulus, A). Upon acquisition of the reversal stage (18 correct out of 20 consecutive trials), the discrimination and reversal component was complete. Following a 15 s TO, three new stimuli were presented and a second discrimination and reversal task was initiated. Stimuli were chosen randomly from a list of 60 for each new session. Under these conditions, two sets of discrimination and reversal could be completed within each daily session. A maximum of 200 trials were available for each component. If a response was not registered within 10 s, the trial was terminated.

2.4. Afternoon self-administration sessions

Cocaine (0.1 mg/kg/injection; cocaine-experienced group) or food (1.0 g banana-flavored pellets; cocaine-naive group) was available under an FR 30 schedule of reinforcement; cocaine (~1.5 ml over 10 s) was delivered using a peristaltic infusion pump (Cole-Parmer, Inc., Chicago, IL). Each reinforcer (cocaine and food) was followed by a 30-s TO. Previous studies with these monkeys found that this cocaine dose was at the peak or on the descending limb of the cocaine dose–response curve (Blaylock et al., 2011), and that despite morning cognition sessions, all monkeys would receive all cocaine or food reinforcers in the afternoon sessions (Gould et al., 2012a). Food or cocaine self-administration sessions occurred 5 days/week and lasted for 120 min or until a maximum of 15 total reinforcers were received (1.5 mg/kg daily cocaine intake). When nAChR drug treatments were initiated, the afternoon sessions were not conducted.

2.5. Experiment 1: effects of cocaine self-administration on nAChR availability

Prior to testing nAChR agonists on working memory performance, PET studies with [^{11}C]-nicotine were conducted in each monkey and occurred ~16 h after the last cocaine self-administration session. On the day of each PET scan, monkeys were anesthetized with 10 mg/kg ketamine hydrochloride and transported to the Wake Forest University School of Medicine PET Center. Monkeys were intubated and anesthesia was maintained by inhaled isoflurane (1.5%) for the duration of the 90-min scan. A 22-ga catheter was placed into the saphenous vein by percutaneous stick. A paralytic (0.07 mg/kg vecuronium bromide, i.v.) was administered and respiration was maintained by a ventilator. [^{11}C]-nicotine, dissolved in 0.9% saline, average 9.3 and 9.4 mCi for the cocaine-naive and cocaine-experienced groups, respectively was injected i.v. at the start of the scan (injection volume of 5.0 ± 2 ml), followed by a 3 ml flush of saline. Heart rate, blood pressure, and blood oxygen saturation were monitored throughout the scan and during recovery. At the end of the study, neostigmine (0.07 mg/kg, i.v.) and glycopyrulate (20 μg/kg, i.v.) were administered to reverse the effects of the paralytic.

Data from PET scans were acquired using a GE 64 slice PET/CT Discovery VCT scanner (GE Medical Systems, Milwaukee, WI, United States) with a ~5–6 mm resolution (Teras et al., 2007). An initial low dose computerized tomographic-based attenuation correction (CTAC) scan was acquired, followed by a 90 min 3D emission scan consisting of 36 sequential frames of the following dimensions (modified from Sihver et al., 1999): 10 × 6 s (0–1 min), 5 × 1 min (1–6 min), 7 × 2 min (6–20 min), 14 × 5 min (20–90 min). Initiation of each PET scan coincided with intravenous injection of [^{11}C]-nicotine. The 3D data were corrected for attenuation and reconstructed transaxially using OSEM VUE point (28 subsets; 2 iterations) with a 3-mm FWHM filter resulting in a 128 × 128 matrix.

The ^{11}C labeled S-(−)-nicotine was prepared from the precursor S-(−)-nornicotine biscamsylate with slight modifications from previously published methods (Halldin et al., 1992; Rose et al., 2010). Briefly, a solution of S-(−)-nornicotine (0.25–0.5 mg) in acetonitrile was reacted with C-11 methyl triflate in the presence of 1,2,2,6,6, pentamethylpiperidine (10 μL of 5% PMP solution in acetonitrile) at room temperature for 3 min. The desired product [^{11}C]-nicotine was separated from the crude reaction mixture using HPLC purification in 24 ± 11% radiochemical yields and >98% radiochemical purity. The specific activity of [^{11}C]-nicotine used in these experiment ranged from 839 mCi/μmol to 2621 mCi/μmol, allowing for < 2 μg of nicotine injected per monkey.

2.6. Experiment 2: effects of nicotine, varenicline, and PNU-282987 on DMS performance

Two monkeys failed to respond at above 50% accuracy (chance) with a 0 s delay and only 1 distracter image after ~200 sessions and were excluded from the study (R-1683, cocaine-naive; R-1381, cocaine-experienced). Acute doses of nicotine tartrate (0.0003–0.56 mg/kg, base), varenicline dihydrochloride (0.0003–0.3, salt), PNU-282987 (0.001–0.56 mg/kg, salt) and saline were administered intramuscularly prior to morning DMS sessions. Based on published reports and preliminary studies in our laboratory, nicotine and PNU-282987 were administered 5 min and varenicline was administered 60 min prior to each test session (see Obach et al., 2006; Gould et al., 2011). Intramuscular drug administration was chosen to minimize side effects seen with intravenous bolus administration (e.g., salivation, tachycardia). A minimum of four doses of each drug, separated by half-log units, were tested twice in each monkey, in random order; if the percent change from the previous session varied by greater than 50% between determinations, a third determination was conducted. Drugs were tested in the following order: nicotine, varenicline, PNU-282987. A 5-day washout period occurred between switching from one test drug to another during which cocaine-experienced monkeys self-administered 0.1 mg/kg/inj (max 15 injections) in afternoon sessions. Following termination of cocaine self-administration sessions, a minimum of 3 cognition sessions were acquired to ensure a stable DMS baseline prior to the administration of the first dose of each nAChR agonist.

2.7. Experiment 3: effects of nicotine, varenicline, and PNU-282987 on stimulus discrimination and reversal learning

Following assessment of all three compounds on DMS performance, stimulus discrimination and reversal learning tasks were initiated. Following ~10 days of training, the effects of nAChR agonists were assessed on these measures of associative learning and behavioral flexibility. Individual doses of nicotine, varenicline, and PNU-282987 that produced the maximum cognitive enhancing effect on working memory in Experiment 2 (see Table 3) were tested once in each monkey, with a minimum of 2 days between testing. Nicotine and PNU-282987 were administered 15 min and varenicline was administered 75 min prior to the start of each session. Pretreatment times were longer in this study in an attempt to control for peak effects during the session; DMS sessions lasted ~90 min whereas discrimination and reversal sessions lasted ~30 min.

2.8. Data analysis

2.8.1. Experiment 1: effects of cocaine self-administration on nAChR availability

PET data were co-registered to individual T1-weighted MRIs acquired using a 3.0 T MR scanner (GE Medical Systems) under ketamine induction (10 mg/kg) and 1.5% isoflurane-maintained anesthesia, using PMOD Biomedical Image Quantification Software (version 3.1; PMOD Technologies, Zurich, Switzerland). Spherical regions of interest (ROIs) were drawn directly on each individual MR image for 15 brain regions associated with the mesocorticolimbic dopamine pathway, cognitive function or areas of dense nAChR distribution. Areas associated with reward and the mesolimbic dopamine system included bilateral caudate nucleus (2.5 mm radii), bilateral putamen (2.5 mm radii), bilateral nucleus accumbens (2.0 mm radii), bilateral amygdala (2.5 mm radii), and unilateral thalamic ROI along the midline (3.0 mm radius). Areas associated with executive function included bilateral anterior cingulate cortex (2.5 mm radii), bilateral dorsolateral prefrontal cortex (PFC; 2.5 mm radii), bilateral orbital PFC (2.5 mm radii), bilateral hippocampus (2.5 mm radii) and unilateral dorsomedial PFC (5.0 mm radius). Lastly, regions were selected based on differences in glucose metabolism between these two groups of monkeys (Gould et al., 2012a) and included unilateral mid-cingulate cortex (2.5 mm radius), unilateral posterior cingulate cortex (2.5 mm radius) and unilateral precuneus (4.0 mm radius), and regions known to be associated with nAChR distribution including bilateral insular cortex (2.5 mm radii) and bilateral cerebellum (4.0 mm radii).

Individual tissue time activity curves were calculated for each ROI. Values from 30 to 50 min post [^{11}C]-nicotine injection were averaged and expressed as uptake values (modified from Sihver et al., 1999). The uptake value for each ROI was divided by the uptake value from the reference region, the centrum semiovalis, a large white matter tract, to generate a normalized ratio of uptake. Recent studies have used white matter tracts as a measure for nondisplaceable binding when the receptor of interest is distributed throughout gray matter (e.g., Giovacchini et al., 2009), including the $\alpha4\beta2^*$ subtype-selective nAChR PET tracer 2-FA (Kendziorra et al., 2010). Further, a ratio analysis method has been shown to minimize the effects of blood flow with other PET tracers (Logan et al., 1994). For analysis, a two-way ANOVA was conducted using region and group as factors followed by post-hoc Bonferroni *t*-tests. In this study, there were no significant differences between the ratio of uptake in the left or right side of any regions where bilateral ROIs were examined and were therefore averaged.

2.8.2. Experiment 2: effects of nicotine, varenicline, and PNU-282987 on DMS performance

The primary dependent variables were percent accuracy and response latencies. Percent accuracy was determined by dividing the number of correct responses by the total number of trials completed at each delay (short, mid, long). Trials were omitted if no response was made during the "sample" or "match" phase. The effects of all drug pretreatments were compared to the previous day's session (baseline) in which greater than 75% of trials were completed and there was a delay-dependent reduction in percent accuracy such that percent accuracies were >80%, between 55 and 80%, and <55% for corresponding short, middle, and long delays. Effects of drug pretreatments were expressed as a percent of baseline determined by dividing the percent accuracy following drug treatment by the percent accuracy of the previous day's session at each corresponding delay.

From each individual dose–response curve, the dose of drug that engendered the greatest percent increase in accuracy at the longest delay was used for a 'best-dose' group analysis. Two-way repeated measure ANOVAs were conducted comparing percent accuracy between group (cocaine-naive versus cocaine-experienced) and drug treatment ('best dose' versus previous day's session) at each delay value. In addition to assessing the acute effects, separate ANOVAs examined sustained effects by comparing the day after drug treatment to baseline (nicotine and PNU-282987, 24 h; varenicline, 25 h post administration). A two-way repeated measure ANOVA compared the maximal effect of pretreatment on baseline performance using drug (saline, nicotine, varenicline, PNU-282987) and group (cocaine-naive, cocaine-experienced) at the longest delay. One-way repeated measure ANOVAs were conducted to examine effects of the 'best dose' of each drug on phase 1 (target), phase 2 (match) response latencies and pellet retrieval latencies compared to when saline was administered, using percent change in response rate from the previous day's session. Analyses were also conducted between drugs, so as to compare the effects of agonists at different nAChR subtypes on DMS performance. When appropriate, Bonferroni post-hoc testing was conducted; $p < 0.05$ was considered significant.

2.8.3. Experiment 3: effects of nicotine, varenicline, and PNU-282987 on stimulus discrimination and reversal learning

The primary dependent variables were total trials completed, total errors committed, response latencies, and pellet retrieval latencies in both the discrimination and reversal stages of the task. In addition, perseverative responding was assessed during the reversal stages, determined by subtracting the number of responses on stimulus C (never reinforced) from the number of responses on A, the previously reinforced stimulus. This number provides a relative measure of the amount of responding across two non-reinforced stimuli during the period when a new stimulus–reinforcement association was being formed (Jentsch et al., 2002). Two-way repeated measure ANOVAs were conducted for each dependent variable (trials completed, errors, etc) comparing group (cocaine-naive versus cocaine-experienced) and drug treatment ('best dose' versus previous day's session). When appropriate, Bonferroni post-hoc testing was conducted; $p < 0.05$ was considered significant.

2.9. Drugs

(−)Cocaine HCl (National Institute on Drug Abuse, Bethesda, MD), nicotine tartrate (Sigma–Aldrich, St. Louis, MO), varenicline ditartrate and PNU-282987 (National Institute on Drug Abuse, RTI, Durham, NC) were dissolved in sterile 0.9% saline. Sodium hydroxide was added to varenicline and nicotine to reach a stable pH range of 5–8.

3. Results

3.1. Experiment 1: effects of cocaine self-administration on nAChR availability

PET imaging of [^{11}C]-nicotine demonstrated a rapid uptake in rhesus monkey brain with peaks in the time–activity curves within 6 min, and rapid washout that became linear around 30 min. The highest uptake was seen in cortical and subcortical regions, with lesser binding in the cerebellum and least binding in white matter, as has been reported in rhesus monkeys (Sihver et al., 1999). For both groups of monkeys, the between-subject variability was low in most regions, rarely exceeding 10% (Table 1). There was a main effect of drug history ($F_{1,105} = 7.75$, $p = <0.01$) and region ($F_{14,105} = 6.04$, $p < 0.001$); post-hoc testing showed a significant difference in the hippocampus between the cocaine-experienced and cocaine-naive monkeys (Table 1).

3.2. Experiment 2: effects of nicotine, varenicline, and PNU-282987 on DMS performance

Individualized short-, mid- and long-delay values resulted in delay-dependent reductions in percent accuracy. To maintain similar levels of baseline performance across the entire study, delays were adjusted on an individual basis (see Table 2 for individualized delays). Thus, baseline performance on the days preceding test sessions were not different across the evaluation of each drug or between groups. At the end of the study, individualized delays and number of distracters necessary to produce delay-dependent reductions were not different between groups (Table 2). The average number of sessions to complete each dose–response curve was 52.4 ± 4.8, and 63.9 ± 6.8 days for cocaine-experienced and cocaine-naive groups, respectively. At the longest delay, pretreatment with nicotine, varenicline and PNU-282987 produced inverted-U-shaped curves in all monkeys when expressed as a percent of the previous day's baseline session (see Fig. 2 for representative dose–effect curves). DMS performance at the longest delay was most sensitive to drug-induced increases in performance (Figs. 2 and 3).

Administration of nAChR agonists resulted in improvements in cognition although there was between-subject variability as to

Table 1
Individual and mean (±SEM) ratios of [^{11}C]-nicotine uptake for each region of analysis.

	Cd	Pt	NAc	Thal	Am	Hp	dmPFC	dlPFC	orbPFC	ACC	mCC	PCC	Prcn	Insula	Cb
Coc-Naive															
R-1681	1.32	1.29	1.33	1.19	1.42	1.34	1.45	1.23	1.19	1.36	1.27	1.32	1.29	1.46	1.03
R-1682	1.22	1.23	1.26	1.15	1.32	1.26	1.36	1.28	1.08	1.31	1.20	1.27	1.23	1.38	1.06
R-1683	1.25	1.26	1.34	1.20	1.38	1.34	1.43	1.28	1.22	1.39	1.19	1.24	1.22	1.44	1.12
R-1696	1.24	1.26	1.30	1.18	1.30	0.87	1.29	1.22	1.10	1.34	1.21	1.27	1.34	1.42	1.10
R-1756	1.18	1.24	1.27	1.20	1.27	1.24	1.40	1.30	1.25	1.30	1.24	1.28	1.16	1.37	1.09
Ave	1.24	1.26	1.30	1.18	1.34	1.21*	1.39	1.26	1.17	1.34	1.22	1.27	1.25	1.41	1.08
±SEM	0.03	0.01	0.02	0.01	0.03	0.10	0.03	0.02	0.04	0.02	0.02	0.01	0.04	0.02	0.02
Coc-Experienced															
R-1374	1.20	1.21	1.31	1.01	1.26	1.36	1.32	1.14	1.04	1.27	1.19	1.28	1.33	1.37	1.12
R-1375	1.29	1.25	1.37	1.13	1.37	1.35	1.09	1.23	1.14	1.31	1.16	1.19	0.97	1.40	1.32
R-1377	1.41	1.42	1.54	1.47	1.51	1.46	1.64	1.28	1.37	1.60	1.32	1.39	1.35	1.69	1.24
R-1381	1.28	1.23	1.36	1.29	1.41	1.39	1.52	1.33	1.36	1.38	1.29	1.38	1.32	1.50	0.97
Ave	1.29	1.28	1.40	1.23	1.39	1.39*	1.39	1.24	1.23	1.39	1.24	1.31	1.24	1.49	1.16
±SEM	0.05	0.05	0.06	0.12	0.06	0.03	0.14	0.05	0.09	0.09	0.04	0.05	0.11	0.08	0.09
% Difference	4.18	1.76	7.58	3.84	3.96	15.13	0.30	−1.34	4.91	3.43	1.42	2.80	−0.65	5.33	7.84
±SEM	3.97	4.35	4.36	9.79	4.40	2.38	9.98	3.71	8.00	6.38	3.60	4.17	8.49	5.89	8.14

Cd, caudate nucleus; Pt, putamen; NAc, nucleus accumbens; Thal, thalamus; Am, amygdala; Hp, hippocampus; dmPFC, dorsomedial prefrontal cortex; dlPFC, dorsolateral PFC; orbPFC, orbital PFC; ACC, anterior cingulate cortex; mCC, mid-cingulate cortex; PCC, posterior cingulate cortex; Prcn, precuneus; Cb, cerebellum; *$p < 0.01$.

Table 2
Individual parameters that produced similar delay-dependent effects on DMS performance at the start and completion of testing; dist., distracter images.

	Start				End			
	Delays (sec)			# dist.	Delays (sec)			# dist.
	Short	Mid	Long		Short	Mid	Long	
Cocaine-naive								
1681	5	60	120	3	5	90	150	7
1682	0	60	120	3	0	90	150	4
1696	5	45	90	3	0	90	120	4
1756	5	30	60	3	0	90	150	3
Cocaine-experienced								
1374	0	60	120	2	0	60	120	3
1375	0	60	120	3	0	90	120	7
1377	0	45	90	3	0	60	120	3

which doses were effective. This variability in dose sensitivity precluded group analysis across the full dose–response curves, so data were arranged based on the dose that produced maximal effects in each monkey at the longest delay. There was a main effect of nicotine ($F_{1,5} = 49.26$, $p < 0.001$), varenicline ($F_{1,5} = 57.61$, $p < 0.001$) and PNU-282987 ($F_{1,5} = 91.79$, $p < 0.001$) on percent accuracy following acute administration, but no effect of cocaine history. Post-hoc tests showed that at the longest delay, percent accuracy was significantly improved from baseline following nicotine ($t = 4.92$, $p < 0.005$; $t = 5.03$, $p < 0.005$), varenicline ($t = 6.26$, $p < 0.05$; $t = 4.62$; $p < 0.01$) and PNU-282987 ($t = 6.40$, $p < 0.005$, $t = 7.14$, $p < 0.001$) for cocaine-naive and cocaine-experienced groups, respectively (Fig. 3). There were no significant effects of any treatment on performance during the short- or mid-delay values. At the longest delay, there was a main effect of varenicline treatment ($F_{1,5} = 11.46$, $p < 0.05$) on percent accuracy 25 h after drug administration (i.e., the second session after drug administration); post-hoc tests indicated that only the cocaine-naive group was significantly higher than baseline ($t = 2.92$; $p < 0.05$; data not shown).

When comparing maximal increases in percent accuracy, there was a main effect of drug treatment but not group ($F_{3,15} = 26.46$, $p < 0.001$) such that nicotine ($t = 4.94$, $p < 0.001$; $t = 7.35$, $p < 0.001$), varenicline ($t = 4.04$, $p < 0.01$; $t = 3.42$, $p < 0.05$) and PNU-282987 ($t = 3.26$, $p < 0.05$; $t = 4.54$, $p < 0.005$) each improved percent accuracy to a greater extent than saline in cocaine-naive and cocaine-experienced monkeys, respectively (Fig. 4; Table 3). In the cocaine-experienced group only, there was a significant difference in the percent maximal increase in accuracy between nicotine and varenicline administration ($t = 3.92$, $p < 0.01$). Despite similar maximal effectiveness of nicotine between groups, the doses of nicotine that produced the greatest cognitive-enhancing effects were lower in 3 of the 4 cocaine-naive monkeys compared to the doses of nicotine that produced the largest effects in the cocaine-experienced monkeys (see Table 3). At the highest doses tested (see Fig. 2 for examples) each drug disrupted responding such that less than 75% of trials were completed. However, doses of each drug that engendered the greatest cognitive enhancement had no significant effect on response or pellet retrieval latencies (data not shown). Saline did not have a significant effect on percent accuracy in any monkey.

3.3. Experiment 3: effects of nicotine, varenicline, and PNU-282987 on stimulus discrimination and reversal learning

Performance improved across the 10 days of training such that all monkeys reliably completed both stimulus discrimination and reversal components during each daily session, while committing few errors. Performance was not significantly different between groups or between discrimination and reversal stages. There was no difference in performance between the first and second discrimination and reversal completed each day. The two discrimination stages and the two reversal stages were therefore averaged to provide one measure of associative learning and reversal learning for each session.

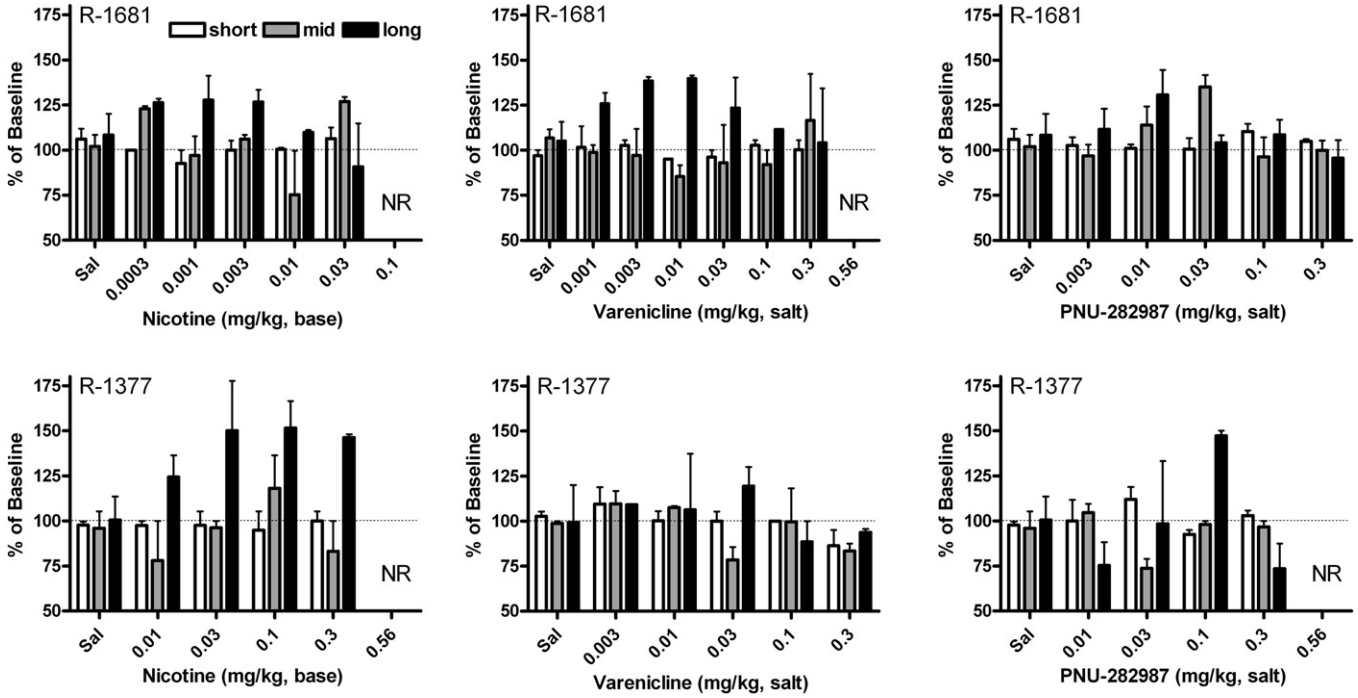

Fig. 2. Delayed Match-to-Sample: Representative dose–response curves following acute nicotine (5 min PT; left), varenicline (60 min PT; middle) and PNU-282987 (5 min PT; right panels) showing percent change from the previous day's baseline in one cocaine-naive monkey (R-1681, top) and one monkey with a cocaine self-administration history (R-1377, bottom); NR, no responding, >25% of trials omitted.

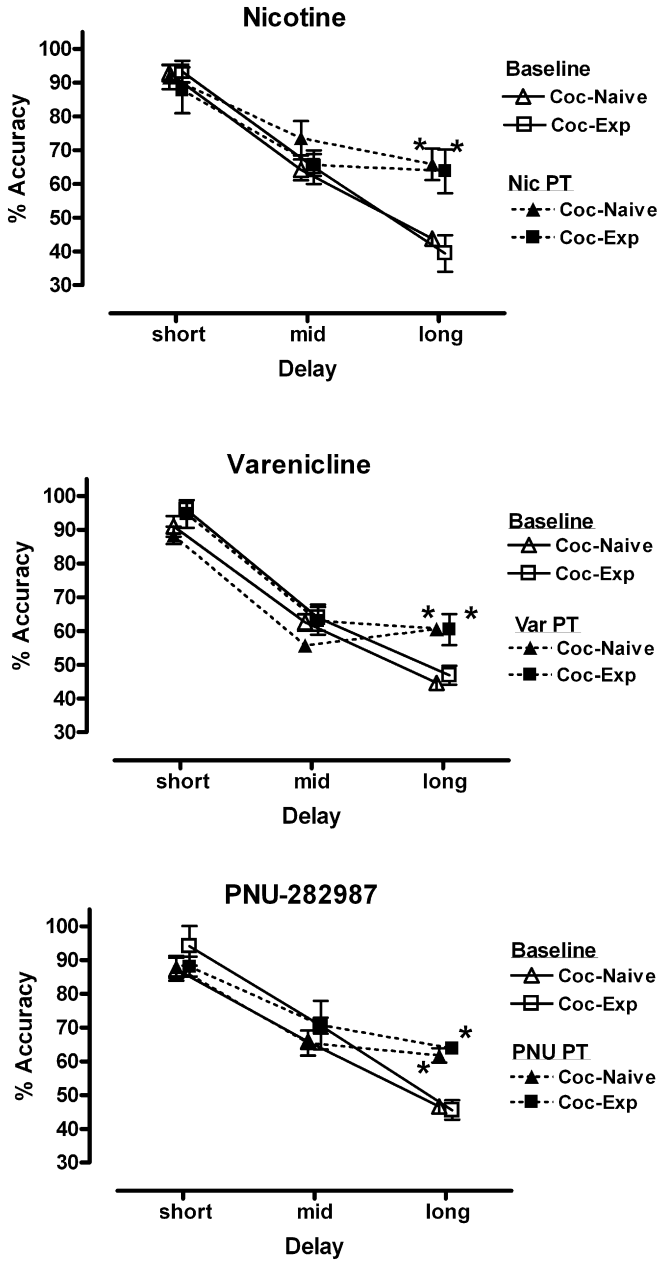

Fig. 3. Delayed Match-to-Sample: Delay-effect curves for cocaine-naive (Coc-Naive) and cocaine-experienced (Coc-Exp) monkeys under baseline conditions (open symbols) and 'best-dose' analysis (filled symbols) for nicotine (top), varenicline (middle) and PNU-282987 (bottom). Curves are offset slightly for clarity; $^{*}p < 0.05$ compared to baseline at the respective delay.

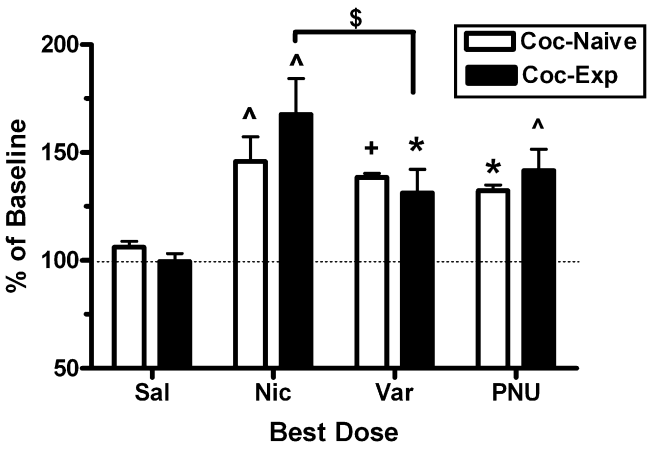

Fig. 4. Delayed Match-to-Sample: Group means (±SEM) for maximal effect of the 'best-dose' of nicotine (Nic), varenicline (Var), PNU-282987 (PNU) and saline (Sal) expressed as a percent of the previous day's baseline (BL) in cocaine-naive (Coc-Naive) and cocaine-experienced (Coc-Exp) monkeys at the longest delay only; $^{*}p < 0.05$, $^{+}p < 0.01$; $^{\wedge}p < 0.005$ significantly different from respective saline administration; $^{\$}p < 0.05$ significant difference between Nic and Var of cocaine-experienced monkeys.

There were no effects of nicotine or varenicline on total trials completed or total errors committed across stimulus discrimination or reversal stages in either group compared to the previous day's baseline (all $p > 0.05$). There was an interaction ($F_{3,15} = 4.69$, $p < 0.05$) between group and treatment on the total trials completed following PNU-282987 administration such that the cocaine-naive group performed a significantly greater number of trials following PNU-282987 than the cocaine-experienced group in both the discrimination ($t = 3.21$, $p < 0.01$) and reversal stages ($t = 2.59$, $p < 0.05$), and that the cocaine-naive group performed significantly greater number of trials following PNU-282987 in the reversal stage only, compared to the previous day's baseline session ($t = 3.28$, $p < 0.05$; Fig. 5). There was not a significant effect of PNU-282987 on the total errors committed. None of the nAChR agonists had an effect on perseverative responding.

4. Discussion

The present study examined nicotinic acetylcholine receptor availability and the influence of nAChR stimulation on cognition in rhesus monkeys with a chronic cocaine self-administration history compared to cocaine-naive monkeys. Monkeys with a cocaine self-administration history showed higher [^{11}C]-nicotine uptake in the hippocampus compared to cocaine-naive monkeys measured via PET imaging, supporting the examination of nicotinic receptor agonists on cognition in both groups of monkeys. When administered acutely, the nonselective nAChR agonist nicotine, the low-efficacy α4β2* subtype-selective nAChR agonist varenicline, and the high-efficacy, potent α7-selective nAChR agonist PNU-282987 significantly improved working memory performance in both groups of monkeys. For the α7-selective nAChR agonist PNU-282987, the same doses than engendered maximal percent increases in accuracy on the DMS task disrupted reversal learning, but only in the cocaine-naive group. These data extend previous studies in rodents, monkeys and humans showing that nAChR

Table 3
Best-dose analysis at the long delay only expressed as a percent of the previous day's baseline, following nicotine (Nic) varenicline (Var), or PNU-282987 (PNU) administration.

	Cum coc intake (mg/kg)	Max % of baseline (dose, mg/kg)		
		Nic	Var	PNU
Cocaine-naive				
1681	0	126 (0.0003)	140 (0.01)	131 (0.01)
1682	0	141(0.001)	135 (0.003)	137 (0.1)
1696	0	137 (0.1)	137 (0.001)	126 (0.03)
1756	0	179 (0.03)	143 (0.001)	136 (0.003)
Ave		145.8	138.6	132.4
SEM		16.2	3.0	4.3
Cocaine-experienced				
1374	2108	201 (0.1)	153 (0.03)	155 (0.003)
1375	1077	150 (0.1)	121 (0.001)	123 (0.3)
1377	1750	152 (0.1)	120 (0.03)	147 (0.1)
Ave		167.6	131.3	141.6
SEM		20.6	13.4	12.0

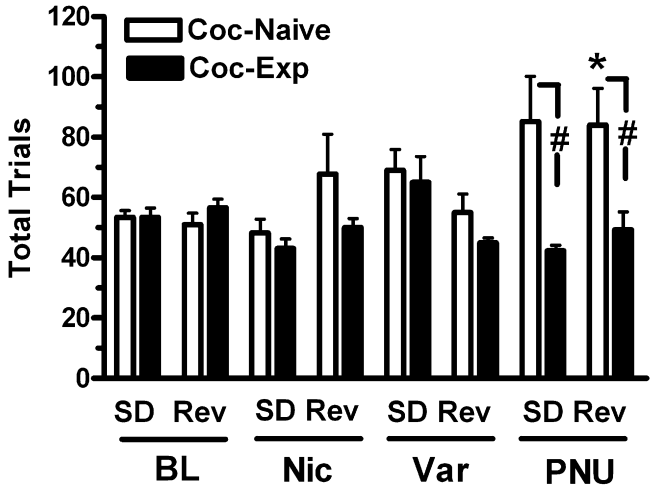

Fig. 5. Group means (±SEM) for the number of trials completed to acquire stimulus discrimination (SD) and reversal (SDR) learning under baseline (BL) conditions and following the doses of nicotine (Nic), varenicline (Var), and PNU-282987 (PNU) that engendered the greatest % accuracy on the DMS task in cocaine-naive (Coc-Naive) and cocaine-experienced (Coc-Exp) monkeys; $^{*}p < 0.05$ significantly different from BL; $\#p < 0.05$ significantly different between groups.

agonists enhance cognitive performance in healthy cohorts (e.g., Rezvani and Levin, 2001; Hahn et al., 2003; Katner et al., 2004; Castner et al., 2011) and demonstrate similar cognitive-enhancing effects on working memory in a monkey model of cocaine abuse.

Regardless of subtype-selectivity, when tested in monkeys performing a DMS task, each nAChR agonist produced similar enhancement on working memory at the long delays in cocaine-naive and cocaine-experienced monkeys. The current results are the first cognitive assessment of varenicline and PNU-282987 conducted in monkeys and are similar to the pro-cognitive effects of acute administration of varenicline and PNU-282987 on measures of attention and memory in drug-naive rodents (Chan et al., 2007; Redrobe et al., 2009; Rollema et al., 2009 Vicens et al., 2011). Similar to other studies in drug-naive rhesus monkeys (e.g., Hironaka et al., 1992; Katner et al., 2004), acute nicotine administration improved working memory performance at the longest delay values, and to a greater extent than either subtype-selective drug alone. In fact, the cognitive enhancing effect of nicotine in our model (average across all monkeys, ~50% increase at the longest delay) was greater than those reported in previous studies (~15% increase at the longest delay; for review see Buccafusco et al., 2005). These differences may be explained by DMS parameters. In the current study, delays and distracter images were manipulated to produce low levels of accuracy (30–55%) at the longest delay whereas in most other studies the longest delays are still associated with >50% accuracy under baseline conditions.

Both α4β2* and α7-selective nAChR agonists can stimulate DA release in striatal and cortical brain regions (e.g., Chan et al., 2007; Livingstone et al., 2009; Rollema et al., 2009) and have shown cognitive enhancing effects in healthy subjects (e.g. Rezvani and Levin, 2001; Hahn et al., 2003; Katner et al., 2004; Castner et al., 2011) as well as animal models of Parkinson's Disease (e.g., Decamp and Schneider, 2006, 2009), a neuropathology associated with hypodopaminergic activity. The relationship between DA function and cognition has been described as an inverted-U-shaped curve such that doses necessary to enhance memory in a hypofunctional DA state may impair cognition in healthy individuals (Cools and D'Esposito, 2011). In monkeys, cocaine-self-administration engendered a hypodopaminergic state (for review see Gould et al., 2012b), altered the sensitivity to a pharmacological challenge (Blaylock et al., 2011) and in the same cohort of monkeys as the present study, produced differences in glucose utilization during a cognitive task (Gould et al., 2012a). Thus, while we expected cognitive enhancing effects of nAChR agonists in both cocaine-experienced and cocaine-naive monkeys, we expected to see differences in the dose-range engendering these effects, and differences in maximal cognitive enhancement. Contrary to our hypothesis, nicotine was equally effective on enhancing working memory in cocaine-experienced and cocaine-naive monkeys. Although not statistically different, the doses of nicotine that engendered the maximal increase in accuracy in 3 of 4 cocaine-naive monkeys were lower than the doses that produced maximal cognitive-enhancing effects in the cocaine-experienced monkeys and the range extended 2.5 log-units (Table 3), suggesting differential sensitivity to nAChR-mediated cognitive enhancement. To further evaluate our hypothesis that cocaine alters the effects of nAChR agonists on cognition, we tested the same doses that engendered peak cognitive enhancing effects on DMS, on a second task known to be mediated via different brain regions, a stimulus discrimination and reversal task (e.g., Chudasama and Robbins, 2006). Although a more in-depth evaluation involving complete dose–response curves is warranted, the doses of PNU-282987 that improved DMS performance in both groups disrupted reversal learning performance in the cocaine-naive group only, supporting a decreased sensitivity to nAChR-mediated cognitive effects in the cocaine-experienced group. The observation that cocaine-experienced monkeys had higher [^{11}C]-nicotine receptor availability in the hippocampus may provide a potential mechanism for this differential sensitivity. These findings extend earlier PET imaging work in these monkeys showing differential glucose utilization in cocaine-experienced vs. cocaine-naive monkeys (Gould et al., 2012a).

Chronic cocaine use is associated with decreased dopaminergic function that persists during abstinence (see Volkow et al., 1999, 2004 for reviews); the effects of cocaine on the acetylcholine system have not been well characterized. Adinoff et al. (2010) reported differential effects of nicotinic or muscarinic agonist and antagonist administration on regional cerebral blood flow in cocaine addicts and healthy controls although both groups included smokers, a potential confound when assessing ACh function. To the best of our knowledge, the present study is the first to examine the effects of cocaine self-administration on nAChR availability *in vivo*. Despite higher binding across most brain regions in the cocaine-experienced group, the only region where nAChR availability was significantly different between cocaine-experienced and cocaine-naive monkeys was in the hippocampus. Greater nAChR availability associated with chronic cocaine exposure parallels findings in rodents and humans following chronic nicotine exposure. Given the strong interactions between DA and ACh neurotransmitter systems (e.g. reviews Williams and Adinoff, 2008; Lester et al., 2010; Maskos, 2010) and similar effects of cocaine and nicotine on mesolimbic reward systems, it was not unexpected to see alterations in the nAChR system following long-term cocaine self-administration that are similar to those noted following nicotine exposure. For example, similar to chronic cocaine use (Volkow et al., 1993; Nader et al., 2006; Martinez et al., 2009 see Volkow et al., 2004 for review) chronic smoking is associated with lower DA D2-like receptor availability as measured by PET (Fehr et al., 2008). Chronic nicotine exposure resulted in greater nAChR binding measured via autoradiography in rodents (Mugnaini et al., 2002; Nguyen et al., 2003; Metaxas et al., 2010), and higher distribution in smokers compared to non-smokers assessed via PET (Muhkin et al., 2008). In contrast to G-protein coupled receptors such as dopamine that are reduced following chronic stimulation (e.g., Nader et al., 2006), the number of ion-channels associated with nAChRs may increase, perhaps in response to decreased receptor

function (e.g., Marks et al., 1993). This may explain the current data – increased receptor availability yet decreased sensitivity to pharmacological challenges of the nAChR system. Although the use of subtype-selective ligands demonstrated selective increases in α4β2* and α7-nAChRs in different brain regions in the aforementioned studies, we cannot speculate on subtype-selective changes based on the current PET data. Although the utility of [^{11}C]-nicotine to assess changes in neurobiology, including the determination of relative receptor distribution has been questioned (e.g., Nordberg et al., 1989; Nyback et al., 1994; Sihver et al., 1999), results from early studies that used [^{11}C]-nicotine to compare nAChR availability between smokers and non-smokers have been corroborated using complex kinetic models, more selective radiotracers, and *ex vivo* autoradiography techniques (e.g., Benwell et al., 1988; Nyback et al., 1994; Breese et al., 1997; Muhkin et al., 2008). Therefore, although novel, selective radiotracers with more optimal profiles for PET imaging exist, [^{11}C]-nicotine may still provide a general assessment of nonselective nAChR availability.

These data highlight several important points. First, a drug may have different effects on cognition based on cognitive demand, domain and underlying substrates mediating cognition (e.g., Cools and D'Esposito, 2011). Reversal learning is mediated in part by the striatum which may play a filtering role between PFC and posterior cortical regions mediating behavioral flexibility to adapt to changing contingencies (for review see van Schouwenberg et al., 2010). Working memory is mediated predominately by cortical regions, including the PFC and temporal cortex and relies on inflexibility such that a stimulus must be retained across a duration of time (for reviews see Chudasama and Robbins, 2006; Cools and D'Esposito, 2011). Secondly, the cognitive-disrupting effects of PNU-282987 suggest a subtype-selective nAChR-mediated effect. α4β2* receptors are located on DA and GABA neurons whereas α7 nAChRs are predominately located on glutamatergic synapses, suggesting a mechanistic explanation for the differential effects on reversal learning (e.g., Livingstone and Wonnacott, 2009). Lastly, repeated exposure to the discrimination and reversal-learning task produced a relatively high level of accuracy across both stages. Thus, under the current parameters, behavior is amenable to cognitive disruptions but not to cognitive-enhancing effects. Although further assessment of DA and ACh function in monkeys with a chronic cocaine self-administration is warranted, the current data provide support for continued evaluation of pharmacological agents such as nAChR agonists for cognitive enhancement to improve executive function in treatment-seeking cocaine users. Future clinical applications should include adjunct cognitive enhancers during initial abstinence to improve behavioral modification or in maintaining abstinence where executive function is integral for re-establishing social and economic success.

Acknowledgments

The authors wish to acknowledge Dr. Robert Kraft and Dr. James Daunais for assistance with MR acquisition, Dr. Donald Gage for assistance with PET data analysis and the technical assistance of Dr. Rachid Nazhi, Kimberly Black, Holly Smith, Tonya Calhoun, Susan Martelle, and Susan Nader. This work was funded by National Institute on Drug Abuse grants DA010584 and DA006634 and the authors declare no conflict of interest.

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