ORIGINAL ARTICLE

Modeling Sensitization to Stimulants in Humans

An [11C]Raclopride/Positron Emission Tomography Study in Healthy Men

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Context: In animals, repeated exposure to stimulant drugs leads to an enhanced drug-induced psychomotor response and increased dopamine release. This phenomenon, known as sensitization, may confer vulnerability to drug addiction or drug-induced psychosis in humans. A similar phenomenon, referred to as endogenous sensitization, is also believed to play a role in the emergence of positive symptoms in patients with schizophrenia.

Objective: To determine whether behavioral and neurochemical sensitization occur in healthy individuals after limited exposure to amphetamine in the laboratory.

Design: Open-label, 1-year follow-up of repeated amphetamine administration in healthy volunteers.

Setting: Department of Psychiatry, McGill University, and McConnell Brain Imaging Center, Montreal Neurological Institute.

Participants: Ten healthy men (mean±SD age, 25.8±1.8 years).

Intervention: Three single doses of amphetamine (dextroamphetamine sulfate, 0.3 mg/kg by mouth) were administered on days 1, 3, and 5.

Main Outcome Measures: Using positron emission tomography and [11C]raclopride, we measured dopamine release in response to amphetamine on the first exposure (day 1) and 14 days and 1 year after the third exposure.

Results: The initial dose of amphetamine caused dopamine release in the ventral striatum (a reduction in [11C]raclopride binding). Consistent with a sensitization-like phenomenon, 14 and 365 days after the third dose of amphetamine there was a greater psychomotor response and increased dopamine release (a greater reduction in [11C]raclopride binding), relative to the initial dose, in the ventral striatum, progressively extending to the dorsal caudate and putamen. A high novelty-seeking personality trait and self-rating assessments indicating impulsivity predicted proneness to sensitization.

Conclusions: Sensitization to stimulants can be achieved in healthy men in the laboratory. This phenomenon is associated with increased dopamine release and persists for at least 1 year.

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ALTERED DOPAMINE NEUROtransmission is believed to play a critical role in the pathogenesis of psychosis and addiction.[1,2] The phenomenon of sensitization that occurs in the midbrain dopamine system when animals are repeatedly exposed to stimulant drugs may help us understand how dopamine neurotransmission becomes dysregulated. Repeated exposure to stimulant drugs or stress results in heightened behavioral and neurochemical responses after reexposure.[3-5] It is generally believed that during the induction of sensitization, the repeated stimulation of dopamine receptors in the ventral tegmental area triggers a cascade of molecular events and changes in neuronal plasticity that, in turn, foster augmented dopamine release.[6] In experimental animals, behavioral sensitization is an enduring,[7,8] time-dependent[3] and context-dependent[9] phenomenon that is associated with a long-lasting increase in drug-induced dopaminergic neurotransmission in the striatum.[3,10-12] Sensitization is reported to cross-react with stress[5] and is variable across individuals.[13] A high locomotor response to novel environments predicts the development of sensitization in rats.[13]

Although widely described in experimental rodents, sensitization has seldom been investigated in humans.[14-18] Sensitization in humans is thought to confer vulnerability to drug addiction[2,19] and is believed to account for psychosis recurrence in long-term methamphetamine users exposed to stimulant drugs or stress after periods of drug abstinence.[20,21] In schizophrenia, endogenous sensitization might underlie the conversion to psychosis in prodromal and remitting patients,[1,22] a hypothesis that has gained partial validity from radioligand positron emission tomography (PET) studies that demon-

Table. Experimental Design

Sensitization Study (n = 10)*							
0 or >22 d	1 d	3 d	5 d		21 d		1 y
PET baseline+	PET AMP	Sham AMP	Sham AMP	14-d latency	PET AMP	Approximately 1-y latency	PET AMP

Control Study (n = 6)						
0	1 d	3 d	5 d		21 d	22 d
PET baseline	AMP	AMP	AMP	14-d latency	PET baseline	AMP

Abbreviations: AMP, participants received amphetamine in a room outside of the positron emission tomography (PET) unit; PET AMP, PET scan performed 1 hour after the administration of amphetamine (dextroamphetamine sulfate, 0.3 mg/kg by mouth); PET baseline, no-drug control scan; PET baseline+, no-drug control scan performed in a counterbalanced order, either before (day 0, n = 5) or after (day 22, n = 5) the sensitization regimen; Sham AMP, sham scan performed 1 hour after administration of amphetamine (these sessions included all aspects of the PET procedure except tracer injection).

*Seven of the 10 participants returned for a final [^{11}C]raclopride amphetamine scan after an approximately 1-year latency (mean ± SD, 407 ± 60 days).

strated exaggerated amphetamine-stimulated dopamine release and symptomatic exacerbation in patients with schizophrenia.[23-25]

Positron emission tomographic neuroimaging with the $D_{2/3}$ receptor ligand [^{11}C]raclopride has been used to investigate dopamine function in humans. There is substantial evidence that an intrasynaptic increase in dopamine translates into a proportional reduction in the binding potential (BP) of [^{11}C]raclopride[26] and that decreasing catecholamine neurotransmission increases BP.[27] This imaging modality has been used successfully to demonstrate dopamine release in response to stimulant drugs in humans.[28-30] The mechanisms underlying the changes in BP in response to changes in dopamine are not fully elucidated. It has been suggested that in the face of an agonist challenge, the internalization of $D_{2/3}$ receptors in the endosomal compartment may, in part, explain the concurrent decrease in [^{11}C]raclopride binding.[26]

The purpose of this study is to test and validate an experimental model of stimulant-induced sensitization on dopamine release in humans by using the PET/[^{11}C]raclopride technique. The specific hypothesis tested is that amphetamine-stimulated dopamine release in the striatum will be enhanced after repeated administration, indicative of neurochemical sensitization.

METHODS

DESIGN OVERVIEW

Participants underwent magnetic resonance imaging (MRI) and 6 experimental sessions (**Table**), receiving 5 oral doses of amphetamine (dextroamphetamine sulfate, 0.3 mg/kg by mouth) in the same physical setting at the same time of day (11 AM or 2 PM). The choice of dose and route of administration implemented in this protocol is based on previous studies[28] that demonstrated that an oral dose of 0.3 mg/kg of dextroamphetamine reliably and safely elicits a significant decrease in [^{11}C]raclopride BP, increased alertness, and measurable levels of amphetamine in plasma. During the sensitization phase, participants received 3 doses of amphetamine with approximately 2 days between each dose (mean±SD, 1.95±0.6 days). A test dose was then administered 2 weeks (mean±SD, 17.2±3.2 days) after the last sensitization dose. The PET/[^{11}C]raclopride scans were conducted during (1) a drug-free session, (2) the first exposure to amphetamine, and (3) the test dose administered 2 weeks after sensitization. Seven of the 10 participants returned for a final [^{11}C]raclopride amphetamine scan after a 12-month latency (mean±SD, 407±60 days). Animal experiments indicate that sensitization is facilitated by consistently pairing the drug with the same context.[31] To that effect, amphetamine doses 2 (mean±SD day 3.1±0.3) and 3 (mean±SD day 5.8±0.73) were administered during sham PET, during which participants underwent all aspects of the PET procedure except radiotracer administration. The main purpose of sham PET was to increase the number of pairings between drug and the PET environment in the expectation that this would facilitate the expression of sensitization. Drug-free baseline (control) PET randomized such that 5 of the 10 participants underwent the drug-free session before receiving the first dose of amphetamine (on experimental day 0) and 5 after completion of the sensitization regimen (on experimental day >22; mean±SD day 31.9±6.5).

A valid measurement of posttreatment amphetamine-induced dopamine release using the PET/[^{11}C]raclopride method described herein requires that $D_{2/3}$ receptor density and affinity, in the absence of amphetamine, remain unchanged as a result of the sensitization regimen. To establish the stability of $D_{2/3}$ density and affinity, measurements of [^{11}C]raclopride BP were obtained in a separate group of healthy men (n=6), 1 before and 1 approximately 2 weeks (mean±SD, 18±2.5 days) after administration of the last of 3 amphetamine doses (see the control study design in the Table).

PARTICIPANTS

Ten men (mean±SD age, 25.8±1.8 years) were recruited to participate in the sensitization study, 7 of whom returned for follow-up PET 1 year later. In addition, 6 healthy men (mean±SD age, 26.5±3.2 years) were recruited to participate in the control study. All the participants scored above the normal population mean on the novelty-seeking subscale of the Tridimensional Personality Questionnaire[32] (participant mean±SD, 20.5±4.1; population mean±SD, 13.7±5.2), which measures individual differences in response to novelty along 4 dimensions on a scale from 0 to 35 (exploratory-excitability vs stoic-reserve, impulsiveness vs reflection, extravagance vs reserve, and disorderliness vs regimentation). Novelty-seeking participants were selected based on the hypothesis that trait novelty-seeking is deemed analogous in humans to the hyperactive motor response to a novel environment in rats,[33] a phenotype believed to predict sensitization.[13] Exclusion criteria were as

follows: current or previous personal history of significant medical illness; personal or first-degree relative history of psychiatric disorder, including but not limited to schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder, and substance abuse or dependence (assessed using the Structured Clinical Interview for *DSM-IV*[34]); current or past use of stimulants for the management of attention-deficit/hyperactivity disorder, narcolepsy, or obesity; current or past use of neuroleptic agents; recreational use of stimulant drugs in the past 12 months; lifetime use of stimulants exceeding 5 or more exposures; regular use of tobacco (>5 cigarettes per day); and positive urine toxicologic test results for illicit drugs (Triage-TM Panel for Drugs of Abuse; Biosite Diagnostics, San Diego, Calif). The experimental and control studies were approved by the Montreal Neurological Institute research ethics board. All the participants provided written informed consent.

PET ACQUISITION PROTOCOL

All the participants were asked to fast and to abstain from caffeine and tobacco for a minimum of 4 hours before each experimental session. They all underwent PET measurements using an ECAT HR+ PET camera (CTI/Siemens, Knoxville, Tenn) with lead septa removed (63-slice coverage, with a maximum resolution of 4.2-mm full-width half-maximum in the center of the field of view). Before each PET session a urine sample was collected for toxicology screening, and a catheter was inserted into the participant's antecubital vein for bolus injection of tracer and blood collection. Attenuation correction was performed via a 10-minute ^{68}Ga transmission scan. Three of the 4 PET measurements conducted as part of the sensitization study (n=10) were performed after open administration of oral amphetamine, 0.3 mg/kg, ingested 60 minutes before the intravenous bolus injection of [^{11}C]raclopride (7 mCi), a drug schedule previously shown by our group to reliably reduce [^{11}C]raclopride BP.[28] In contrast, the 2 PET measurements conducted as part of the control study were performed while participants received no medication. Emission data were collected across 60 minutes in time frames of progressively longer duration. All the participants underwent high-resolution MRI using a 1.5-T scanner (Vision; Siemens) for the purpose of anatomical PET/MRI co-registration.

PARAMETRIC IMAGE GENERATION AND VOXELWISE ANALYSIS

The PET images were reconstructed using a 6-mm full-width half-maximum Hanning filter. Individual dynamic radioactivity PET data were averaged along the time dimension, coregistered to the individual's MRI, and transformed into standardized stereotaxic space.[35] The dynamic PET data were corrected for motion artifacts.[36] Parametric images were generated by computing [^{11}C]raclopride BP at each voxel using a simplified kinetic model that uses the cerebellum as a reference tissue devoid of dopamine $D_{2/3}$ receptors to describe the kinetics of the free and specifically bound ligand.[37] The application of this kinetic model to [^{11}C]raclopride has previously been shown to be insensitive to changes in cerebral blood flow.[38]

REGION OF INTEREST ANALYSIS AND MRI ATLAS-BASED SEGMENTATION

The MRI volumes were corrected for image intensity nonuniformity[39] and were linearly and nonlinearly transformed into standardized stereotaxic space[40] using automated feature matching to the Montreal Neurological Institute template.[41] Automated MRI tissue type classification and segmentation[42] were applied to generate a binary representation of anatomical structures, including the caudate, putamen, and ventral striatum (VS). Five bilateral areas from the segmented brains were selected for region-of-interest (ROI) analysis based on previous works[43,44]: the VS (limbic striatum), the precommissural and postcommissural dorsal caudate (DC) (associative striatum), the precommissural dorsal putamen (DP) (associative striatum), and the postcommissural DP (PDP) (sensorimotor putamen). [^{11}C]Raclopride BP values from each ROI were then extracted and corrected for partial volume effects[45].

BEHAVIORAL AND PHYSIOLOGIC ASSESSMENT OF EARLY AMPHETAMINE EFFECTS

Mood and alertness were assessed at baseline and at 15-minute intervals throughout each experimental session using visual analog scales (VASs)[46] and the Bipolar Profile of Mood States (POMS).[47] The Addiction Research Center Inventory[48] Benzedrine Scale was administered at the end of every experimental session to measure the subjective effects of amphetamine. Physiologic recordings, including electro-oculograms for eye blink rate and heart rate, were performed in 3-minute blocks at baseline and at regular intervals after amphetamine administration (45, 75, 90, and 120 minutes) (F1000 System; Focused Technology, Ridgecrest, Calif). Blood samples for determining plasma cortisol, prolactin, and amphetamine levels were collected via the indwelling catheter at baseline and 45, 90, and 120 minutes after drug administration. Plasma cortisol and prolactin concentrations were measured by means of radioimmunoassay using commercially available kits (Kodak Clinical Diagnostics Ltd, Amersham, England). Plasma amphetamine concentrations were analyzed using electron-capture gas chromatography after extraction and derivatization of amphetamine.[49] The procedure is known to be sensitive to less than 1 ng/mL in plasma. The intra-assay coefficients of variation determined at 50 ng have been shown to range from 2.0% to 2.7% (n=6). The mean interassay coefficient of variation for 25-ng samples is 5.46% (n=10).

STATISTICAL ANALYSIS

In the sensitization study, *t*-maps were generated[38] to assess the contrasts between the drug-free control scan and amphetamine scans at doses 1, 4, and 5 and the profile of time-dependent changes in [^{11}C]raclopride BP as a function of repeated amphetamine administration (BP at dose 1 > BP at dose 4 > BP at dose 5). In the control study, a *t*-map was generated[38] to assess the contrast between the 2 drug-free control scans. Voxel significance was set at $t \geq 4.2$, corresponding to $P < .05$ corrected for multiple comparisons across the entire striatum based on random field theory.[50] The BP values extracted from ROI analysis during amphetamine administration (doses 1 and 4) and baseline control scans were analyzed using 3-way analysis of variance for dependent samples (treatment × ROI × hemisphere). Sphericity was assessed using the Mauchly test, and, when indicated, corrections were made using Greenhouse-Geisser adjustments. When appropriate, least significant difference *t* tests, Bonferroni corrected, were applied to determine the significance of regional differences in BP among the amphetamine dose 1, the amphetamine dose 4, and the drug-free baseline scans. A separate 3-way analysis of variance was conducted to assess differences between BP values extracted from ROI analysis during amphetamine doses 1, 4, and 5 (follow-up) and drug-free baseline for the 7 participants who completed the follow-up study (1 year later). In the control study, measurements of regional [^{11}C]raclopride BP before and 2 weeks after the amphetamine regimen were compared using least significant difference *t* tests, Bonferroni corrected. Behavioral mea-

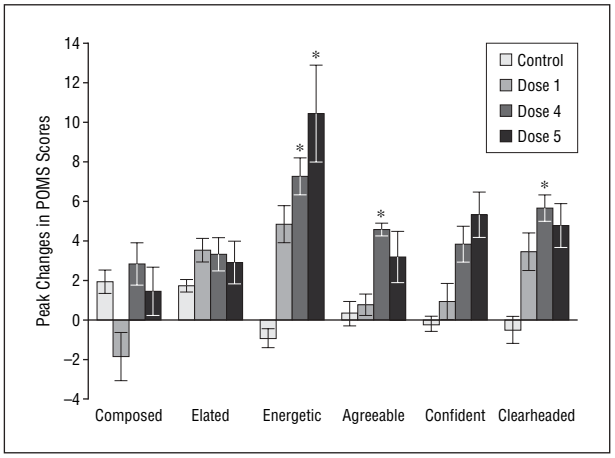

Figure 1. Subjective effects of amphetamine exposure. Profile of Mood States (POMS) scores (peak change from baseline) recorded during the drug-free control scan and the 3 amphetamine positron emission tomography sessions at doses 1, 4 (n=10), and 5 (n=7) after amphetamine (0.3 mg/kg by mouth). *$P<.05$, significantly increased compared with dose 1. Error bars represent SEM.

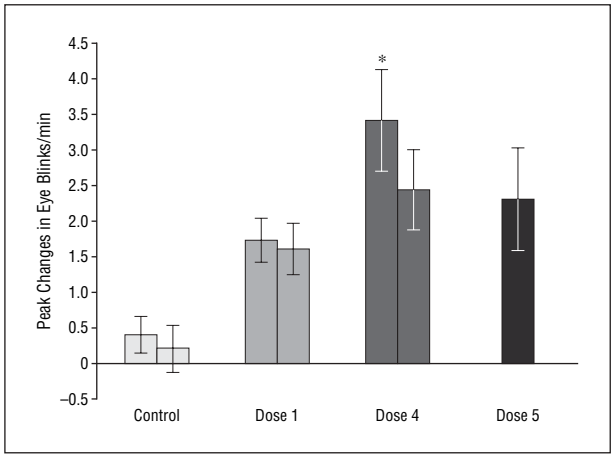

Figure 2. Effects of amphetamine exposure on eye blink rate. Left-side bars: n=10; right-side bars and dose 5: n=7. Error bars represent SEM. *Significantly different from dose 1 ($P=.02$).

surements obtained during the control study were analyzed as described previously herein. Pearson product-moment correlation was applied to [^{11}C]raclopride BP extracted from ROIs to assess whether the novelty-seeking personality trait could predict the extent of neurochemical sensitization ([^{11}C]raclopride BP at doses 4 and 5 minus [^{11}C]raclopride BP at dose 1) and whether the development of behavioral sensitization (behavioral response at doses 4 and 5 minus behavioral response at dose 1) correlated with the reduction in [^{11}C]raclopride BP. Voxelwise linear correlation maps were also generated to test the relationship between sensitization-induced decreases in [^{11}C]raclopride BP and novelty-seeking personality score.

RESULTS

BEHAVIORAL AND PHYSIOLOGICAL MEASURES

Subjective Ratings

Compared with the first amphetamine administration (dose 1), reexposure to a fourth amphetamine dose (dose 4) led to increased energy (POMS energetic: $F_{4,36}=4.36$, $P=.03$; dose 1 vs dose 4: $P=.06$), alertness (VAS alert: $F_{4,36}=11.6$, $P<.001$; dose 1 vs dose 4: $P=.048$), clearheadedness (POMS clearheaded: $F_{4,36}=3.02$; $P=.05$; dose 1 vs dose 4: $P=.009$), and positive mood (POMS agreeable: $F_{4,36}=3.68$, $P=.04$; dose 1 vs dose 4: $P=.002$) (**Figure 1**). Conversely, reexposure to the fourth or fifth dose of amphetamine did not significantly affect amphetamine-induced euphoria (POMS elated and VAS high, euphoria, and rush), anxiousness (VAS anxious), or drug wanting (VAS want-drug) relative to first exposure. The "energy" response to amphetamine remained elevated after the 1-year latency (POMS energetic: $F_{5,30}=3.33$, $P=.056$; dose 1 vs dose 5: $P=.045$, 1-tailed).

Behavioral sensitization to the effects of amphetamine was also achieved, albeit to a lesser extent, in the control study comparing the effects of amphetamine between doses 1 and 4 (Addiction Research Center Inventory: $F_{2,10}=127.6$, $P=.001$; dose 1 vs dose 4: $P=.002$; POMS clearheaded: $F_{2,10}=7.10$, $P=.02$; dose 1 vs dose 4: $P=.03$).

Physiologic Measures

Early amphetamine exposure yielded a time-dependent increase in the number of eye blinks per minute at every session (main effect of time: $F_{4,36}=7.47$; $P=.005$) Relative to the first dose (dose 1), reexposure to amphetamine after the 2-week latency period (dose 4) resulted in a small but significant increase in blinks per minute (mean±SD, 1.1±0.4) (main effect of session: $F_{4,36}=7.47$, $P=.001$; dose 1 vs dose 4: $P=.02$) (**Figure 2**). This effect was still present on amphetamine reexposure 1 year later, although it was not statistically significant (Figure 2). Heart rate response to amphetamine administration was not significantly affected by preexposure to amphetamine ($F_{4,32}=1.25$; $P=.31$).

Neuroendocrine Measures

Relative to the drug-free condition, the first amphetamine dose was associated with a significant increase in cortisol ($F_{1,9}=7.80$; $P=.02$) but not prolactin ($F_{1,9}=1.20$; $P=.30$) plasma levels. There were no differences in amphetamine-induced changes in cortisol or prolactin plasma levels within participants across the different amphetamine sessions.

Plasma Amphetamine

Plasma amphetamine concentrations increased in all sessions equally (main effect of time: $F_{3,15}=64.91$; $P<.001$), with plasma levels peaking on average at 120 minutes (mean±SD: dose 1, 28.5±11 ng/mL, and dose 4, 30.1±11 ng/mL). There was no difference between sessions (main effect of session: $F_{3,15}=0.22$; $P=.73$). Amphetamine plasma levels at 1-year follow-up were not analyzed.

PET/[^{11}C]RACLOPRIDE

Parametric Map *t*-Statistical Tests

Voxelwise analysis of the whole brain revealed significant bilateral clusters of decreased [^{11}C]raclopride BP in

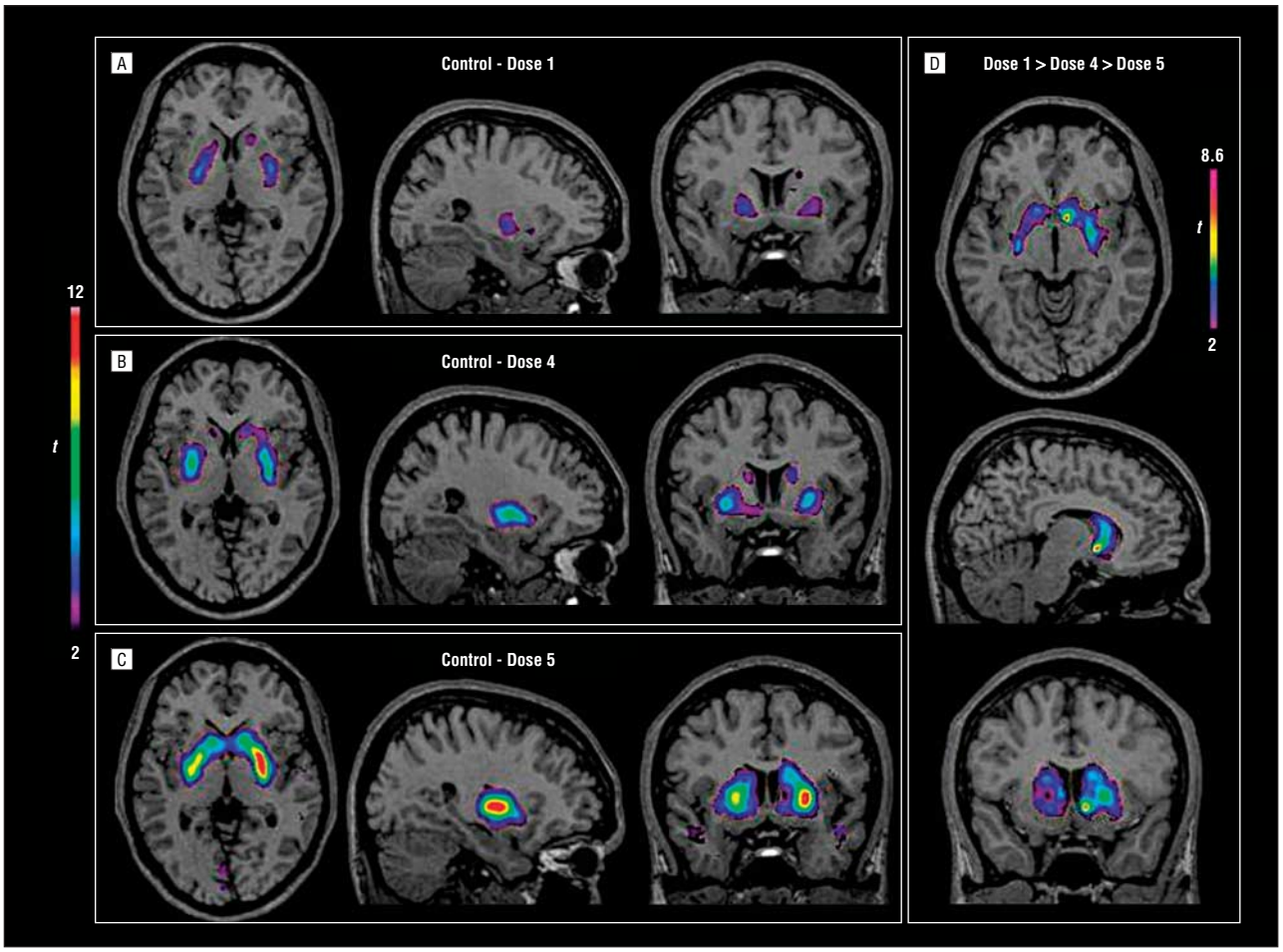

Figure 3. *t*-Statistical maps of [^{11}C]raclopride binding potential (BP) change illustrating a decrease in [^{11}C]raclopride BP after dose 1 (A), dose 4 (B), and dose 5 (C) amphetamine administrations (0.3 mg/kg by mouth) relative to the drug-free control condition (x, y, z=28, 2, 0). D, General linear model with dose as a regressor illustrating the progressive decrease in [^{11}C]raclopride BP as a factor of repeated amphetamine doses (x, y, z=9, 7, –6). Colored *t*-maps are overlaid on an averaged T1-weighted magnetic resonance image of all the participants.

response to amphetamine doses 1, 4, and 5 relative to the drug-free control scan ($t \geq 4.2$; $P < .05$) (**Figure 3**A-C). The clusters appear smaller in height and extent in the drug-free, dose 1 *t*-map compared with the drug-free, dose 4 or drug-free, dose 5 *t*-maps, suggesting increased dopamine release in response to doses 4 and 5. The region of statistically significant reduction in [^{11}C]raclopride BP for dose 1 (relative to control) was confined to the VS and the PDP. However, with doses 4 and 5, there was progressive anterodorsal extension of this region to include the DC and the anterior precommissural DP. Figure 3D illustrates the trend toward decreased BP as a factor of repeated drug administration. No significant clusters were detected in the comparison between drug-free [^{11}C]raclopride BP obtained before and after the sensitization-inducing regimen in the control study.

ROI Analysis

Two-way repeated-measures analysis of variance of [^{11}C]raclopride BP using ROI and session (drug-free, dose 1, dose 4) as factors confirmed the *t*-map results (**Figure 4**). Amphetamine doses 1 and 4 resulted in a decreased [^{11}C]raclopride BP relative to the drug-free session in 2 subcompartments of the striatum (ROI × session interaction: $F_{4,36} = 3.89$; $P = .01$). In bilateral VS and PDP, this effect corresponded to a significant decrease in the mean ± SD [^{11}C]raclopride BP of –17.7% ± 9% in the VS (Bonferroni corrected for 1-tailed planned comparison; $P = .03$) and –7.3% ± 3% in the PDP ($P = .03$) after dose 1 of amphetamine and –28.4% ± 9% in the VS ($P = .007$) and –14.3% ± 3% in the PDP ($P = .001$) after dose 4. The first dose of amphetamine did not significantly reduce [^{11}C]raclopride BP in the anterior and posterior DC or in the anterior precommissural DP. Amphetamine dose 4 resulted in a greater [^{11}C]raclopride BP reduction than dose 1 in VS and PDP, corresponding to an additional mean ± SD –12.1% ± 5% (VS; $P = .02$) and –7% ± 3.5% (PDP; $P = .03$) reduction in [^{11}C]raclopride BP but no difference in DC (–0.3% ± 2%; $P = .99$). The inspection of individual data indicated that 7 of 10 participants displayed a change in BP greater than 10% in the VS. At 1-year follow-up (dose 5, n=7), amphetamine further reduced [^{11}C]raclopride BP relative to the drug-free session (mean ± SD: –24.23% ± 12.5% in the VS, –7.84% ± 4.5% in the DC, and –20.10% ± 4.8% in the PDP). This effect corresponded to significant BP decreases from dose 1 (ROI × session interaction: $F_{6,36} = 2.48$; $P = .04$) (–15.40% ± 5.4% in the VS, $P = .02$; –7.38% ± 5.2% in the DC, $P = .09$; and –13.97% ± 5.3% in the PDP, $P = .01$) and from dose 4

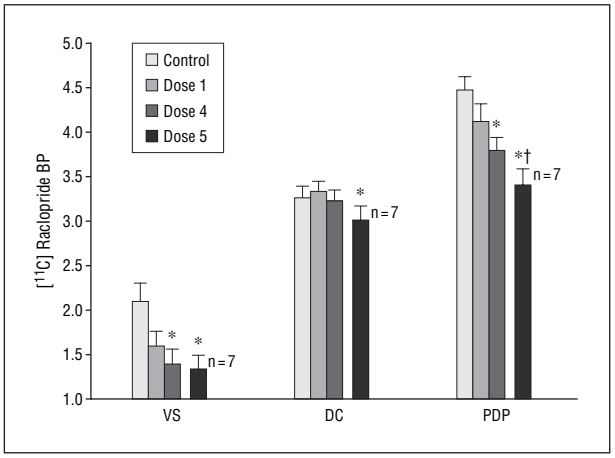

Figure 4. Mean [^{11}C]raclopride binding potential (BP) in 3 subcompartments of the striatum during the control drug-free scan and after amphetamine administration before (dose 1) and after repeated amphetamine (dose 4) (n=10) and at 1-year follow-up (n=7). DC indicates associative precommissural dorsal caudate; PDP, postcommissural dorsal putamen; VS, ventral striatum. *Significantly different from dose 1 ($P<.05$). †Significantly different from dose 4 ($P<.05$). Error bars represent SEM.

(–9.09%±2.5% in the DC and –9.05%±3.2% in the PDP). This effect was present in 6 of the 7 participants studied at 1 year.

To investigate whether repeated exposure to amphetamine affected baseline (drug-free) [^{11}C]raclopride BP, we compared the baseline [^{11}C]raclopride BP of participants who underwent the drug-free scan before first exposure (n=5; mean±SD striatal BP=3.0±0.2) with that of those whose scan was obtained after the last exposure (dose 4) (n=5; mean±SD striatal BP=2.9±0.36) and found that the 2 groups did not differ in baseline [^{11}C]raclopride BP ($t=0.469$; $P=.65$). This finding was again confirmed in the 6-participant cohort (control study) in which baseline [^{11}C]raclopride BP was measured before and after the sensitization-inducing regimen. Specifically, the mean±SD striatal BP was 2.35±0.15 before and 2.36±0.23 after repeated amphetamine administration (main effect of session: $F_{1,5}=0.01$; $P=.94$). Voxelwise analyses confirmed that baseline (drug-free) [^{11}C]raclopride BP was not significantly decreased by the repeated amphetamine sensitization regimen.

BRAIN-BEHAVIOR RELATIONSHIPS

There were regionally specific correlations between dopamine release and various behavioral responses that sensitized to repeated amphetamine exposure. Among those, the increase in eye blink rate (dose 4–dose 1: PDP, $r=–0.73$; $P=.02$), energy (dose 4–dose 1: PDP, $r=–0.67$; $P=.03$; dose 5–dose 1: VS, $r=–0.69$; $P=.04$), and alertness (dose 5–dose 1: VS, $r=–0.75$; $P=.02$) correlated with the reduction in [^{11}C]raclopride BP (dose 4–dose 1). Moreover, the magnitude of the reduction in [^{11}C]raclopride BP in the DC was proportional to novelty-seeking trait scores (dose 5–dose 1: DC, $r=–0.73$; $P=.06$) (**Figure 5**) and impulsiveness (dose 5–dose 1: DC, $r=–0.85$; $P=.01$).

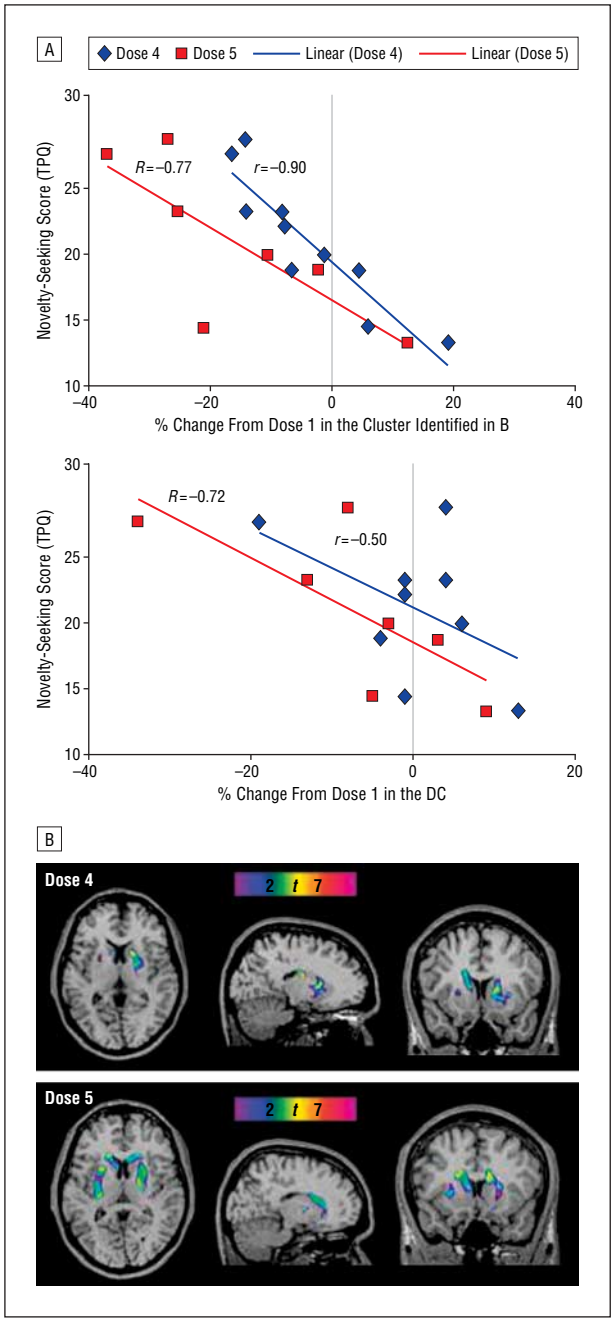

Figure 5. Relationship between dopamine sensitization and novelty-seeking personality. A, Comparison of the percentage change in [^{11}C]raclopride binding potential (BP) compared with dose 1 and the novelty-seeking score. The higher the novelty-seeking score, the greater the effect of (dose 4 and dose 5) amphetamine-induced changes in [^{11}C]raclopride BP from dose 1; this effect involves changes in the dorsolateral regions. B, Voxelwise regression maps illustrating the relationship between the novelty-seeking score and sensitization-induced changes in [^{11}C]raclopride BP. Top, Percentage difference between dose 4 and dose 1 (x, y, z=13, 15, 7); bottom, percentage difference between dose 5 and dose 1 (x, y, z=1, 15, 15). DC indicates precommissural and postcommissural dorsal caudate; TPQ, Tridimensional Personality Questionnaire.

COMMENT

Although widely described in experimental animals, sensitization to amphetamine has seldom been investigated in humans.[15,16] Herein we report, using the [^{11}C]raclo-

pride PET method, that repeated amphetamine administration in humans leads to persistent behavioral and neurochemical sensitization, characterized by increased psychomotor, energy, agreeableness, and alertness responses on reexposure, together with a proportional increase in amphetamine-stimulated dopamine release, primarily observed in the VA and PDP and progressing to include the DC at 1-year follow-up. Consistent with previous articles,[28,44] early amphetamine administration (dose 1 vs drug-free baseline) resulted in a decreased [^{11}C]raclopride BP confined to the VS and PDP. The amphetamine-induced dopamine response grew progressively across time, in amplitude and extent, from the initial amphetamine scan to the 14-day and 1-year follow-up studies, consistent with observations in rodents, indicating that sensitization is a delayed and enduring phenomenon, occurring after withdrawal periods of 2 weeks or more and persisting for up to 1 year.[3,8]

These results suggest a regional disparity in the temporal emergence of sensitization, with the DC demonstrating only evidence of dopamine response to amphetamine at 1 year. This progression is reminiscent of effects reported in nonhuman primates after repeated cocaine administration where changes occurring initially in the VS eventually spread to more dorsal regions. This may reflect a difference between the dopamine projections to ventral and dorsal striatal regions in their ability to express sensitization, as suggested by some animal experiments.[51-53] However, an alternative explanation for the lack of effect observed in the DC in the early phase of sensitization might be the presence of threshold effects. Effects of amphetamine on [^{11}C]raclopride BP being relatively modest in the DC,[28,29,44] it may be that sensitization-related changes are also present but undetected in the DC after the 14-day drug-free period.

Also consistent with previous clinical studies[15,16] indicating that sensitization of certain effects (eg, vigor) may coexist with tolerance to others (eg, "liking"), repeated amphetamine exposure increased the arousing/psychostimulant and motor effects of the drug (alertness, energy, and eye blink rate) but had little or no effect on drug-induced high and euphoria. This finding is in line with the general hypothesis that dopamine mediates only some of the behavioral components of sensitization.[3] Furthermore, this observation is in agreement with what is known about the functional organization of the striatum.[54] Specifically, the increase in eye blink rate was associated with higher dopamine in the motor subdivision of the striatum (PDP), whereas alertness was associated with a change in the limbic striatum (VS), which is known to play a role in motivated responses and sustained attention. Finally, enhanced energy was associated with higher dopamine levels in the VS and PDP, perhaps reflecting the close interaction of striatal subdivisions and the anatomical arrangement of the striatum, which promotes a hierarchical flow of information from the limbic to the motor system.[54]

The finding that behavioral sensitization may be achieved experimentally in humans and that it is associated with an enduring enhancement of dopamine release in response to amphetamine rests on the following methodologic and conceptual considerations: (1) Did the drug sensitization regimen affect $D_{2/3}$ receptor density (or affinity), hence modifying the $D_{2/3}$ baseline set point across time? (2) Could the enhancement of amphetamine behavioral and neurochemical effects be confounded by a change in the plasma levels of amphetamine? (3) Are stimulant-induced changes in [^{11}C]raclopride BP stable across time and reproducible within the participant? (4) What is the role of context or anticipation of drug effects, if any? (5) How generalizable is this finding? (6) Why is there no evidence of sensitization in drug-dependent participants?[55]

1. The validity of the proposed interpretation, that the change in [^{11}C]raclopride BP during the last 2 amphetamine scans (doses 4 and 5) reflects a change in the extent to which amphetamine stimulates dopamine release, rests on the assumption that baseline BP is unaffected by the sensitization-inducing regimen. [^{11}C]Raclopride BP represents a ratio between the concentration of binding sites (B*max*) and the affinity of [^{11}C]raclopride for $D_{2/3}$ receptors (K*d*). A change in B*max* or K*d* would render the study difficult to interpret. Although an abundant literature suggests that the development or expression of sensitization does not entail major changes in dopamine D_2 receptor density,[10] reports of D_3 overexpression[56] and changes in D_2 receptor affinity have been made by some researchers[57] although not by others.[10] In the present study, half of the participants underwent the drug-free scan (baseline) at the end rather than at the beginning of the drug regimen, in effect testing for a possible effect of repeated amphetamine exposure on dopamine receptor density. [^{11}C]Raclopride BP measurements obtained before vs after sensitization were not significantly different. This was further confirmed in a separate group of controls (n=6) in whom drug-free [^{11}C]raclopride BP was measured before and 14 days after administration of the same amphetamine regimen described previously herein and found to be unchanged.

2. Plasma levels of amphetamine were almost identical across sessions, suggesting that differences in amphetamine drug disposition could not account for the enhancement of the dopamine response to amphetamine.

3. In the present study, [^{11}C]raclopride BP was measured across 1 year. The stability and reproducibility of this method have previously been demonstrated in test-retest studies: the long-term stability of baseline [^{11}C]raclopride BP (11 months)[58] and the within-participant reproducibility of an amphetamine-induced decrease in ligand binding ([^{123}I]IBZM single-photon emission computed tomography)[59] have been demonstrated.

4. In the present design, all drug administrations took place in the PET environment to facilitate the expression of behavioral sensitization.[60] What proportion of the behavioral and neurochemical effects described herein could be accounted for by responses to associative cues and anticipation is not known. Indeed, evidence of dopamine release in anticipation of reward has been observed in humans during placebo administration and in primates faced with cues that predict reward.[61,62] Nonetheless, although the expression of sensitization can be modulated by context,[60,63,64] neuroadaptive changes thought to underlie neurochemical sensitization are

known to occur in vitro[65,66] and independent of the drug-paired context.[67,68] Until further experiments designed to test for conditioning are completed, the possibility that this effect may have contributed to an enhanced response to stimulant cannot be discarded.

5. The present study population consisted of healthy men scoring high on novelty-seeking traits. Whether these findings of sensitization to amphetamine can be generalized to other nonclinical or clinical populations is unknown, although plausible. Neurochemical sensitization correlated with the novelty-seeking score, an observation analogous to observations made in animal experiments, supporting theories linking this personality trait to vulnerability for substance abuse[32,69]: rodents with a high locomotor response to novel environments, compared with low responders, exhibit higher stress and drug-induced firing in mesencephalic dopaminergic neurons, sensitize more readily to amphetamine, and demonstrate a higher propensity to self-administer drugs of abuse.[33,70-72]

6. A report that detoxified cocaine-dependent patients exhibited an apparent blunting of dopamine responsiveness to methylphenidate compared with controls may seem incompatible with the present results.[55] Note, however, that in this study the paradigm involved a novel drug (methylphenidate) administered in a novel environment (PET suite), possibly diminishing the probability that a sensitized response would be expressed. Indeed, Volkow and colleagues[73] argued that a dysfunctioning dopamine system in long-term drug users might be responsible for decreased sensitivity to non–drug-associated context and nondrug reinforcers, a theory that is supported by functional MRI experiments demonstrating blunted response in cocaine abusers to salient nondrug stimuli[74] along with increased response to drug cues. Another plausible explanation for the blunted dopamine response to methylphenidate in long-term cocaine users could be that the decreased baseline [^{11}C]raclopride BP in these individuals, interpreted as decreased dopamine D_2 receptor levels, in fact reflects elevated dopamine levels at baseline. Specifically, relative to stimulant-naïve individuals, long-term cocaine users might be exhibiting cross-sensitization[75-79] to the stress related to the novel PET environment or, alternatively, might be anticipating drug reward,[61,80] in either case releasing more dopamine during the baseline scan, hence making it difficult to detect further reductions in [^{11}C]raclopride BP. Finally, the possibility still exists that although sensitization occurs early during drug exposure, it could be followed by other subsequent neuroadaptive mechanisms (changes in system integrity) related to the amount or duration of drug used that might result in blunted dopamine responses.

Altogether, the limitations discussed herein notwithstanding, the evidence presented herein strongly suggests that sensitization, expressed in the form of persistent changes in brain dopamine neurochemistry, may occur in humans after exposure to stimulants. This finding has important clinical and pathophysiologic implications.

Sensitization-like phenomena are believed to be central to the development of drug-seeking behavior.[2,19] Results of animal studies[81] indicate that sensitization increases the motivation to self-administer drugs, possibly via a mechanism that involves dopamine. It is thought that enhanced dopamine response to drugs may act to increase the incentive value of the drug,[2,19] a hypothesis supported by PET studies showing that the dopamine response to amphetamine correlates with desire for the drug.[28,82] The finding of a relationship between proneness to sensitization and novelty-seeking points to an interesting mechanism linking temperament to vulnerability to addiction.[83]

Second, a phenomenon similar to sensitization may also explain why clinically stable remitted patients with chronic-relapsing disorders such as psychosis or addiction relapse in response to environmental stressors or drugs of abuse.[84]

Psychostimulants are commonly prescribed to children with attention-deficit/hyperactivity disorder. Although studies[85,86] have yielded no conclusive evidence that the therapeutic use of methylphenidate is unsafe, the present findings emphasize the need to further investigate the consequences of long-term treatment with stimulant drugs.

In conclusion, the present results support the feasibility of studying sensitization to stimulants in non–drug-using individuals in the laboratory. Future studies should determine the extent to which conditioning/drug-associated context have contributed to the effects and whether this effect can be generalized to other study populations, including detoxified drug users, adults with attention-deficit/hyperactivity disorder, and individuals with a history of trauma.

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