Amphetamine Primes Motivation to Gamble and Gambling-Related Semantic Networks in Problem Gamblers

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Previous research suggests that gambling can induce effects that closely resemble a psychostimulant drug effect. Modest doses of addictive drugs can prime motivation for drugs with similar properties. Together, these findings imply that a dose of a psychostimulant drug could prime motivation to gamble in problem gamblers. This study assessed priming effects of oral D-amphetamine (AMPH) (30mg) in a within-subject, counter-balanced, placebo-controlled design in problem gamblers ($n=10$), comorbid gamblerdrinkers ($n=6$), problem drinkers ($n=8$), and healthy controls ($n=12$). Modified visual analog scales assessed addictive motivation and subjective effects. A modified rapid reading task assessed pharmacological activation of words from motivationally relevant and irrelevant semantic domains (Gambling, Alcohol, Positive Affect, Negative Affect, Neutral). AMPH increased self-reported motivation for gambling in problem gamblers. Severity of problem gambling predicted positive subjective effects of AMPH and motivation to gamble under the drug. There was little evidence that AMPH directly primed motivation for alcohol in problem drinkers. On the reading task, AMPH produced undifferentiated improvement in reading speed to all word classes in Nongamblers. By contrast, in the two problem gambler groups, AMPH improved reading speed to Gambling words while profoundly slowing reading speed to motivationally irrelevant Neutral words. The latter finding was interpreted as directly congruent with models, which contend that priming of addictive motivation involves a linked suppression of motivationally irrelevant stimuli. This study provides experimental evidence that psychostimulant-like neurochemical activation is an important component of gambling addiction.

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INTRODUCTION

Problem gambling is often characterized as a behavioral addiction (Ibanez *et al*, 2003; Potenza, 2001). Like substance addictions, problem gambling is thought to involve disturbances in neurochemical function. In line with this, correlational studies have found anomalies in a number of neurochemical systems in problem gamblers, including dopamine, norepinephrine, and serotonin (Bergh *et al*, 1997; Moreno *et al*, 1991; Roy *et al*, 1988). To date, no research appears to have used a pharmacological probe within a controlled experimental framework to assess neurochemical processes underlying problem gambling.

The motivation to engage in appetitive behavior in general, including psychoactive drug use, can be primed by exposure to a dose of the target reinforcer (Cornell *et al*,

1989; Duarte *et al*, 2003; Le *et al*, 1998; Leri and Stewart, 2001; Shalev *et al*, 2002). In a seminal study, Konorski (1967) trained dogs to perform two different responses, one for food and one for water. When the animals were later tested while both hungry and thirsty, a priming dose of food led to the food-seeking response whereas a priming dose of water led to the water-seeking response. This finding demonstrates the motivational specificity of priming effects.

Psychoactive drugs are widely used as primes to assess addictive motivation. Drug priming specifically refers to the case in which the noncontingent delivery of a pharmacological agent activates or reinstates a previously established drug-seeking or drug-taking response (Stewart and de Wit, 1987). Like drug reinforcers, gambling has been found to produce priming-like effects in problem gamblers. For example, exposure to a brief gambling episode is associated with greater reported desire to gamble and loss of control over gambling in problem vs nonproblem gamblers (Loba *et al*, 2001). Also, in a laboratory-based setting, problem gamblers' monetary risk behavior (wagering) escalates over the course of trials during a gambling episode (Ladouceur *et al*, 1986, 1987, 1991). These findings indicate that, like drugs of abuse in drug abusers, exposure to gambling

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activity can activate motivation to gamble and gambling behavior in problem gamblers.

A common process implicated in drug priming is the release of dopamine in the nucleus accumbens (eg Self and Nestler, 1998; Shaham and Stewart, 1996). However, the degree of priming is also strongly affected by the degree of commonality between the prime and target drugs. Drugs from the same class as the target drug are often effective primes (eg amphetamine (AMPH) for cocaine) whereas drugs from a different class than the target (eg THC for cocaine) usually are not (Schenk and Partridge, 1999; Shalev *et al*, 2002; Speelman *et al*, 1999). Thus, drug priming appears to involve both a common process and a specific process or processes, related to the particular neurochemical effects of the target reinforcer.

A number of findings suggest that gambling can induce effects that closely resemble a psychostimulant drug effect. Problem gamblers use strikingly similar language to describe a bout of gambling as psychostimulant abusers use to describe the effects of their drug use (eg arousal, excitement, increased concentration, elevated confidence) (Hickey *et al*, 1986). The profile of an episode of gambling and psychostimulant use is also similar in that both are characterized by marked behavioral perseveration (Dickerson *et al*, 1987; Ridley *et al*, 1988). Neuroimaging research further indicates that anticipation or receipt of money induces selective patterns of activation in brain dopamine pathways (Knutson *et al*, 2001). These pathways are also critically involved in the reinforcing effects of psychostimulant drugs (Mackey and van der Kooy, 1985; Spyraiki *et al*, 1982; Yokel and Wise, 1978).

These kinds of evidence imply that a psychostimulant drug may recruit a set of effects similar to those recruited by gambling itself. If so, a dose of a psychostimulant drug may serve to prime motivation to gamble much like a 'dose' of gambling. To assess this possibility, we employed the prototypic psychostimulant, D-AMPH, as a pharmacological prime in problem gamblers and Nongambler controls.

To test the selectivity of AMPH's priming effects we also examined the drug's effects on motivation for alcohol in problem drinkers. To date, no research appears to have examined such potential priming effects of AMPH in this population. In healthy volunteers, alcohol itself can induce both stimulant and sedative effects (Boerngen-Lacerda and Souza-Formigoni, 2000; King *et al*, 2002; Martin *et al*, 1993; Schechter and Lovano, 1982). Correlational evidence also indicates some correspondence in the subjective effects of alcohol and AMPH in healthy volunteers (Holdstock and de Wit, 2001). Nevertheless, alcohol's most pronounced and consistent subjective effects are sedative (Holdstock and de Wit, 1998, 2001; Schuckit *et al*, 1991; Walsh *et al*, 1991) consistent with its designation as a CNS depressant, whereas AMPH's primary effects are stimulant (de Wit *et al*, 2002; Heishman and Henningfield, 1991; Zacny *et al*, 1992). Research with animals further indicates that the discriminative stimulus properties of alcohol are unlike those of AMPH (Druhan *et al*, 1991). The AMPH stimulus primarily involves mono-amine activation (Brauer *et al*, 1997; Furmidge *et al*, 1991; Ranaldi *et al*, 2000; Sasaki *et al*, 1995), whereas the alcohol stimulus primarily involves GABA-A activation and glutamate inhibition (Jackson *et al*, 2003; Kostowski and Bienkowski, 1999; Shelton and Grant,

2002; Stoleran and Olufsen, 2001), along with some serotonergic elements (Maurel *et al*, 1997). In animal studies, systemic AMPH, at a range of doses, does not reliably prime alcohol seeking in animals familiar with alcohol (Halladay *et al*, 1999; Hubbell *et al*, 1991; Linseman, 1990), but consistently primes seeking of another psychostimulant—cocaine—in animals familiar with cocaine (de Wit and Stewart, 1981; Lynch *et al*, 1998; Schenk and Partridge, 1999).¹ Based on these animal findings, we would not expect AMPH to prime motivation for alcohol in problem drinkers. To further assess this issue, we also included a group of problem gamblers with concurrent alcohol problems in the present design. In line with previous studies (Loba *et al*, 2001; Krystal *et al*, 1994), motivation to gamble and motivation for alcohol were assessed by means of self-report using modified visual analog scales.

To further examine processes involved in the effects of AMPH, we also incorporated a task that assessed activation of gambling-related memory networks or semantic domains. A strategy widely used to assess activation of memory networks is the semantic priming procedure (Neely, 1991). Semantic priming is defined as an improvement in reaction time (ie key press or vocal reading response) to a target word (eg doctor) when it is preceded by a semantically related prime word (eg nurse) relative to a semantically unrelated prime word (eg peach) (Ellis and Hunt, 1993, p 60). Variants of this task have also been used in addiction research (Weingardt *et al*, 1996; Weinstein *et al*, 2000; Zack *et al*, 1999).

Primed motivation to engage in addictive behavior has been linked with increased 'incentive salience' of target reinforcers (Robinson and Berridge, 1993, 2001). From a cognitive science perspective, salience involves selective activation of concepts related to the target reinforcer in memory (Bower, 1981; Volkow *et al*, 2002). Such activation should be directly measurable in terms of faster access to motivationally relevant vs motivationally irrelevant concepts. To test this hypothesis, we modified the conventional semantic priming task to assess direct drug-induced priming of addictive memory networks. Thus, while a verbal associate serves as the prime in conventional semantic priming procedures, in the present study, AMPH served as the priming stimulus for activation of motivationally relevant words. A voice-activated computerized task measured reading speed (ms) to gambling-related target words and words from several other categories under AMPH and placebo, but in the absence of any preceding verbal primes. On any given trial, subjects simply saw a ready signal and responded to the subsequent target word as quickly as possible. This procedure represents a melding of two established methodologies: pharmacological priming and semantic priming. To distinguish this procedure from conventional semantic priming tasks, we refer to it as the Lexical Salience Task.

¹ At some doses, microinjections of amphetamine into the nucleus accumbens have been found to increase drinking behavior in rats, primarily by altering the processes that normally serve to regulate drinking cessation rather than the processes that serve to prime alcohol seeking or to initiate drinking (Samson *et al*, 1999).

It was predicted that AMPH would significantly increase motivation to gamble in problem gamblers. This would be evident in self-reported motivation to engage in gambling and by faster response time (RT) to gambling-related (eg wager) vs motivationally irrelevant, neutral words (eg window) on the Lexical Salience Task. AMPH was not expected to prime motivation for alcohol in problem drinkers.

MATERIALS AND METHODS

Study Overview and Design

A double-blind, placebo-controlled, counter-balanced, between-within design was employed. The between-subjects variables were Gambler Status (Gambler, Nongambler) and Drinker Status (Drinker, Nondrinker). These variables were fully crossed, resulting in four cells: Gambler Nondrinkers (G; $n = 10$), GamblerDrinkers (GD; $n = 6$), Drinker Nongamblers (D; $n = 10$), and Nongambler Nondrinker Controls (C; $n = 12$).²

The within-subjects variable was Treatment: AMPH vs placebo. Order of Treatment was randomly counter-balanced across subjects (Ss). Ss attended four sessions in all: A drug screening and interview, physician's exam, and two procedurally identical test sessions, 1 week apart. They received \$500 for participation.

Subjects

Ss (11 females, 25 males), ages 21–58 years ($M = 36.6$), were recruited by newspaper advertisements. All were drug- and medication-free. Ss with a history of mental illness, apart from problem gambling or drinking, including learning disabilities or attention deficit hyperactivity disorder, were excluded from the study. Detailed subject characteristics are provided in the Results section.

Apparatus and Materials

A score ≥ 5 on The South Oaks Gambling Screen (SOGS; Lesieur and Blume, 1987) defined problem gambling; a score < 4 defined nonproblem gambling.³ The maximum loss (\$) in a single gambling episode (Max-Loss) served as a behavioral index of problem gambling severity. These two indices of problem gambling severity correlated at $r = 0.71$, $p < 0.001$. A score ≥ 9 on The Alcohol Dependence Scale (ADS; Ross *et al*, 1990) defined problem drinking; a score < 8 defined nonproblem drinking. The Timeline Follow-back (TLFB; Sobell and Sobell, 1992) measured alcohol use in the 90 days preceding screening. Drinks per week provided a behavioral index of problem drinking severity.

² The terms Nongambler and Nondrinker were used for brevity. Some subjects (Ss) who were designated as Nongamblers (ie Groups D, C) gambled socially (no evidence of problem gambling) and all Ss designated as Nondrinkers (ie Groups G, C) drank socially (no evidence of problem drinking).

³ In Group G, five Ss reported casino games (slot machines, cards) as their predominant form of gambling; four said they engaged in multiple forms of gambling (casino, racetrack, sports lottery, bingo); and one primarily played bingo. In Group GD, two Ss endorsed multiple forms; two endorsed sports lottery; while casino and bingo were each endorsed by one S.

Ss were naïve to the effects of psychomotor stimulants as determined by self-report and a score < 5 on the Drug Abuse Screening Test (DAST; Skinner, 1982). Ss were not clinically depressed: scores < 8 on the short form of the Beck Depression Inventory (BDI; Beck and Beck, 1972). The Eysenck Personality Inventory (EPI; Eysenck and Eysenck, 1963) measured Extraversion and Neuroticism.

During test sessions, a modified version of the Multiple Affective Adjective Checklist (MAACL; Zuckerman and Lubin, 1965) measured Ss' global affective state on five subscales: Anxiety, Depression, Hostility, Positive Affect, and Sensation Seeking. The checklist was modified to provide a graduated rating of current affect (0–4; Not at All–Extremely) for each adjective.

Modified visual analog scales measured the subjective-motivational effects of AMPH and placebo. Ss reported the extent to which they agreed (0–4; Not at All–Completely) with each of seven statements, based on their current feelings during the test sessions. The statements were as follows: (a) *Right now, I am feeling the good effects of the medication.* (b) *I like this medication.* (c) *Right now, I am feeling the bad effects of the medication.* (d) *I dislike this medication.* (e) *I would like to take this medication again.* (f) *Right now, I would like to go gambling.* (g) *Right now, I would like to drink some alcohol.*

Using wording from The Situational Confidence Questionnaire (SCQ; Annis and Graham, 1988) Ss provided two additional ratings: confidence (0–100%; Not at All–Completely) to resist gambling *Right now, if there were a casino across the street*, and to resist drinking *Right now, if there were a bar across the street*.

The Lexical Salience Task (see below) was administered on a PC, programmed in MicroExperimental Laboratories (MEL, v. 2.01; Schneider, 1988), and run entirely within MS-DOS. A microphone, held in place by a gooseneck clamp and attached to the computer by a cable, measured vocal reading speed (ie onset of the vocal response). The computer recorded Ss' responses with millisecond accuracy. A serial response box (Psychology Software Tools, Pittsburgh, PA), also attached to the computer by cable, enabled on-line coding of response accuracy.

Blood pressure and heart rate were measured by an unobtrusive wrist cuff (Model HEM-601, Omron Inc., Vernon Hills, IL) attached above the Ss' nondominant hand. Ss could not see the readings from the device, precluding possible reactivity to this information.

Activation of Semantic Domains: The Lexical Salience Task

Five categories of word stimuli were employed in the Lexical Salience Task, with 30 items in each category: Gambling, Alcohol, Positive Affect, Negative Affect, and Neutral. The items for each category are shown in the appendix. Gambling words were drawn from previous research on cognitive biases in problem gamblers (McCusker and Gettings, 1997) with supplemental items generated based on face validity (eg jackpot). Alcohol words were drawn from previous research on cognitive biases in problem drinkers (Stetter *et al*, 1995; Zack *et al*, 1999). Positive Affect items were derived from items on The Profile of Mood States (Shacham, 1983) and the stimulant subscales of the

Addiction Research Center Inventory (Haertzen, 1965). Negative Affect items were derived from previous research with anxious and depressed nonproblem gamblers and drinkers (Bradley and Mathews, 1983; Mogg *et al*, 1995). Neutral items were the names of parts of a building drawn from a compendium of word frequency norms (Battig and Montague, 1969). There were no differences in the mean length, number of syllables, first letter, or frequency of occurrence in print of the words across the five categories. This controlled for the possible influence of these non-semantic moderators of memory activation.

As indicated in the Introduction, the Lexical Salience Task was a version of the rapid reading task, modified to assess the effect of a pharmacological prime rather than a semantic prime on activation of motivationally relevant concepts (eg gambling, alcohol) *vs* motivationally irrelevant (ie neutral) concepts in memory. Thus, individual word targets were administered without any verbal primes. Vocal reading RT (ms) to target words was the dependent variable.

To maximize priming effects, target words were degraded with asterisks (eg w*a*g*e*r) (Stanovich and West, 1983; Weingardt *et al*, 1996). The task parameters also conformed to those of conventional semantic priming studies (Neely, 1991). The task administered 20 practice trials and 150 (5 categories $\times$ 30 stimuli/category) test trials. Items from the five categories were randomly distributed over test trials. The items for the practice trials were fruit words (eg a*p*p*l*e). The sequence of events on each trial was identical. A focus stimulus (&&&&) appeared in the center of the screen for 350 ms to orient attention to target location. The focus stimulus was followed by a blank screen (200 ms), after which the target appeared in the same location. The target remained on the screen until S responded. The interval between target offset and onset of the next focus stimulus was 550 ms.

During the task, S faced the computer screen at a distance of 60 cm. The stimuli were 0.5 cm in height and appeared in white against a black background. An experimenter, seated behind S, recorded response accuracy (correct, misread) after every trial by means of the serial response box.

Procedure

The study was carried out in compliance with ethical principles of the Helsinki Declaration (1975). Prior to participation, S signed a consent form, outlining the study requirements and confirming confidentiality and ethics approval of the study by the IRB of the Centre for Addiction and Mental Health.

Ss were instructed to abstain from caffeine and alcohol for 12 h prior to the start of each session, and to fast on the mornings of their test sessions. The sequence of events was identical on each test session. Upon arrival at the laboratory (0845), S received a breathalyzer test to confirm she/he was alcohol-free. A baseline reading of heart rate and blood pressure was taken at this time, and at 30-min intervals thereafter until S was dismissed. At 0900, S received a standard breakfast designed to minimize variability in the absorption of AMPH. A visually identical capsule containing 30 mg D-AMPH or placebo was administered with

breakfast on each session. S read magazines in a quiet waiting room while the dose was being absorbed.

S began the Lexical Salience Task 90 min after dosing, at which time the subjective-behavioral effects of oral AMPH are maximal (Brauer *et al*, 1996). Upon completion of the task (3–5 min), S completed the modified visual analog scales and the MAACL.

Data Analytic Plan

Gender effects were analyzed by χ^2 . Continuous data were analyzed by analysis of variance (ANOVA). In cases where significant between-group differences emerged under placebo, analyses of covariance (ANCOVA) were conducted with placebo responses as the covariate. In cases where multiple indices assessed a particular construct (eg positive subjective effects; negative subjective effects), multivariate analyses of variance (MANOVAs) were first performed. Significant multivariate interactions were followed up with univariate ANOVAs. Significant ANOVA interactions were investigated by simple effects analyses (Winer, 1971). Complementary correlational analyses assessed the relationship between self-reported positive, negative, and motivational effects of AMPH and indices of the severity of problem gambling and problem drinking. A parallel set of analyses assessed the correlation between reading speed to Gambling words, Alcohol words, and Neutral control words, and the indices of addictive severity. Possible mediator effects were controlled in these analyses by partial correlation.

In line with standard procedure in studies using rapid reading methodology (Neely, 1991), scores greater than 2.5 SDs from the mean of a given word condition were designated as outliers, and excluded from subsequent analyses. Errors (ie misreading target words) were also excluded from the RT analyses. Preliminary ANOVAs confirmed that the frequency of outliers ($M=2.2$ of 30 trials) and errors ($M=2.0$ of 30 trials) did not vary as a function of Gambler Status, Drinker Status, or Treatment (drug *vs* placebo).

RESULTS

Subject Characteristics

Table 1 reports the mean (SD) subject characteristics scores for all four groups. A two-way χ^2 found no difference in the gender ratio (44% female) of the four groups, $p>0.94$. A series of 2 (Gambler Status) $\times$ 2 (Drinker Status) ANOVAs compared the groups on each continuous variable. The table shows that there were no significant group differences in mean age, $p's>0.08$. A main effect of Gambler Status on the SOGS confirmed that severity of problem gambling was significantly greater in Gambler groups (G, GD) than in Nongambler groups (D, C), $F(1, 32) = 97.73$, $p<0.0001$. The lack of interaction in this analysis, $p>0.49$, indicated that severity of problem gambling did not differ between Groups G and GD nor between Groups D and C. A main effect of Gambler Status also emerged for Max-Loss, $F(1, 32) = 118.74$, $p<0.0001$, together with an absence of other significant effects, $p's>0.18$. Thus, the maximum loss in a single gambling episode (Max-Loss) reliably

Table 1 Mean (SD) Subject Characteristics for Gamblers (G; $n = 10$), Gambler/Drinkers (GD; $n = 6$), Drinkers (D; $n = 8$), and Controls (C; $n = 12$)^a

	Group			
	G	GD	D	C
Age (years)	32.6 (11.1)	40.8 (9.6)	39.5 (11.3)	35.8 (7.0)
Gender (M:F)	7:3	4:2	5:3	9:3
SOGS	8.4* (3.4)	8.0* (3.3)	0.6 (1.1)	0.2 (0.4)
Max-Loss ^b	1578* (1651)	2008* (3928)	325 (919)	0 (0)
ADS	4.6 (3.9)	12.2* (6.7)	14.3* (9.3)	1.1 (1.8)
Drinks/week	4.4 (4.1)	30.5* (15.0)	35.1* (16.3)	1.6 (2.5)
DAST	0.5 (0.5)	0.2 (0.4)	0.9 (1.5)	0.3 (0.7)
BDI	3.8 (3.8)	4.7* (2.9)	5.5* (4.6)	0.6 (1.0)
EPI-E	14.7 (4.9)	12.8 (4.6)	11.1 (4.3)	13.6 (2.6)
EPI-N	9.5 (5.7)	12.3* (6.8)	9.6 (7.1)	4.6 (3.6)

^aSOGS = South Oaks Gambling Screen score (≥ 5 = 'Problem Gambling'); Max-Loss = Maximum loss (\$) in a single gambling episode; ADS = Alcohol Dependence Scale score (≥ 9 = 'Problem Drinking'); DAST = score on Drug Abuse Screening Test (≥ 5 = problem drug use). BDI = BDI-short form score (≥ 8 = clinical depression); EPI-E = score on the Eysenck Personality Inventory-Extraversion subscale; EPI-N = score on the Eysenck Personality Inventory-Neuroticism subscale.

^bA single outlier on Max-Loss, 4.7 SD above the mean, led to a significant positive skew in this variable. Therefore, a logarithmic transformation was applied, which negated this effect.

*Significant difference from controls (Group C), $p < 0.05$.

distinguished Gamblers from Nongamblers, but did not vary as a function of Drinker Status.⁴

Analyses of problem drinking variables (ADS, drinks/week) yielded main effects of Drinker Status, $F(1, 32) > 28.62$, $p's < 0.0001$, coupled with no interactions or main effects of Gambler Status, $p's > 0.15$. Thus, severity of problem drinking as assessed by ADS and drinks per week reliably distinguished between Drinkers and Nondrinkers, but did not vary as a function of Gambler Status.

Analysis of DAST scores yielded no significant effects, $p's > 0.14$. Analysis of BDI scores yielded a main effect of Drinker Status, $F(1, 32) = 6.79$, $p = 0.014$, and no other significant effects, $p's > 0.07$. Table 1 shows that Drinkers (Groups GD and D) were more depressed than Nondrinkers

⁴ As noted in the footnotes to Table 1, a single outlier led to a significant positive skew in Max-Loss scores, which was negated by a logarithmic transformation. The present ANOVA assessed the log-transformed Max-Loss scores.

(Groups G and C). Analysis of EPI-Extraversion scores yielded no significant effects, $p's > 0.12$. Analysis of EPI-Neuroticism scores yielded marginal main effects of Drinker Status, $F(1, 32) = 4.12$, $p = 0.051$, and Gambler Status, $F(1, 32) = 3.86$, $p = 0.058$, but no interaction, $p > 0.57$.

Physiological Effects of AMPH

Heart rate. A 2 (Gambler Status) $\times 2$ (Drinker Status) $\times 2$ (Treatment: AMPH, placebo) $\times 7$ (Time: 0, 30, 60, 90, 120, 150, 180 min after dosing) ANOVA yielded a Treatment $\times$ Time interaction, $F(6, 192) = 14.07$, $p < 0.001$, but no interactions or main effects of Gambler or Drinker Status, $p's > 0.08$. Mean (SD) heart rate rose from 73.9 (9.0) beats/min at dosing to a maximum of 86.0 (13.8) beats/min 120 min after receipt of AMPH. Heart rate tended to decline from 80.3 (6.6) to 77.3 (10.2) beats/min during this interval under placebo.

Blood pressure. A $2 \times 2 \times 2 \times 7$ MANOVA with two measures (systolic/diastolic) assessed blood pressure under AMPH and placebo. The analysis yielded a significant multivariate Treatment $\times$ Time interaction, $F(12, 20) = 3.82$, $p = 0.004$, and no significant interactions or main effects involving Gambler or Drinker Status, $p's > 0.09$. Mean (SD) blood pressure rose from 124.4/78.7 (8.4/5.4) to 141.1/88.2 (14.4/9.0) mmHg 90 min after receipt of AMPH. In contrast, blood pressure tended to decline from 128.3/81.3 (7.8/7.2) to 125.3/77.2 (15.0/10.2) mmHg during this interval under placebo. The lack of interactions among Treatment, Gambler Status, and Drinker Status on heart rate and blood pressure indicates that AMPH had consistent physiological effects in the four groups.

Self-Report Measures

Multiple Affective Adjective Checklist. A $2 \times 2 \times 2 \times 5$ (Subscale: Anxiety, Depression, Hostility, Positive Affect, Sensation Seeking) ANOVA of the modified MAACL scores yielded no significant Treatment $\times$ Subscale interaction, nor any effects involving Gambler or Drinker Status, $p's > 0.27$. A main effect of Treatment, $F(1, 32) = 10.18$, $p = 0.003$, reflected a higher mean overall rating, regardless of Subscale, under drug ($M = 1.34$, $SD = 0.37$) than placebo ($M = 1.13$, $SD = 0.41$). A main effect of Subscale, $F(4, 128) = 172.29$, $p < 0.0001$, reflected higher mean ratings, irrespective of Treatment, on the Positive Affect ($M = 2.60$, $SD = 0.72$) and Sensation Seeking ($M = 2.50$, $SD = 0.85$) subscales, than on the Anxiety ($M = 0.43$, $SD = 0.48$), Depression ($M = 0.40$, $SD = 0.45$), or Hostility ($M = 0.27$, $SD = 0.32$) subscales.

Positive effects. Panels in Figure 1 show the mean (SEM) modified visual analog scale scores for the effects of AMPH and placebo in each group and indicate significant effects.

A $2 \times 2 \times 2 \times 3$ (Measure) MANOVA assessed Good Effects, Liking, and Desire to Take Again. The analysis yielded a multivariate main effect of Treatment, $F(3, 30) = 6.05$, $p = 0.002$, and no other significant effects, $p's > 0.30$. Thus, AMPH led to a generally consistent increase in positive subjective effects across the four groups (see panels (a)–(c)).

Negative effects. A $2 \times 2 \times 2 \times 2$ MANOVA assessed the effects of Treatment on measures of Bad Effects and Disliking. The analysis yielded a multivariate Treatment $\times$ Gambler Status $\times$ Drinker Status interaction, $F(2, 31) = 3.92$, $p = 0.030$. Univariate ANOVAs for each measure revealed the source of the interaction. There were no significant effects involving Disliking, p 's > 0.36 , whereas the ANOVA of Bad Effects yielded a Treatment $\times$ Gambler Status $\times$ Drinker Status interaction, $F(1, 32) = 5.33$, $p = 0.028$. Simple effects analyses (Winer, 1971) found that AMPH increased Bad Effects ratings in Group D, $t(32) = 4.52$, $p < 0.001$, but did not significantly alter ratings in the other three groups, p 's > 0.06 (see panels (d) and (e)).

Motivational effects. A $2 \times 2 \times 2 \times 2$ (Desire: Gamble, Alcohol) ANOVA assessed the effects of AMPH on ratings of Desire to Gamble and Desire for Alcohol. The ANOVA yielded a significant four-way interaction, $F(1, 32) = 8.52$, $p = 0.006$. Simple effects analyses determined that AMPH produced a significant increase in Desire to Gamble in Group G, $t(32) = 2.63$, $p < 0.05$, but not in the other three groups, p 's > 0.30 (panel f). AMPH significantly increased Desire for Alcohol in Group GD, $t(32) = 2.19$, $p < 0.05$, but had no significant effects in the other three groups, p 's > 0.30 (panel g).

A preliminary ANOVA revealed significant baseline differences in Confidence to Resist Gambling and Alcohol under placebo. To determine if AMPH differentially affected Confidence to Resist Gambling and Alcohol in Gamblers and Drinkers when baseline differences in these ratings were controlled, two 2×2 ANCOVAs were conducted on confidence scores under AMPH, using the corresponding confidence scores under placebo as the covariates. The ANCOVA of Confidence to Resist Gambling under AMPH yielded a main effect of Gambler Status, $F(1, 31) = 5.18$, $p = 0.030$, and no other significant effects, p 's > 0.15 (panel h). Thus, when baseline differences under placebo were controlled, Gamblers reported significantly lower Confidence to Resist Gambling under AMPH than Nongamblers. The ANCOVA of Confidence to Resist Alcohol under AMPH yielded no significant effects, p 's > 0.19 (panel i).

Correlational analyses. Pearson partial correlations, controlling for ratings under placebo, assessed the relation between the positive, negative, and motivational effects of AMPH and the indices of problem gambling and problem drinking.⁵ Significant correlations ($p < 0.05$, two-tailed) are reported.

The Max-Loss index of problem gambling correlated positively with Good Effects, $r = 0.52$, Liking, $r = 0.46$, Desire to Take Again, $r = 0.53$, and Desire to Gamble, $r = 0.44$. Disliking correlated negatively with Max-Loss, $r = -0.46$ and SOGS, $r = -0.45$.

The ADS index of problem drinking correlated negatively with Good Effects, $r = -0.43$, while Drinks per Week

correlated negatively with Liking, $r = -0.39$, and Desire to Take Again, $r = -0.43$.

Lexical Salience Task and Activation of Semantic Domains

Baseline reading speed under placebo. A $2 \times 2 \times 5$ ANOVA of RT to the five types of words under placebo yielded a main effect of Word Condition, $F(4, 128) = 10.95$, $p < 0.001$, and no other significant effects, p 's > 0.22 . Therefore, between-group differences in reading speed under AMPH do not reflect pre-existing differences under placebo.

Effects of AMPH on reading speed. Table 2 shows the group mean (SD) RT scores for the five word conditions under placebo along with the change from placebo induced by AMPH. The table shows that AMPH led to faster RT (positive change scores) in all conditions in the Nongambler groups (D, C). In contrast, both of the Gambler groups (G, GD) demonstrated pronounced slowing of RT to Neutral words (negative change scores) under AMPH, coupled with a modest improvement in RT to Gambling words.

A $2 \times 2 \times 2 \times 5$ ANOVA assessed reading RT to the five types of words under AMPH and placebo. The analysis yielded a significant Gambler Status $\times$ Treatment $\times$ Word Condition interaction, $F(4, 128) = 3.76$, $p = 0.006$, and no two-way or higher order Drinker Status $\times$ Treatment interactions, p 's > 0.21 . Figure 2 plots the mean (SEM) difference in reading RT (placebo minus AMPH) for each word condition in Nongamblers and Gamblers, and depicts the three-way interaction.

In Nongamblers, the figure shows that AMPH led to faster reading speed across all word conditions. In these Ss, simple effects comparisons found no reliable differences in the degree of change in reading speed across the five word conditions, p 's > 0.30 . Additional individual analyses found that the increase in reading speed under AMPH relative to placebo was significant for each word condition except Alcohol, p 's < 0.05 .

In Gamblers, the figure reveals a markedly different pattern. As predicted, AMPH significantly facilitated reading speed to Gambling words, $t(128) = 1.77$, $p < 0.05$, one-tailed. In contrast, the drug significantly slowed reading speed to Neutral words, $t(128) = -7.56$, $p < 0.0001$. AMPH did not significantly alter reading speed in the other three word conditions, p 's > 0.35 .

Correlational analyses. Correlational analyses assessed the relation between reading speed under AMPH to Gambling words, Alcohol words, and Neutral control words and indices of problem gambling and problem drinking. AMPH can have both general and specific effects on RT to diverse stimuli. These analyses were conducted in a manner that isolated the specific effects of AMPH on each class of words (eg Gambling) while controlling, by partial correlation, for its effects on the remaining classes of words.

In line with the hypotheses, a negative correlation emerged between Max-Loss and RT to Gambling words, $r = -0.43$, $p = 0.026$, one-tailed. Thus, the greater the severity of problem gambling, the faster the reading speed to Gambling words under AMPH. RT to Neutral words was

⁵ All correlations in the study were based on scores from noncontrol Ss ($n = 24$). The mean and SD score for control Ss ($n = 12$) on Max-Loss was 0 (see Table 1). Similarly, the modal score for controls was 0 on SOGS ($n = 10$), ADS ($n = 8$), and Drinks per Week ($n = 6$). This led to heavy-tailed distributions for these indices that could not be normalized by transformation.

Figure 1 Mean subjective-motivational effects of amphetamine (30 mg; ■) and placebo (□) on modified visual analog scales (0–4: Not at All–Completely; Confidence to Resist 0–100%: Not at All–Completely) in problem gamblers (G; $n = 10$), comorbid gamblerdrinkers (GD; $n = 6$), problem drinkers (D; $n = 8$), and healthy controls (C; $n = 12$). *Simple effect of Treatment, AMPH vs placebo, $p < 0.05$, two-tailed. **Main effect of Gambler Status (G/GD vs D/C) under AMPH, corrected for placebo by covariance, $p < 0.05$, two-tailed. Error bars show SEM.

Table 2 Group Mean (SD) Reading Response Time (RT; ms) in Fiveword Conditions Under Placebo, and RT Change from Placebo Under AMPH (Δ = placebo minus AMPH) for Gamblers (G; $n = 10$), GamblerDrinkers (GD; $n = 6$), Drinkers (D; $n = 8$), and Controls (C; $n = 12$)

Group	Treatment	Word condition				
		Gambling	Alcohol	Positive Affect	Negative Affect	Neutral
G	Placebo	749 (187)	768 (180)	748 (163)	734 (177)	778 (198)
	AMPH- Δ	9 (135)	40 (101)	18 (99)	17 (110)	-39 (134)
GD	Placebo	853 (142)	834 (166)	813 (128)	800 (141)	901 (198)
	AMPH- Δ	22 (119)	-37 (101)	-4 (45)	-32 (96)	-92 (160)
D	Placebo	711 (185)	702 (161)	736 (170)	684 (162)	755 (204)
	AMPH- Δ	34 (99)	2 (113)	32 (109)	11 (103)	49 (100)
C	Placebo	783 (160)	767 (117)	766 (117)	766 (122)	806 (143)
	AMPH- Δ	37 (125)	8 (128)	19 (106)	29 (110)	4 (139)

Positive change (Δ) scores indicate that AMPH led to faster reading RT relative to placebo. Negative change (Δ) scores indicate that AMPH slowed reading RT relative to placebo

Figure 2 Mean effect of amphetamine (30 mg) on reading speed (ms difference from placebo) to words from five categories: Gambling, Alcohol, Positive Affect, Negative Affect, and Neutral, in nonproblem gamblers ($n = 20$) and problem gamblers ($n = 16$). Positive scores indicate faster reading speed under AMPH than placebo. Negative scores indicate slower reading speed under AMPH than placebo. * $p < 0.05$, one-tailed; ** $p < 0.05$, two-tailed; *** $p < 0.0001$, two-tailed.

positively correlated with Max-Loss, $r = 0.50$, $p = 0.022$, and SOGS, $r = 0.56$, $p = 0.010$. Thus, the greater the severity of problem gambling the slower the reading speed to Neutral words under AMPH. Severity of problem drinking did not correlate reliably with RT to Alcohol, Gambling, or Neutral words, p 's > 0.20 .

To assess the correspondence between the self-report and cognitive indices of motivation, correlations were computed between Desire to Gamble and RT to Gambling words and between Desire for Alcohol and RT to Alcohol words. Correlations controlled for self-report and RT responses under placebo. The correlation between the two indices of gambling motivation was significant, $r = -0.52$, $p = 0.015$. Thus, greater Desire to Gamble under AMPH coincided with faster RT to Gambling words under AMPH. The correlation between the two alcohol indices was not significant, $p > 0.18$.

DISCUSSION

Background and Predictions

The literature on problem gambling suggests that gambling can induce effects that closely resemble a psychostimulant drug effect. Accordingly, it was predicted that AMPH would activate or prime motivation to gamble in problem gamblers.

Self-Report Data⁶

The self-report findings provide a consistent pattern of evidence that AMPH primed gambling motivation. The drug significantly increased mean Desire to Gamble in Group G and significantly reduced mean Confidence to Resist Gambling in both Groups G and GD. In addition, the severity of problem gambling, as indexed by Max-Loss, significantly predicted the magnitude of AMPH-induced Desire to Gamble.

The idea that gambling and AMPH induce similar experiences implies that degree of problem gambling should predict positive subjective effects of the drug as well as motivation to experience the drug again. In line with this reasoning, problem gambling severity was positively correlated with AMPH-based ratings of Good Effects and Liking and negatively correlated with ratings of Disliking. Severity of problem gambling also predicted AMPH-based ratings of Desire to Take Again. In other words, the rated reinforcing efficacy of a psychostimulant drug was directly linked to severity of problem gambling. AMPH did not significantly alter mean Desire for Alcohol in Group D or mean Confidence to Resist Alcohol in Groups D or GD. In addition, there were no significant correlations between problem drinking severity and any positive subjective or motivational effects of AMPH.

AMPH did increase mean Desire for Alcohol in the GamblerDrinker group. In the context of the present pattern of evidence it seems most parsimonious to view this finding

⁶ Throughout the discussion all effects of AMPH are stated relative to placebo and all correlational analyses control for placebo.

as an indication of an adjunctive response that is secondarily activated by a gambling-like state induced by the drug. In other words, comorbid problem gambler-drinkers often drink while gambling (Baron and Dickerson, 1999), so that a gambling-like experience should activate an association to drink.

The self-report data indicate that Drinkers found some of the subjective effects of AMPH unpleasant. In Group D, AMPH induced a significant increase in ratings of Bad Effects. In addition, higher scores on measures of problem drinking predicted lower AMPH-based ratings of Good Effects, Liking, and Desire to Take Again. This pattern of findings relating to alcohol contrasts markedly with the pattern of findings relating to gambling.

Lexical Salience Task and AMPH-Induced Semantic Activation

The Lexical Salience Task provided an assessment of AMPH's activation of motivationally relevant and irrelevant (Neutral) semantic domains. Cognitive tasks such as this provide an objective index of processes that are executed automatically, that is, effortlessly (Hasher and Zacks, 1979). Such responses are less susceptible to 'voluntary' factors like experimental demand or Ss' beliefs regarding appropriate behavior (see McKenna and Lewis, 1994).

AMPH is a potent psychomotor stimulant and has been shown to induce faster reaction times across a wide range of cognitive tasks (Hamilton *et al*, 1983; McKetin *et al*, 1999; Servan-Schreiber *et al*, 1998). Considering simply its generic stimulant properties, AMPH would be expected to induce faster reading speed irrespective of the type of stimulus. This is precisely the pattern of data that was displayed by Nongamblers (Ss in Groups D and C). AMPH produced a statistically equivalent speeding of reading across all fiveword classes.

By contrast, in Gamblers (Ss in Groups G and GD), AMPH selectively facilitated reading speed to Gambling words while concurrently slowing reading to Neutral words. These effects, which are incongruent with the drug's generic stimulant effects, are directly congruent with an analysis based on primed motivation to gamble.

The activation or priming of an incentive motivational system operates to suppress other motivational systems as well as irrelevant activities and cues (Konorski, 1967; Kostowski, 2002). In Robinson and Berridge's (1993, 2001) model of addiction, incentive motivation is dysregulated by repeated exposure to addictive substances, which results in pathological 'wanting' or craving. As a corollary to this model, Kostowski (2002) proposed that such pathological drug 'wanting' involves concurrent pathological suppression of irrelevant activities and these combined factors mediate compulsive drug seeking to the exclusion of normal adaptive behaviors. This general framework makes sense of the present findings. The self-report data show that AMPH had primed incentive motivation to gamble in these Ss. Thus, the selective speeding to Gambling words can be interpreted as targeted wanting, while the concurrent slowing to Neutral words reflects linked suppression of irrelevant stimuli.

From a clinical perspective, the pattern of findings displayed by gamblers could be viewed as an experimental

analog of a gambling-centered preoccupation. Activation of semantic networks has also been found to skew drug-related decisions (Weingardt *et al*, 1996; Weinstein *et al*, 2000; Zack *et al*, 1999) and drug-seeking behavior (Stein *et al*, 2000). Thus, the pattern of cognitive activation observed in gamblers under AMPH would be expected to skew decisions toward more gambling (eg 'play another round') and to suppress gambling-irrelevant, adaptive behaviors (eg go home).

Correlational analyses revealed that problem gambling severity directly predicted the degree of drug-induced improvement in reading speed to Gambling words as well as the slowing of reading to Neutral words. This indicates that the polarizing effects of AMPH on access to gambling-related vs unrelated concepts is linked to gambling pathology. Also, self-reported Desire to Gamble significantly predicted reading speed to Gambling words under AMPH. This provides statistical evidence that the two procedures were assessing two dimensions of the same phenomenon.

The finding that AMPH primes gambling motivation is consistent with the animal literature on cross-priming, in which a dose of one psychoactive drug primes self-administration of another drug (Petry, 1997; Schenk and Partridge, 1999; Ulm *et al*, 1995). Cross-priming has often been investigated within a reinstatement paradigm; this refers to the resumption of a previously extinguished drug-seeking response by noncontingent exposure to the priming drug (Shalev *et al*, 2002; Stewart and de Wit, 1987). The precise mechanisms that mediate cross-priming and reinstatement are complex (Schenk and Partridge, 1999; Shalev *et al*, 2002; Spealman *et al*, 1999). Nonetheless, the occurrence of cross-priming can be viewed as evidence that the two drugs affect common neurochemical substrates that are functionally related to the incentive-motivational properties of the two drug reinforcers.

In contrast to the case for gambling, there was little evidence that AMPH directly primed motivation for alcohol in problem drinkers on either the self-report or cognitive indices. Hence the present findings in gamblers cannot be attributed to a generic ability of AMPH to activate addictive motivation. However, it should be noted that the relationship between the subjective effects of AMPH and alcohol appears to be complex.

A recent within-subjects study in healthy volunteers assessed individual differences in response to alcohol and AMPH (Holdstock and de Wit, 2001). In a correlational analysis, Ss who reported pronounced stimulant-like effects of alcohol (0.8 g/kg) also reported some greater stimulant-like effects of AMPH (20 mg). These findings suggest some commonalities in the subjective effects of moderate doses of alcohol and AMPH in nonproblem drinkers. The relationship between the subjective effects of alcohol and AMPH in problem drinkers remains to be determined.

AMPH is a potent, unconditioned dopamine agonist (Furmidge *et al*, 1991; Gold *et al*, 1989). Panksepp (1998) has proposed that activation of the mesolimbic dopamine system gives rise to an incentive state (ie 'seeking') that involves affective processes which invigorate search behavior (p 152). This formulation provides an explanatory framework for problem gamblers' heightened readiness to detect gambling words under AMPH in the present study.

The present findings may also relate to previous research on dopaminergic modulation of semantic memory networks. In a conventional semantic priming paradigm with no motivationally relevant words, L-dopa led to a small but significant slowing of RT to target words that were peripherally related to their respective (verbal) primes in healthy volunteers (Kischka *et al*, 1996). These investigators argued that 'dopamine increases the signal-to-noise ratio in semantic networks by reducing the spread of semantic processing, thereby leading to a focusing of activation' (p 1107). The slowing of RT to motivationally irrelevant, neutral words by AMPH in the two subgroups of problem gamblers is suggestive of such a dopaminergic modulating effect. However, although AMPH is primarily associated with dopamine activation, the drug also engages other neurochemical systems (see Brauer *et al*, 1997). Therefore, the present findings for gamblers cannot be exclusively attributed to dopamine activation.

Limitations

This study had a number of limitations. For one, the size and diversity of the groups was modest. As well, diagnoses of clinical depression or ADHD were exclusionary criteria. There is a high comorbidity with each of these factors and problem gambling (Potenza *et al*, 2001; Specker *et al*, 1995). Moreover, each of these disorders involves disturbances in neurochemical systems activated by psychostimulant drugs (Brown and Gershon, 1993; Solanto, 2002). Therefore, it remains to be determined if the present findings extend to such cases.

Summary and Conclusions

This study provides an internally consistent pattern of evidence that AMPH primes motivation to gamble in problem gamblers, as indexed both by self-report and by rapid reading performance. In addition to the mean effects, there was a consistent pattern of correlational evidence that the severity of problem gambling predicted the positive subjective and motivational effects of AMPH as well as the drug's effects on access to motivationally relevant and irrelevant semantic domains. In short, the findings provide experimental evidence that neurochemical activation, similar to that engaged by psychostimulant drugs, is an important component of gambling addiction.

Future Directions and Methodology

The present findings raise important questions about the potential role of other neurochemical systems in problem gambling. In particular, opiate addiction shares significant common mechanisms with psychostimulant addiction (eg Bozarth, 1986; Vanderschuren *et al*, 1999). In addition, the finding that the opioid antagonist naltrexone can be beneficial in the treatment of problem gamblers (Grant and Kim, 2002) underscores the importance of investigating the role of the opioid system in problem gambling.

The study also highlights important methodological issues. The present assessment utilized two distinct procedures: cognitively 'effortful' self-report and automatically executed rapid reading responses. The two procedures

provided evidence that was mutually consistent and complementary. The Lexical Salience Task proved particularly valuable for assessing AMPH-induced activation and inhibition of diverse semantic domains. The finding that, in gamblers, a stimulant drug-like AMPH slowed gambling-unrelated responses while speeding gambling-related ones was counter-intuitive. This finding provides clear evidence for an important but often overlooked dimension of addictive motivation, namely, the inhibition of motivationally irrelevant alternative activities (Goldstein and Volkow, 2002). Inclusion of similar procedures could be valuable in research aimed at identifying and assessing potential medications for the treatment of pathological gambling.

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APPENDIX

WORD STIMULI FOR LEXICAL SALIENCE TASK

Gambling: ace bet bingo blackjack cards cash casino chips dealer dice gamble game jackpot keno lottery lotto luck odds payoff player poker races risk roulette score slots stakes track wager winner

Alcohol: alcohol ale beer bender blitzed bombed booze bottle bourbon brandy buzz cocktail drink gin hammered lager liquor loaded rum rye scotch shooter smashed tavern tipsy vodka wasted whiskey wine wrecked

Positive affect: alert aroused bliss bold brave calm clever courage daring ecstasy exciting fun hopeful joy keen lively loving pep powerful quick rush sexy skillful smart strong thrill upbeat vigorous warm witty

Negative affect: angry anxious beaten confused dizzy dread fail grouchy guilty helpless hopeless hurt insane lonely misery nasty nervous outcast panic sad shaky shame sick stress tense unhappy upset uptight weak worry

Neutral: arch boiler brick buttress cabinet cable carpet chute clock closet doorway duct garage gate landing latch lattice outlet patio pillar platform rafter railing roof sink stairs step trough window wing