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Effects of *d*-amphetamine in human models of information processing and inhibitory control

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Abstract

Although stimulants are generally associated with enhanced information processing, reports of stimulant effects on behavioral functions that rely on inhibitory processes have been inconsistent. The present research tested the joint effects of *d*-amphetamine on information processing and inhibitory control in healthy adults ($N = 22$) with no reported history of illicit stimulant use or drug dependence. Information processing was measured by a rapid information processing (RIP) task and inhibitory control was measured using a stop-signal task. Performance was measured in response to 15 mg/70 kg, 7.5 mg/70 kg, and 0 mg/70 mg (placebo) doses of *d*-amphetamine, administered double-blind in a randomized, within-subjects design. Results showed that *d*-amphetamine improved information processing in a dose-dependent manner. By contrast, no enhancement of response inhibition was observed. Stimulant effects were also observed in physiological and subjective effects measures. The findings indicate that a stimulant drug can enhance aspects of cognitive functioning without producing a concomitant improvement in inhibitory control of behavior. The findings highlight the complex nature of stimulant effects on human behavior and the utility of performance tasks as models of complex behavioral and cognitive functions.

Keywords

d-Amphetamine; Response inhibition; Information processing; ADHD; Human

1. Introduction

Stimulant drugs are commonly reported to improve performance in humans (e.g., Koelega, 1993; Weiss and Laties, 1962). Studies have shown that stimulants, such as nicotine, caffeine, and amphetamines, can allay fatigue, increase vigilance, speed reaction time, prolong effort, and generally increase work output (for review, see Koelega, 1993). The stimulant drugs, methylphenidate (Ritalin) and *d*-amphetamine, are prescribed to treat behavioral and cognitive impairments associated with attention deficit/hyperactivity disorder (ADHD) and other disorders of self-control (Tannock, 1998). It also has been suggested that illicit use of stimulants, such as *d*-amphetamine and cocaine, might be motivated in part by a desire to self-medicate behavioral and cognitive deficits (e.g., Khantzian, 1985; Schiffer, 1988).

The cognitive mechanisms by which stimulants improve performance are unclear. However, facilitation is commonly attributed to an enhancement of information processing under the drug (Koelega, 1993; Wesnes et al., 1987). Processing information is a complex cognitive activity that involves attention, working memory, and response selection. Working memory refers to the maintenance of current, relevant information for the purpose of performing complex cognitive operations, such as decision-making. Self-paced, interactive tasks have been used to measure capacity of information processing. The rapid information processing (RIP) task is a commonly used measure that adjusts the rate with which visual information is presented as a function of the subject's ability to encode and respond to the information (Battig and Buzzi, 1986). Correct responding increases the presentation rate and omissions and errors slow the presentation rate. Thus, the presentation of information is adjusted to a rate at which the individual can accurately encode and respond. The average rate obtained during a test estimates information processing capacity, which depends on the subject's level of sustained attention and working memory capacity.

The RIP task has been used extensively as a model of information processing capacity in behavioral pharmacology research. Studies of RIP task performance show increased information processing capacity following the administration of cholinergic stimulants, such as nicotine (e.g., Baldinger et al., 1995; Hasenfratz and Battig, 1994) and non-specific stimulants, such as caffeine (Hasenfratz et al., 1993). Moreover, these improvements do not simply reflect relief from temporary withdrawal-induced performance deficits, but rather represent actual, above-baseline facilitation of information processing.

Although stimulants are generally associated with enhanced information processing, reports of stimulant effects on behavioral functions that rely on inhibitory processes have been inconsistent. Studies of children with ADHD (Tannock et al., 1995) and healthy adults (de Wit et al., 2002) show that the stimulants, methylphenidate and *d*-amphetamine can improve inhibitory control. However, other studies show that *d*-amphetamine and cocaine can impair inhibitory control in adults (Fillmore et al., 2002, 2003). Much of this research employs stop-signal tasks to measure drug effects on the ability to inhibit a pre-potent (i.e., instigated) behavioral response (for a review, see Fillmore, 2003). The stop-signal task is based on a model in which behavioral control is determined by countervailing activating and inhibiting processes (Logan, 1994; Logan and Cowan, 1984). Go- and stop-signals elicit these activating and inhibitory processes, and the time in which each process is completed determines the behavioral outcome. Response inhibition is determined by the probability of successfully inhibiting a response to stop-signals.

Response inhibition is assumed to be closely related to working memory capacity. Some researchers argue that response inhibition operates in a bottom-up fashion to affect working memory (e.g., Barkley, 1997), and others propose that working memory operates in a top-down manner to affect response inhibition (Finn, 2002). Regardless of the direction of causal influence, there is general agreement that increased working memory capacity should be associated with greater inhibitory control of behavior. Given that stimulants can enhance working memory performance, they should also reliably improve inhibitory control. Thus, it is unclear why stimulants are reported to have inconsistent effects on inhibitory control. However, it is difficult to draw conclusions regarding the relationship between stimulant effects on information processing rates and inhibitory control because studies have not assessed the concomitant effects of a stimulant on these two measures within the same individual.

The present research tested the joint effects of *d*-amphetamine on working memory performance and inhibitory control in a group of healthy adults with no reported history of illicit stimulant use or drug dependence. The study used a well-documented and reliable

model of working memory performance (i.e., the RIP task) and inhibitory control (i.e., the stop-signal task). Working memory performance and inhibitory control were measured in response to 15 mg/70 kg, 7.5 mg/70 kg, and 0 mg/70 mg (placebo) doses of *d*-amphetamine, administered double-blind in a randomized, within-subjects design. The design also involved a replication factor whereby each dose was administered twice to examine the reproducibility of the findings.

2. Method

2.1. Subjects

Twenty-two healthy adult volunteers (10 men and 12 woman) participated in the study. Subjects' ages ranged between 18 and 30 years (mean = 21.5, S.D. = 3.2). Potential volunteers with histories of serious physical disease, current physical disease, impaired cardiovascular functioning, chronic obstructive pulmonary disease, seizure, head trauma, CNS tumors, or past histories of psychiatric disorder, (i.e., Axis I, DSM IV) were excluded from participation. Female volunteers had to have an effective form of birth control in use. Volunteers reported using alcohol ($n = 14$) and caffeine ($n = 22$). The subsample who used alcohol reported a mean weekly alcohol consumption of 9.3 standard drinks (S.D. = 8.2). Average, daily caffeine consumption of the sample was 46.5 mg (S.D. = 52.1). Two volunteers also reported tobacco and marijuana use and one individual reported using a hallucinogen once in the past month. No other substance use was reported within 1 month prior to initial screening. Volunteers had to have: a minimum of grade 8 education, demonstrated reading ability, and no uncorrected vision or auditory problems. The education level of the sample ranged from 12 to 17 years (mean = 14.1, S.D. = 1.5). The study was approved by the University of Kentucky Medical Institutional Review Board, and subjects provided their written, informed consent prior to participating. Volunteers were paid \$350 for their participation.

2.2. Apparatus and materials

2.2.1. Rapid information processing (RIP) task—A self-paced, interactive working memory task measured subjects' information processing capacity. The task was performed on a PC computer and operated by Micro Experimental Laboratory software (Schneider, 1995). Subjects sat directly in front of a computer display and keyboard. A fixed pseudo random sequence of 250 digits consisting of the digits 1–8 was presented on the display. The digits were 11.5 cm × 6 cm in size, and appeared in yellow on a blue background. Each digit was presented for 67 ms with an initial inter-stimulus-interval (ISI) of 600 ms. Subjects were required to press a key whenever they saw a digit that represented the third digit of a 3-digit sequence (a triad) that was comprised of even digits (e.g., 6, 2, 4) or of odd digits (e.g., 5, 1, 7). Thus the task required subjects to constantly update information in working memory in order to detect triads. The entire 250 digit sequence contained 11 even-digit triads and 10 odd-digit triads. The initial presentation rate of a test was 90 digits per min. Each correct response to a triad speeded the digit presentation rate by decreasing the ISI by 33 ms. A failure to respond to a triad or a response to a non-triad slowed the presentation rate by increasing the ISI by 33 ms. Thus the task measured rate of information processing by adjusting the presentation rate according to the subject's ability to constantly encode and update information in working memory in order to detect triads. A test lasted 5 min during which the 250 digit sequence was presented in a repeated loop. A subject's level of working memory (i.e., information processing capacity) during a test was measured by the average number of digits presented per min on the test, with greater digits per min indicating a greater information processing capacity. No performance feedback was provided to the subject or to the experimenter during testing.

2.2.2. Stop-signal task—Response inhibition was measured by a stop-signal choice reaction time task (Logan and Cowan, 1984). The task has been used in other research to study inhibitory control in response stimulants (e.g., Fillmore et al., 2002) and depressants (Fillmore and Vogel-Sprott, 1999). The task was performed on a PC computer and operated by Micro Experimental Laboratory software (Schneider, 1995). The task engaged subjects in responding to go-signals, when stop-signals occasionally informed them to inhibit the response. The go-signals for the choice response were two 1.5 cm × 0.5 cm letters (O and X), presented one at a time in the center of a computer monitor. The letters were preceded by a 500 ms preparation interval in which a fixation point (a plus sign) appeared in the center of the computer screen. A letter was displayed for 500 ms, and the computer screen was blank for a 1.5 s inter-stimulus interval before the next letter was displayed. This provided a 2 s period in which the subject could respond to the letter. A participant responded to a letter by pressing one of two adjacent keys on the computer keyboard using the index and middle fingers of the preferred hand. One key was pressed to indicate that one of the letters appeared, and the adjacent key was pressed to indicate that the other letter appeared.

A single test presented each of the two letters equally often, for a total of 176 letter presentations. A stop-signal occurred on 28% of the 176 presentations (i.e., 50 times) during a test. The stop-signal was a 500 ms 900 Hz tone generated by the computer at a comfortable listening level. Participants were instructed to withhold (i.e., inhibit) their response when a stop-signal was presented. Stop-signals were presented 10 times at each of five delays (i.e., 10, 75, 150, 225, and 300 ms) with respect to the onset of a letter presentation. The order of letters, stop-signals, and delays was random. The variable delayed onset and random presentation of stop-signals prevents subjects from predicting their occurrence. A test required 7.75 min to complete. No performance feedback was provided to the subject or to the experimenter during testing.

Response inhibition was measured by the number of stop-signal trials in which a subject could successfully inhibit a response. Response activation was measured by the mean RT to the go-signals during a test (i.e., the average time from the onset of a letter presentation until a computer key press). Shorter RTs indicated faster overall responding to go-signals (greater response activation). The inhibition and activation measures on stop-signal tasks are highly reliable across trials (alpha coefficients >0.90) and stable over sessions (test–retest reliabilities >0.85) (e.g., Fillmore and Vogel-Sprott, 1999; Mulvihill et al., 1997).

Choice response errors to go-signals (i.e., pressing the wrong key) were also recorded. However, these are rare, and only occur to approximately 5% of the go-signals under alcohol (Fillmore and Vogel-Sprott, 2000; Mulvihill et al., 1997), and drug-free (Logan et al., 1984).

2.2.3. Subjective effects—Subjective effects of *d*-amphetamine were measured on a 12-item visual-analogue scale (VAS). Subjects rated each item by placing a vertical mark through a 100 mm line, with the left-side (0 mm) indicating “not at all”, and the right-side (100 mm) indicating “very much”. The mm distance was measured by a ruler and was scored from 0 to 100. The items rated were as follows: “Do you feel Stimulated?”, “Sedated?”, “Hungry?”, “Anxious?”, “Light-Headed?”, “Thirsty?”, “Sleepy?”, “Sick to your Stomach?”, “Down?”, “High?”, “Drug Effect?”, and “like the Drug Effect?”. Responses to items pertaining to stimulation and liking are sensitive to *d*-amphetamine effects, and were included as dose manipulation checks.

Subjective effects were also assessed by the short form of the Addiction Research Center Inventory (ARCI) (Jasinski, 1977; Martin et al., 1971) and by the Profile of Mood States

(POMS) (McNair et al., 1971). The ARCI and POMS were included as part of an unrelated study that involved the same participants and results pertaining to these measures are not reported in this study.

2.2.4. Physiological effects—Heart rate, measured as beats per min (BPM) and systolic and diastolic blood pressure (mmHg) were recorded using an automated blood pressure machine (Sentry II, NBS Medical, Inc., Costa Mesa, CA). Acute *d*-amphetamine administration increases heart rate and blood pressure and thus physiological monitoring was included as a dose manipulation check.

2.3. Intake screen and assessment

The study was conducted at the Residential Research Facility at the University of Kentucky. Volunteers were recruited via notices posted on community bulletin boards and by word of mouth. All volunteers were tested individually and were informed that the study examined the effects of various drugs (e.g., stimulants, benzodiazepines, barbiturates) on mood and behavior. They were given no information about the specific drug examined in the study. During an initial screening/assessment session all potential volunteers provided informed consent and completed a comprehensive medical history questionnaire, drug-use questionnaire, and demographic questionnaire. For purposes of a different study, volunteers also completed a battery of questionnaires that measured personality, impulsivity, depression, and symptoms of ADHD. Vital signs were assessed and routine, clinical laboratory blood chemistry tests were conducted on all potential volunteers. All medical information was reviewed by a physician who determined eligibility for study participation. Subjects also were familiarized and practiced on the RIP and stop-signal tasks to ensure asymptotic and stable performance levels.

Prior to the dose administration sessions, subjects participated in one “practice” session to acclimate them to the entire testing procedure of the dose administration sessions. The practice session was identical to the dose administration sessions described in Section 2.4. Subjects received a placebo during the practice session.

2.4. Dose administration sessions

Performance was tested in response to three *d*-amphetamine doses: 0 mg/70 kg, 7.5 mg/70 kg, and 15 mg/70/kg. Doses were administered in random order, under double-blind conditions. Each dose was administered twice, on two separate sessions. The replication of each dose administration tested the reproducibility of the dose–response effects observed. Each of the six dose administration sessions required 8 h to complete and was conducted on a different day, with a minimum inter-session interval of 48 h and a maximum interval of 1 week. Subjects were at the laboratory only for scheduled sessions and returned home after each session was completed. On average, subjects completed approximately two sessions per week.

2.4.1. Pre-session preliminary checks—Subjects were required to fast and abstain from caffeinated beverages for 4 h prior to each session. At the beginning of each session, volunteers completed a pre-session questionnaire that collected information about tobacco and alcohol consumption, hours slept during the past 24 h, recent medication use, illness since the previous session, and symptoms or changes in routine associated with the study medication. Subjects performed a standard field sobriety test of motor coordination and provided a breath sample using a breath-analyzer to verify a zero blood alcohol concentration (BAC) (Alco-Sensor III, Intoximeters, Inc., St Louis, MO). Carbon-monoxide level from a breath sample (piCO Smokerlyzer Breath CO Monitor, Bedfont Scientific Ltd., UK) was also measured to verify smoker status. A urine sample was obtained to test for the

presence of cocaine/benzoylecgonine, benzodiazepines, barbiturates, tetrahydrocannabinol (THC), *d*-amphetamine, and opiates (On Trak Testkits, Roche Diagnostics Corporation, Indianapolis, IN). Females were also tested for pregnancy via urine analysis. With the exception of a single occasion in which an individual tested positive for cocaine/benzoylecgonine and another tested positive for THC, no other volunteers tested positive for any drug during the study. The two subjects who tested positive were informed of the result and had their session rescheduled. After pre-session checks, subjects received a small meal consisting of two cereal bars and unsweetened orange juice. No smoking was allowed during the sessions.

2.4.2. Baseline testing and dose administration—Testing began in the morning with a baseline (i.e., pre-capsule) test battery that included tests on the RIP and stop-signal task, administration of the VAS, ARCI, POMS, and assessment of physiological measures. The test battery required approximately 25 min to complete. Immediately after baseline testing, subjects received one of the three *d*-amphetamine doses: 0 mg/70 kg, 7.5 mg/70 kg, or 15 mg/70 kg. Drug doses were prepared by encapsulating *d*-amphetamine in identical opaque capsules combined with lactose filler. Placebo capsules contained only lactose. Capsules were taken orally with water. Doses were prepared by the University of Kentucky Investigational Pharmacy.

2.4.3. Post-capsule testing—The test battery (i.e., RIP and stop-signal tests, VAS, ARCI, POMS, and physiological measures) was administered at 1, 2, and 3 h post-capsule. Time course analyses of oral *d*-amphetamine dose effects on physiological and subjective measures typically show peak effects between 2 and 3 h following administration (Fillmore et al., 2003; Rush et al., 1998; Vree and Henderson, 1980). Subjects relaxed and read magazines or watched television during the periods between testing. No volunteers experienced any adverse reaction to the drug or any procedure.

2.5. Criterion measures of performance and data analyses

2.5.1. RIP task performance—Information processing capacity was measured by a subject's mean digit processing rate during a test. The measure was expressed as the average number of digits processed per min. Faster mean processing rate indicates greater working memory function.

2.5.2. Stop-signal performance—The proportion of successfully inhibited responses (p-inhibition) on stop-signal trials provided a general measure of the ability to inhibit responses for a subject. Larger p-inhibition scores indicate a greater probability of inhibiting a response to a stop-signal (greater inhibitory control of behavior). The p-inhibition scores were examined in relation to stop-signal delay (i.e., proportion of inhibited responses to the 10 stop-signals presented at each of the five delays). Inhibitions are more likely to occur when the stop-signal delays are shorter, and their likelihood diminishes as the delay of the stop-signals increases (Logan, 1994).

Response activation to go-signals was measured by a subject's mean RT (ms) to the 126 go-signal trials presented during a test (i.e., the average time from the onset of go-signals until a computer key press). This produced a mean RT_{go} score for a volunteer for each test.

Omission errors and choice errors on go-signal trials were also recorded. Omission errors occurred when a subject failed to respond to a letter and choice errors occurred when a subject pressed the incorrect key in response to a letter. Both types of errors were infrequent, occurring on less than 2% of go-signal trials, regardless of dose condition.

2.5.3. Data analyses—The treatment effects on performance, VAS, and physiological measures were each analyzed by 3 dose (0 mg/70 kg, 7.5 mg/70 kg, and 15 mg/70 kg) $\times$ 4 time (pre-capsule, 1, 2, and 3 h post-capsule) $\times$ 2 replication (first administration, second administration) analyses of variance (ANOVA). Simple effect comparisons of dose effects on post-capsule tests were examined by Bonferroni-adjusted *t*-tests that maintained a family-wise error rate of 0.05.

3. Results

3.1. Dose effects on RIP task performance

A 3 (dose) $\times$ 4 (time) $\times$ 2 (replication) ANOVA of subjects' mean processing rate obtained a significant dose $\times$ time interaction ($F_{6,126} = 4.0$, $P = 0.001$). No significant main effect or interactions involving the replication factor were obtained ($P_s > 0.110$). Thus the dose effects demonstrated reproducibility. Given this evidence, subjects' scores under each dose were averaged over the replication factor and are presented in Fig. 1. Similar pre-capsule processing rates were evident in each dose condition. The mean pre-capsule processing rates in the three dose conditions ranged between 99.2 and 102.2 digits per min, and a simple effect test found no significant difference among the pre-capsule processing rates ($P = 0.264$). Processing rates increased 2 h following active doses and this increase was maintained at the 3 h post-capsule test. Follow up simple effect tests compared the mean processing rate under each active dose to placebo. At 1 h post-capsule, processing rates under both active doses did not differ significantly from placebo ($P_s = 1.0$). At 2 h post-capsule, a significant increase in processing rate compared with placebo was observed in response to 7.5 mg/70 kg *d*-amphetamine ($P = 0.026$), but not to 15 mg/70 kg *d*-amphetamine ($P = 0.093$). Finally, at 3 h post-capsule, both active doses significantly increased processing rate compared with placebo ($P_s < 0.021$).

The degree to which the RIP task reliably assessed subjects' processing rates over time was also tested. Reliability of subjects' baseline mean processing rates was examined across the six dose administration sessions. The intraclass correlation among baseline scores across sessions (McGraw and Wong, 1996) obtained a coefficient alpha of 0.97, indicating that individual differences among subjects' baseline processing rates showed a high degree of consistency over sessions.

3.2. Dose effects on stop-signal task performance

Inspection of stop-signal task data and debriefing of subjects revealed that four individuals failed to either follow or comprehend task instructions. Their data were excluded from analyses. A 3 (dose) $\times$ 4 (time) $\times$ 5 (stop-signal delay) $\times$ 2 (replication) ANOVA of subjects' p-inhibition scores obtained a significant main effect of time ($F_{3,51} = 3.1$, $P = 0.034$) and stop-signal delay ($F_{4,68} = 66.0$, $P < 0.001$). No other main effects or interactions were obtained ($P_s > 0.05$). Fig. 2 illustrates the main effect of time by plotting subjects' overall p-inhibition scores at each hour, averaged over the five stop-signal delays and the replication factor. The mean pre-capsule p-inhibition scores in the three dose conditions ranged between 0.627 and 0.669. No improvement of response inhibition was observed under active doses. The figure shows that p-inhibition scores tended to decrease over time and this effect was observed in all dose conditions. The reliability analysis of subjects' overall baseline p-inhibition scores across sessions obtained a coefficient alpha of 0.98, indicating a high degree of consistency in inhibitory control over sessions.

To illustrate the main effect of stop-signal delay, Fig. 3 plots subjects' p-inhibition scores observed under each dose as a function of delay. The figure plots p-inhibition scores observed at 2 h post-capsule, when *d*-amphetamine effects might be most likely to be

observed. The figure shows a high degree of similarity in p-inhibition scores across dose conditions. As expected, the probability of inhibiting diminished as a function of increasing stop-signal delay. This function was representative of all pre- and post-capsule tests in all dose conditions.

A 3 (dose) $\times$ 4 (time) $\times$ 2 (replication) ANOVA of subjects' RTgo scores also obtained a significant main effect of time ($F_{3,51} = 3.9$, $P = 0.015$). No other main effects or interactions were obtained ($P_s > 0.05$). Fig. 4 illustrates subjects' RTgo scores under each dose, averaged over the replication factor. RTgo scores were similar across dose conditions with the mean pre-capsule RTgo scores ranging between 548.1 and 574.2 ms. The figure also shows that RTgo scores decreased slightly over time in all dose conditions.

3.3. Dose effects on physiological measures

3 (dose) $\times$ 4 (time) $\times$ 2 (replication) ANOVAs obtained significant dose $\times$ time interactions for heart rate ($F_{6,126} = 13.0$, $P < 0.001$), systolic blood pressure ($F_{6,126} = 6.1$, $P < 0.001$) and diastolic blood pressure ($F_{6,126} = 3.0$, $P = 0.008$). No significant effects involving the replication factor were obtained. Table 1 presents the mean physiological measures for each dose, averaged over the replication factor. The table also summarizes the results of follow up tests that compared each active dose to placebo at 3 h post-capsule when maximal effects were expected. The table shows that systolic and diastolic blood pressure increased in a dose-dependent fashion, with maximal increases observed at 3 h post-capsule. Heart rate decreased over time under placebo, but remained fairly constant under active doses.

3.4. Dose effects on subjective measures

For illustrative purposes, only four VAS items of the 12-item measure are reported here. The items were ratings of: stimulated, high, any drug effect, and liking the drug effect. These items have been shown to be among the most sensitive to stimulant effects (e.g., Fillmore et al., 2003). 3 (dose) $\times$ 4 (time) $\times$ 2 (replication) ANOVAs obtained significant dose $\times$ time interactions for all four VAS ratings ($P_s < 0.001$). No significant effects involving the replication factor were obtained ($P_s > 0.10$). Table 2 presents the mean VAS ratings for each dose, averaged over the replication factor. The table also summarizes the results of follow up tests that compared each active dose to placebo at 3 h post-capsule when maximal effects were expected. The table shows that ratings increased in a dose-dependent fashion, with maximal increases observed at 2 and 3 h post-capsule.

4. Discussion

This study tested the joint effects of *d*-amphetamine on working memory performance and inhibitory control in healthy adults. The study found that working memory performance, as measured by the RIP task, improved in a dose-dependent manner. By contrast, no enhancement of response inhibition, as measured by the stop-signal task, was observed under any dose of *d*-amphetamine. Prototypic stimulant effects were also observed in physiological and subjective effect measures. The findings indicate that a stimulant drug can enhance aspects of cognitive functioning without producing a concomitant improvement in inhibitory control of behavior. The evidence is based on well-established models of working memory and inhibitory control that provided highly reliable and stable measures of these functions. The evidence is further strengthened by the reproducibility of the effects. Each dose was administered twice in the experiment and no differences in dose-response functions were observed between administrations for any measure.

Evidence that *d*-amphetamine can enhance information processing as measured by RIP task performance is a new finding. Past demonstrations of stimulant-induced cognitive

improvements using the RIP task involved cholinergic stimulants, such as nicotine (e.g., Baldinger et al., 1995) and the non-specific stimulant, caffeine (Hasenfratz et al., 1993). The present results extend the previous findings by showing that similar enhancing effects on information processing can be produced by a dopaminergic-acting stimulant drug. The failure to observe any concomitant improvement in response inhibition in the present research is also interesting. The lack of improvement cannot be attributed to any ceiling effects on subjects' level of response inhibition. Average baseline p-inhibition scores indicated a <0.7 probability of inhibiting a response to a stop-signal. This level of inhibitory control is comparable to that observed in other studies that used the stop-signal task (Fillmore and Blackburn, 2002; Fillmore et al., 2002). The lack of improved inhibitory control also cannot be attributed to any drug-induced changes in subjects' response activation to go-signals (RTgo scores) on the task. No effects of *d*-amphetamine on subjects' RTgo scores were observed. Apart from a slight decrease in RTgo scores over time, this measure of response activation was highly stable across dose administrations.

Stop-signal performance also showed that response inhibition diminished as a function of increasing the stop-signal delay. Fig. 3 shows the negative slope functions that relate the probability of inhibiting a response to the stop-signal delays. The slopes are consistent with previous studies showing that stop-signal latencies affect the probability of response inhibition (Fillmore and Rush, 2002; Logan and Cowan, 1984). Moreover, the presence of these slopes provides verification that subjects understood the task requirements and followed instructions. In studies of other populations, such as young children, task performance can be affected by inattention and by random response strategies, owing to a lack of motivation or interest on the part of the subject (e.g., Schachar et al., 1995; Tannock et al., 1995). Such response styles are detected by the slope function. Randomly inhibiting and executing responses generates a flat slope function because inhibitions are equally likely to occur at all stop-signal delays under such a strategy. This was not observed in the present study. Rather, the negative slopes demonstrate that response inhibition was under some degree of stimulus control of the stop signals in all dose conditions.

Evidence for drug-induced improvement of information processing without accompanying facilitation of inhibitory control is important because it suggests some level of independence between these operations. It is commonly assumed that stimulant medications in the treatment of ADHD produce a global enhancement of cognitive functioning (Koelega, 1993). However, recent studies of children with ADHD have shown that stimulant effects on cognitive functioning can be dissociated. Studies using stop-signal assessments show that children with ADHD display impaired behavioral control that can be ameliorated by stimulant drugs (e.g., for review, see Fillmore, 2003). However, the behavioral and cognitive mechanisms of control display different dose-response functions. Dose-related improvements in response inhibition are characterized by an inverted U-shape function, whereas effects on response activation reveal linear dose-response curves (e.g., Schachar et al., 1995; Tannock et al., 1995). Such observations, along with the present findings, challenge the assumption that stimulants have a unitary mechanism of action that results in a uniform facilitation of performance independent of behavioral and cognitive domains (e.g., response inhibition, memory, etc.). As a result, performance observations that are based on a single task might not provide a complete assessment of the behavioral effect of a stimulant drug.

Failure to observe a stimulant-induced enhancement of inhibitory control in healthy adults might appear at odds with previous reports that *d*-amphetamine improved inhibitory control in this population (de Wit et al., 2000, 2002). However, the facilitating effects in those studies were confined to individuals who displayed poor levels of response inhibition at baseline. Poor inhibition was determined in those studies by a median split of subjects into

high and low baseline inhibition levels. That evidence, along with findings of stimulant-induced inhibitory facilitation in children with ADHD, could suggest stimulant-induced enhancement of response inhibition might be specific to individuals with poor basal levels of inhibitory control. The possibility that amphetamine-induced improvement might be confined to subjects with low baseline inhibition was also considered in the present study. However, inspection of subjects' pre-capsule levels of response inhibition revealed a highly homogenous group. Confidence intervals showed that 68% of the sample had baseline p-inhibition scores confined within a narrow range of 0.598–0.703, thereby precluded any meaningful separation of the sample into groups of high and low inhibitors.

Prior stimulant use history also appears to be an important determinant of acute stimulant effects on inhibitory control. Individuals with a history of long-term cocaine abuse show acute impairment of response inhibition following a dose of cocaine or *d*-amphetamine (Fillmore et al., 2002, 2003). There is growing evidence that long-term habitual stimulant users display neuropsychological impairments and have neuroanatomical abnormalities, including deficits of inhibitory control (e.g., Fillmore and Rush, 2002; Lane et al., 1998). Some investigators suggest that repeated dopaminergic activation of prefrontal pathways by chronic stimulant use eventually impairs inhibitory functions, leading to a loss of control over behavioral impulses (e.g., Lyvers, 2000; Volkow et al., 1996). Neuronal changes owing to chronic stimulant use could alter the acute behavioral response to stimulants in those with a long history of stimulant use.

The present findings contribute to our growing understanding of how stimulant drugs affect behavioral control in humans. The results suggest that moderate doses of *d*-amphetamine can enhance aspects of information processing without increasing inhibitory control of behavior. The findings highlight the complex nature of stimulant effects on human behavior and the utility of performance tasks as models of complex behavioral and cognitive functions. The present findings are new and raise many questions concerning stimulant effects on information processing and behavioral control. Future research is needed to examine dose–response functions of other stimulant medications, such as those used in clinical practice (e.g., methylphenidate). Studies are also needed to systematically examine how acute behavioral responses to stimulant drugs might be affected by stimulant abuse history and by preexisting deficits of inhibitory control.

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Fig. 1. Mean processing rate (digits per min) on the RIP task at pre-capsule, and at 1, 2 and 3 h post-capsule in response to 0.0 mg/70 kg (placebo), 7.5 mg/70 kg, and 15 mg/70 kg *d*-amphetamine ($N = 22$). Each mean represents the average of two separate dose administrations. Capped vertical lines illustrate the standard error of the mean.

Fig. 2.

Mean probability of inhibiting a response (p-inhibition) to 50 stop-signals on the stop-signal task at pre-capsule, and at 1, 2 and 3 h post-capsule in response to 0.0 mg/70 kg (placebo), 7.5 mg/70 kg, and 15 mg/70 kg *d*-amphetamine ($N = 18$). Each mean represents the average of two separate dose administrations. Capped vertical lines illustrate the standard error of the mean.

Fig. 3.

Mean probability of inhibiting a response (p-inhibition) to stop-signals at 2 h post-capsule under 0.0 mg/70 kg (placebo), 7.5 mg/70 kg, and 15 mg/70 kg *d*-amphetamine ($N = 18$). p-Inhibition scores are plotted as a function of stop-signal at delay. Each mean represents the average of two separate dose administrations. Capped vertical lines illustrate the standard error of the mean.

Fig. 4. Mean millisecond reaction time to go-signals (RTgo scores) on the stop-signal task at pre-capsule, and at 1, 2 and 3 h post-capsule in response to 0.0 mg/70 kg (placebo), 7.5 mg/70 kg, and 15 mg/70 kg *d*-amphetamine ($N = 18$). Each mean represents the average of two separate dose administrations. Capped vertical lines illustrate the standard error of the mean.

Table 1

Mean physiological effects across time under each dose condition, $N = 22$. Each mean represents the average of two separate dose administrations

Pre-capsule		Post-capsule		
		1 h	2 h	3 h ^a
Systolic BP (mmHg)				
0 mg/70 kg	123.9 (2.7)	123.7 (2.5)	123.3 (2.4)	126.2 (2.4)
7.5 mg/70 kg	124.6 (2.4)	128.2 (2.7)	129.8 (2.4)	130.9 (2.2)
15 mg/70 kg	124.1 (2.4)	130.3 (2.5)	135.2 (2.3)	137.4 (2.6)*
Diastolic BP (mmHg)				
0 mg/70 kg	68.8 (1.6)	69.7 (1.3)	69.3 (1.9)	73.1 (1.6)
7.5 mg/70 kg	66.4 (2.6)	73.0 (1.8)	75.9 (1.6)	76.0 (1.4)
15 mg/70 kg	66.9 (1.4)	75.1 (1.5)	77.0 (2.4)	77.6 (2.4)
Heart Rate (BPM)				
0 mg/70 kg	70.7 (2.5)	65.6 (2.3)	63.1 (2.5)	63.3 (2.3)
7.5 mg/70 kg	70.9 (2.1)	66.6 (2.2)	68.9 (2.0)	69.3 (2.3)*
15 mg/70 kg	69.4 (1.9)	68.9 (2.2)	70.5 (2.2)	71.3 (2.1)*

Parentheses indicate standard error of the mean.

^a Bonferroni-adjusted *t*-tests compared each active dose to placebo at 3 h post-capsule when maximal effects were expected.

* $P < 0.05$, adjusted for family-wise error rate.

Table 2Mean subjective VAS ratings across time under each dose condition, $N = 22$

	Pre-capsule	Post-capsule		
		1 h	2 h	3 h ^a
VAS rating: stimulated				
0 mg/70 kg	11.9 (3.3)	11.1 (2.9)	9.9 (1.9)	9.0 (2.5)
7.5 mg/70 kg	11.8 (3.1)	12.1 (3.0)	19.3 (3.3)	22.1 (3.8)*
15 mg/70 kg	12.4 (2.9)	14.3 (3.0)	29.4 (5.8)	29.2 (5.7)*
VAS rating: high				
0 mg/70 kg	7.5 (2.4)	7.5 (2.0)	6.1 (1.7)	3.9 (1.0)
7.5 mg/70 kg	5.4 (1.6)	7.3 (1.9)	12.9 (3.5)	12.0 (3.1)*
15 mg/70 kg	3.9 (1.3)	8.6 (2.6)	20.2 (4.9)	16.1 (4.9)
VAS rating: any effect				
0 mg/70 kg	2.1 (0.6)	11.1 (2.7)	8.5 (2.3)	5.0 (1.7)
7.5 mg/70 kg	2.1 (0.8)	11.1 (3.3)	14.6 (4.2)	15.4 (3.9)*
15 mg/70 kg	2.0 (0.7)	12.0 (3.1)	23.7 (5.7)	26.3 (5.9)*
VAS rating: like effect				
0 mg/70 kg	1.6 (0.5)	7.6 (2.6)	6.3 (2.4)	5.1 (2.2)
7.5 mg/70 kg	1.8 (0.6)	8.4 (3.1)	16.3 (4.7)	16.9 (4.6)*
15 mg/70 kg	1.9 (0.6)	9.4 (3.0)	22.5 (6.1)	23.1 (6.1)*

Each mean represents the average of two separate dose administrations. Parentheses indicate standard error of the mean.

^a Bonferroni-adjusted *t*-tests compared each active dose to placebo at 3 h post-capsule when maximal effects were expected.

* $P < 0.05$, adjusted for family-wise error rate.