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Vigilance Demand and the Effects of Stimulant Drugs in a 5-Choice Reaction-Time Procedure in Mice

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Abstract

Stimulant drugs used for treating attention-deficit-hyperactivity disorder (ADHD) increase signal-detection accuracy in 5-choice serial reaction-time (5-CSRT) procedures. These increases may result from drug-induced increases in control exerted by the stimuli that prompt responses, which was assessed in the present study. Mice were trained with food reinforcement to nose-poke into one of five holes after its illumination (signal), and effects of methylphenidate, *d*-amphetamine, and pentobarbital were assessed. Subsequently, the time from trial onset to signal was changed from fixed to variable for one group of subjects. A "warning" stimulus (change in ambient lighting) preceding the signal was added for a second group. Effects of the drugs were re-assessed. Dose-related increases in accuracy of signal detection (nose-pokes in hole where a signal was displayed) were obtained with methylphenidate and *d*-amphetamine, but not with pentobarbital. When the pre-signal time was variable, increases in signal detection were not obtained with either stimulant. When a warning stimulus preceded the signal the increases in accuracy were similar to those obtained without the warning stimulus. Hence, a procedure that increased vigilance demand (using a variable pre-stimulus period) eliminated the effects of drugs useful in treating ADHD, whereas a procedure that decreased vigilance demand (adding the warning light) had no appreciable effects on the response to stimulant drugs. Taken together the present results suggest that the 5-CSRT has predictive validity for selecting drugs effective for treating ADHD, though effects can depend critically on the stimulus conditions employed and the vigilance required by the procedure.

Keywords

5-choice serial reaction-time (5-CSRT) procedure; stimulus control; vigilance; signal detection; sustained attention; attention deficit hyperactivity disorder; psychostimulants; mouse

Introduction

Variants of Five-Choice Serial Reaction Time (5-CSRT) procedures have been used extensively to assess attention behaviorally and pharmacologically (Fizet et al., 2016; Robbins 2002), and their use has expanded into other domains such as impulsivity (Dalley et

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al., 2008). The procedures are derived from a “continuous-performance task” frequently used in human subjects to assess effects of therapeutic drugs used in treatment of disorders of attention (Riccio et al., 2001). As used in rodents, the 5-CSRT procedure involves an operant-conditioning chamber equipped with an array of five holes which can be illuminated (usually briefly) from behind (signal stimulus). A poke of the nose into the hole most recently illuminated is the reinforced response. Drugs that are used clinically to treat ADHD have been shown to increase the percentage of correct responses. For example, methylphenidate and *d*-amphetamine have been reported to increase accuracy on this procedure (Koffarnus and Katz, 2011; Navarra et al. 2007; Paine et al. 2007), though there are exceptions (Cole and Robbins, 1987).

The 5-CSRT procedure, as often employed, is a complex of responses and stimulus conditions that differs along various dimensions from those often used in studies of operant behavior. Differences between the signal stimulus and discriminative stimuli, as typically utilized, involve its brief duration, and that it may no longer be present when the appropriate response is emitted and consequated. Further, the signal stimuli may be presented in five different locations. Nonetheless, the signal stimuli have contingency relations with the responses emitted and reinforcers presented which render them discriminative stimuli by the standard definition (cf. Catania, 2013). In addition, the 5-CSRT procedure involves multiple defined responses (nose pokes into alternative holes) available to the subject. In a typical behavioral procedure involving discriminative stimuli there is usually only a single response, as in so-called “go no-go” procedures, or two different responses, such as in conditional discrimination or matching-to-sample procedures. However, it should be noted that though not explicitly defined or specifically recorded, multiple alternative responses are available to subjects at all times with their own sources of reinforcement (see Herrnstein, 1970 for a discussion of R_o). The multiplicity of responses and the context of brief presentation of discriminative stimuli often not present when the response occasioned is reinforced, make interpretations of performances in terms of attention more readily accepted. However, making the extant contingencies explicit and analyzing them functionally may help to improve understanding of the behavioral control and the effects of drugs.

The present study was designed to assess effects of changes in the standard 5-CSRT procedure that enhanced or decreased control over behavior by the signal stimulus. In one variation, a “warning” stimulus preceded the signal stimulus. The term warning is used to only indicate a temporal relation between that stimulus and the subsequent signal. Based on findings using acoustic startle procedures (e.g. Geyer and Swerdlow, 1998) it was anticipated that adding this stimulus would substantially change the discriminative control of behavior and alter the effects of drugs. In a second variation of the 5-CSRT procedure the signal stimulus was presented on a temporally variable schedule. Based on behavioral literature (e.g. Stubbs, 1980) it was anticipated that a change from fixed to variable timing of the signal stimulus would again change the discriminative control of behavior and alter the effects of drugs.

Methods

Subjects.

Twelve male Swiss-Webster mice (Taconic Farms, Germantown, NY) served as subjects. Diet was controlled to maintain the subjects at approximately 85% of their adult free-feeding weights, which resulted in weights ranging from 25 to 30 g in different subjects. When not in session, subjects were individually housed in home cages within a temperature- and humidity-controlled vivarium with a light cycle of 07:00 to 19:00 h. Fresh water was continuously available in the home cages. Husbandry and other care were in accordance with NIDA institutional animal care and use guidelines and the Guide for the Care and Use of Laboratory Animals (1996).

Apparatus.

Sessions were conducted in mouse operant-conditioning chambers designed for 5-choice serial reaction-time procedures (MED-NP5M-B1; Med-Associates Inc., St. Albans, VT, USA). On one curved wall of the chamber, 1.43 cm above the grid floor, were five 1.27-cm diameter circular holes equally spaced across its length. Behind each hole were an infrared beam and photodetector that bisected the hole opening and a light-emitting diode that could illuminate the hole. Interruption of the light beam and was defined as a response, with casual observations indicating that interruptions virtually uniformly occurred with a nose poke into the hole. Centered on the opposite wall was a food tray into which 20-mg food pellets (BioServ, Frenchtown, NJ) could be delivered as reinforcement for responses. A light-emitting diode within the food tray was used to illuminate the food tray during pellet delivery. At the top of the opposite wall was a light bulb (houselight) that provided general illumination of the chamber. The chambers were contained within light-proof, ventilated enclosures that provided sound attenuation. White noise was delivered to the chamber at all times to mask extraneous noise.

Procedure.

Sessions were conducted for all subjects at approximately the same time each day. All subjects were initially trained with the houselight on to poke their noses into a hole (response) under an FR 1 schedule of reinforcement. A 4-s “signal” stimulus light was randomly illuminated behind one of the five holes of the operant conditioning chamber, and responses to the lit hole (correct responses) during, or for 60 s after, its illumination (limited hold) produced a 20-mg food pellet delivered to the tray on the opposite wall, along with the houselight turning off and illumination of the food tray for 3 s. Responses to any other hole (incorrect responses), responses prior to illumination of the signal stimulus light (pre-signal responses), or failures to respond prior to the completion of the limited hold (omissions) were followed by a 5-s timeout period during which all lights were turned off and responses had no scheduled consequence. After the reinforcement period or a timeout, the houselight was re-illuminated, and 5 s later a signal stimulus was illuminated behind a randomly selected hole. The durations of the signal stimulus and limited hold were gradually decreased to 1 and 5 s, respectively (final parameters) over 10 successive sessions. Sessions started with a 5-min blackout which preceded onset of stimuli and ended after 100 food

presentations or 40 min, whichever occurred first; which was typically about 25 min including the 5-min blackout.

After responding stabilized at the above final parameters, the effects of methylphenidate, *d*-amphetamine, and pentobarbital were assessed as described below. Subsequently the subjects were split into two groups of six subjects each for the study of the warning-light and variable time between trial start and signal onset (pre-signal interval). The number of subjects per group was selected on the basis of past experiments in which statistically significant results were obtained. For the warning-light condition, the houselight turned off for 0.5 sec 2 s before illumination of the signal stimulus. For the variable-pre-signal interval condition, the pre-signal interval averaged 5 s, but varied from 1 to 16 s. All other aspects of the procedures were as described above. Once responding under these modified conditions was determined to be stable (after two to three weeks with no apparent increasing or decreasing trends in the four parameters of performance detailed below over the last five sessions), drug testing began again, with the effects of the same drugs re-determined.

Drugs.

Methylphenidate hydrochloride, *d*-amphetamine sulfate and pentobarbital sodium were obtained from Sigma Aldrich (St. Louis, MO, USA). All drugs were dissolved in sterile water and doses in mg refer to the salt forms. Injections were administered i.p. immediately before subjects were placed in the operant chamber, and a 5-min blackout period elapsed before the session start. Sessions were conducted five days per week, with drug tests occurring on Tuesdays and Fridays. The Thursday sessions served as vehicle control sessions. At least two days separated the testing of doses of each drug.

Data Analysis.

Four dependent variables were calculated. Percent correct was defined as the number of trials in which a response was emitted to the correct hole within the response period, divided by the number of trials in which a response (correct or incorrect) was emitted within the response period (x100). Response omissions were calculated as the number of trials in which no response was emitted during the response period, divided by total trials (pre-signal, correct, incorrect, and omission trials) x100. Pre-signal responses were defined as those responses that were emitted in any hole during the interval between the start of the trial and the onset of the signal stimulus. Latency was defined as the time to any response during the response period after the onset of the signal stimulus. Trials in which responses were not emitted and trials in which pre-signal responses were emitted were not included in latency calculations. The dependent measures from control sessions were compared among procedures using a t-test with stated degrees of freedom. Dependent measures were assessed using a two-way ANOVA for each drug treatment with procedure (fixed vs. variable stimulus or with vs without a warning stimulus) and drug dose as factors, and with Holm-Sidak post-hoc comparisons.

Results

Effects of Fixed-vs. Variable-Pre-signal Times.

The percentage of correct responses during the control conditions were not different under the two procedures (Figure 1A). Similarly, the percentages of trials during which responses were omitted were not different with fixed- and variable-pre-signal times (Figure 1B). Statistical analysis (*t*-tests) supported these conclusions (t_{80}=0.73; NS and t_{80}=−0.6; NS, respectively). In contrast, the change from fixed- to variable pre-signal times increased the percentage of pre-signal responses (Figure 1C; t_{80}=−7.46; p<0.001). Additionally, latencies to respond correctly (Figure 1D) under both conditions were uniformly shorter than those for incorrect responses (t_{94}=−17.9; p<0.001 and t_{62}=−5.42; p<0.001, for fixed- and variable-pre-signal times, respectively). Further, latencies for correct responses were marginally increased by the change from fixed- to variable-pre-signal times (t_{79}=−2.05; p<0.05), whereas latencies to respond incorrectly were not different under the two conditions (t_{77}=1.57; NS).

Methylphenidate produced a trend for increases in the percentage of correct responses when assessed with the fixed-pre-signal time procedure (Figure 2A, filled symbols). In contrast, across the same range of doses there was no indication of a methylphenidate-induced increase in the percentage of correct responses with the variable-pre-signal time procedure (Figure 2A, open symbols). The statistical analysis showed a significant effect of the type of pre-signal time on accuracy ($F_{1,25}$=30.9; p<0.005), though the effect of dose was not statistically significant ($F_{5,25}$=0.86; NS). There was a dose-related increase in the number of trials in which responses were omitted under the fixed-pre-signal time procedure that was not evident with the variable-pre-signal time procedure (Figure 2B). The effect of dose on omissions was not statistically significant ($F_{5,25}$=1.53; NS), though the effect of pre-signal time on omissions approached significance ($F_{1,25}$=6.54; p=0.051). The percentage of trials on which pre-signal responses occurred was variable under both conditions (Figure 2C) and was significantly affected by dose ($F_{5,25}$=4.84; p<0.005). There also was an effect of type of pre-signal time on pre-signal responses that approached significance ($F_{1,25}$=5.84; p=0.060). There were no effects of methylphenidate dose or type of pre-signal time on correct ($F_{5,25}$=0.82; NS) or incorrect ($F_{5,24}$=0.57; NS) latencies to respond (Figure 2D).

Like methylphenidate, *d*-amphetamine increased the percentage of correct responses under the fixed-pre-signal time procedure (Figure 3A, filled symbols). The same range of *d*-amphetamine doses, in contrast, did not increase correct responses under the variable-pre-signal time procedure (Figure 3A, open symbols). The statistical analysis showed a significant effect of the type of pre-signal time on accuracy ($F_{1,43}$=20.6; p<0.001), though the effect of dose was not statistically significant ($F_{4,43}$=2.07; NS). Holm-Sidak post-hoc tests indicated significant increases with 1.0 (t=3.42; p<0.01) and 3.0 mg/kg (t=3.00; p<0.02), compared to saline, under the fixed-pre-signal time procedure. There was also a dose-related trend (Figure 3B) towards an increase in trials with response omissions ($F_{4,44}$=2.10; p=0.097). Post-hoc tests indicated a significant effect of 3.0 mg/kg on omissions, compared to saline, when the pre-signal time was a fixed length (t=2.77; p<0.05), though no significance was obtained in post-hoc tests with the variable-pre-signal time procedure. The percentage of trials on which pre-signal responses occurred (Figure 3C,

filled symbols) was dose-dependently decreased under the fixed-pre-signal time procedure, though less affected when the pre-signal time was variable (Figure 3C, open symbols). The effect of *d*-amphetamine dose on pre-signal responses was statistically significant ($F_{4,38}$=7.00; p<0.001), as was the effect of type of pre-signal time ($F_{1,38}$=32.5; p<0.001). There were no significant effects of *d*-amphetamine on latencies to respond (Figure 3D) under either condition (F values < 1.28; NS).

In contrast to the effects of the stimulant drugs, pentobarbital doe-dependently decreased the percentage of correct responses under both the fixed- or variable-pre-signal time procedures (Figure 4A). The effects of pentobarbital dose on accuracy were statistically significant ($F_{5,44}$=4.41; p<0.002), whereas type of pre-signal time was not ($F_{1,44}$=0.26; NS). Omissions under either pre-signal time procedure were not affected by pentobarbital dose (Figure 4B; $F_{5,44}$=1.16; NS). There was an increase in the percentage of trials on which pre-signal responses occurred under the fixed-pre-signal time procedure (Figure 4C) though this effect was not statistically significant ($F_{5,44}$=0.62; NS). However, there was a significant effect of pre-signal time type on pre-signal responses ($F_{1,44}$=4.41; p<0.025). There were no effects of pentobarbital dose on latencies to respond (Figure 4D) under either condition (F values < 1.73; NS).

Effects of Warning Stimulus.

The percentage of correct responses during the control conditions was slightly decreased by adding the warning stimulus compared with that obtained without the warning stimulus (Figure 5A; t_{87}=3.83; p<0.001). In contrast, the percentage of trials on which responses were omitted was not different under the two stimulus conditions (Figure 5B; t_{87}=0.52; NS). The percentage of trials with pre-signal responses was slightly increased by adding the warning stimulus (Figure 5C; t_{87}=−2.51; p<0.02). Additionally, latencies to respond correctly (Figure 5D) were uniformly shorter than those for incorrect responses under both conditions (t_{84}= −13.8; p<0.001 and t_{90}=−10.0; p<0.001, without and with the warning stimulus, respectively). Latencies of correct responses were marginally increased with the warning stimulus compared to without (t_{87}=−3.09; p<0.005), whereas the small decrease in latencies to respond incorrectly with the warning stimulus was not statistically significant (t_{87}=1.68; p=0.097).

Methylphenidate increased the percentage of correct responses when assessed with and without the warning stimulus (Figure 6A). However, those increases only approached significance ($F_{5,58}$=2.02; p=0.090), whereas the effects of the warning stimulus were not significant ($F_{1,58}$=0.32; NS). There was also a dose-related increase in trials in which responses were omitted under either procedure (Figure 6B), with significant effects of dose ($F_{5,58}$=2.87; p<0.025) but not of stimulus procedure ($F_{1,58}$=0.25; NS). Methylphenidate decreased the percentage of trials on which pre-signal responses occurred in a non-monotonic manner under both conditions (Figure 6C). The effect of methylphenidate dose was significant ($F_{5,58}$=2.97; p<0.02), but the effect of stimulus procedure was not ($F_{1,58}$=0.19; NS). There were no significant effects of methylphenidate dose on latencies (Figure 6D) for correct or incorrect responses (F values < 2.18; p values > 0.069).

The percentage of correct responses was increased by *d*-amphetamine under both stimulus conditions (Figure 7A, filled symbols) with maximal effects at different doses for each. The increases in correct responses approached statistical significance ($F_{4,42}$=2.19; p=0.087), whereas the effect of stimulus condition was not statistically significant ($F_{1,42}$=0.001; NS). Post-hoc tests indicated significant increases with 3.0 mg/kg (t=2.73; p<0.05), compared to saline, under the warning-stimulus condition. There was also a dose-related increase in the percentage of trials in which a response was omitted (Figure 7B). The dose-related increase in response omissions was statistically significant ($F_{4,43}$=3.07; p<0.05) and the effects of warning stimulus condition only approached statistical significance ($F_{1,43}$=3.90; p=0.055). The percentage of trials on which pre-signal responses occurred (Figure 7C) was related to dose ($F_{4,43}$=3.63; p<0.02) with a significant effect of warning stimulus condition ($F_{1,43}$=8.58; p<0.005). There were no significant effects of *d*-amphetamine on correct or incorrect response latencies (Figure 7D) under either condition (F values < 2.18; p values > 0.089).

Pentobarbital decreased the percentage of correct responses under each stimulus condition (Figure 8A), though the decreases only approached significance ($F_{5,47}$=2.19; p=0.071). The effects of pentobarbital on correct responses were not significantly different under the two stimulus conditions ($F_{1,47}$=2.00; pNS). There were no significant effects of pentobarbital dose or stimulus conditions on response omissions (Figure 8B; F values < 1.56; NS). Pentobarbital dose-dependently increased the percentage of pre-signal responses (Figure 8C: $F_{5,47}$=2.51; p<0.05), with no significant difference in effects under the two stimulus conditions ($F_{1,47}$=1.13; NS). There were no significant effects of pentobarbital on latencies to respond (Figure 8D) under either condition (F values < 1.39; NS).

Discussion

In the present study two approaches were taken to modify the stimulus conditions from those of a standard 5-CSRT procedure. In the first, the interval between trial onset and signal presentation was altered from fixed to variable duration. With the fixed duration, methylphenidate and *d*-amphetamine, two drugs used in the treatment of ADHD, increased the percentage of trials in which correct responses were emitted. However, those drugs were ineffective in increasing accuracy when the time from trial onset to signal was variable. In a second approach, a warning stimulus preceded onset of the signal stimulus. Methylphenidate and *d*-amphetamine increased the accuracy of signal detection similarly whether or not a warning stimulus preceded the signal. Pentobarbital, a compound presumably without clinical efficacy in treating ADHD, had no effect on accuracy under any conditions of the present study.

The effectiveness of both methylphenidate and *d*-amphetamine in increasing the percentage of correct responses is evidence of the predictive validity of the 5-CSRT procedure in identifying drugs with efficacy in the treatment of ADHD. Further evidence for that validity is that the plasma levels of *d*-amphetamine effective in a 5-CSRT procedure in rats were similar to those that were reported to be clinically effective (Slezak, et al., 2018). The absence of effects of pentobarbital under the same conditions, and reports of negative results with several other compounds not used for ADHD (e.g., Koffarnus and Katz, 2011),

suggests pharmacological specificity of its predictive validity. However, atomoxetine is useful in treating ADHD and mixed effects have previously been reported on variants of the 5-CSRT procedures (Koffarnus and Katz, 2011; Navarra et al. 2007; Robinson et al. 2008). Thus, a concordance between the clinical utility of drugs and performance on the 5-CSRT procedure may be restricted to compounds sharing molecular mechanisms with methylphenidate and *d*-amphetamine (van der Kooij and Glennon, 2007) rather than those sharing clinical efficacy.

The increase in accuracy obtained with the fixed-duration pre-signal time was not obtained when the pre-signal time was variable. A previous study (Bizarro et al., 2004), examining both *d*-amphetamine and methylphenidate and using rats as subjects, did not report this difference in outcomes. A number of factors varied between this and the study of Bizarro et al. (2004) that may account for the discrepancies. Foremost among those potential factors is the species used and differences in training and testing procedures. At present, it is only possible to suggest the above variables as determining differences, and that speculation is in need of experimental verification.

The 5-CSRT procedure is often used for examining attention behaviorally and its functional neurochemistry (*e.g.*, Fizet et al., 2016; Robbins, 2002). However, the implications of concomitant increases and decreases produced by stimulant drugs on the percentage of correct responses and the percentage of trials on which responses were completely omitted needs to be considered. The absence of a response under conditions in which the discriminative stimuli for that response were present meets the common definition of inattention, suggesting that the 5-CSRT procedure may have predictive validity for discerning effective pharmaceuticals, but does not fully encompass what is meant by the concept of attention. Nonetheless, it is questionable whether ordinary definitions should dictate interpretations of laboratory findings. Indeed, inherent in the concept of predictive validity is the premise that the outcomes of a laboratory test may have little to no resemblance with events outside the laboratory (Carlton, 1978; 1983). Therefore, the predictive validity of the 5-CSRT procedure should not be mistaken for a more encompassing laboratory translation of the concept of attention, and is best considered a partial interpretation (Carnap, 1936) of sorts.

An increase in the number of trials in which responses were omitted after methylphenidate or *d*-amphetamine administration was obtained in the present study with a fixed-but not a variable-duration pre-signal time. Though the control frequency of omissions remained similar under both conditions, the differential sensitivity of omissions suggests a difference in the functional control of that behavior during the pre-signal period under the two conditions. It is possible that the fixed duration of the pre-signal time facilitated adventitious reinforcement of responses by the signal stimulus, and that responses maintained in that manner were more sensitive to disruption by the stimulants than were responses during the variable pre-signal period. Fixed timing of events is a well-known facilitating condition for adventitious reinforcement (e.g., Morse, 1955; Morse and Skinner, 1957; Skinner, 1948). Obviously, this speculation is in need of experimental analysis to assess whether omissions under fixed- and variable-pre-signal periods are functionally dissimilar.

The variants to the more common 5-CSRT procedure employed here can be considered ones that change the demand for observing behavior (or vigilance) if accuracy and reinforcement frequency is to be maintained. In the change from fixed to variable pre-signal signal times, the potential for temporal stimulus control over observing behavior possible with the fixed delay is absent, increasing vigilance demand. With the addition of the "warning stimulus" presently employed, vigilance was necessary only during the short time after that stimulus. This conceptual analysis is testable with a procedure that employs an explicit observing response (e.g., Holland, 1958) and thereby operationalizes vigilance. Such a procedure could be applied to the 5-CSRT procedure with little difficulty and would also allow an assessment of the specific effects of drugs on observing behavior *per se*. It has been demonstrated previously that *d*-amphetamine can alter observing behavior, though effects differed among subjects (e.g. Clark, 1969) and may be influenced by schedule of reinforcement for the response producing primary reinforcement (Branch, 1975).

The present results suggest that the effects of stimulant drugs on performance under a 5-CSRT procedure are more nuanced than simply an effect on attention. With a fixed but not a variable pre-signal period, both stimulants increased the percentage of correct responses. Additionally, the possible demands of different conditions of the study that can influence the effects of the stimulant drugs suggest the need for objectively examining observing behavior as a factor in the control of behavior under this procedure. Further, the present findings are consistent with the notion that the behavioral effects of drugs are intricately sensitive to the environmental conditions under which they are studied.

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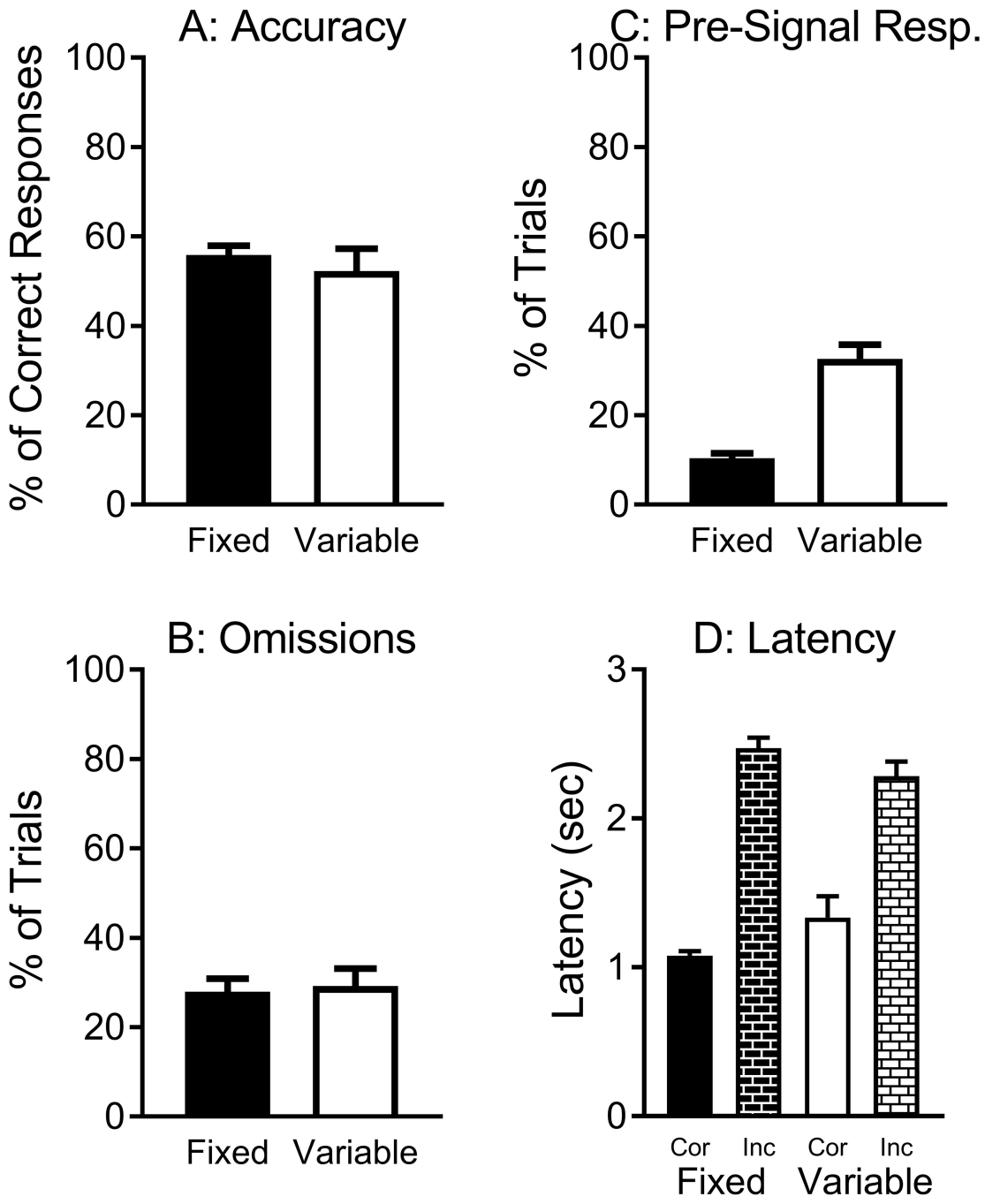

Figure 1.

Performances in the absence of drug treatments (average of control sessions during tests of drugs) under the 5-CSRT procedure with a fixed (black or black pattern bars) and variable (white or white pattern bars) pre-signal period. The measures of performance are described in the Methods section. Vertical bars about the points represent 1 SEM.

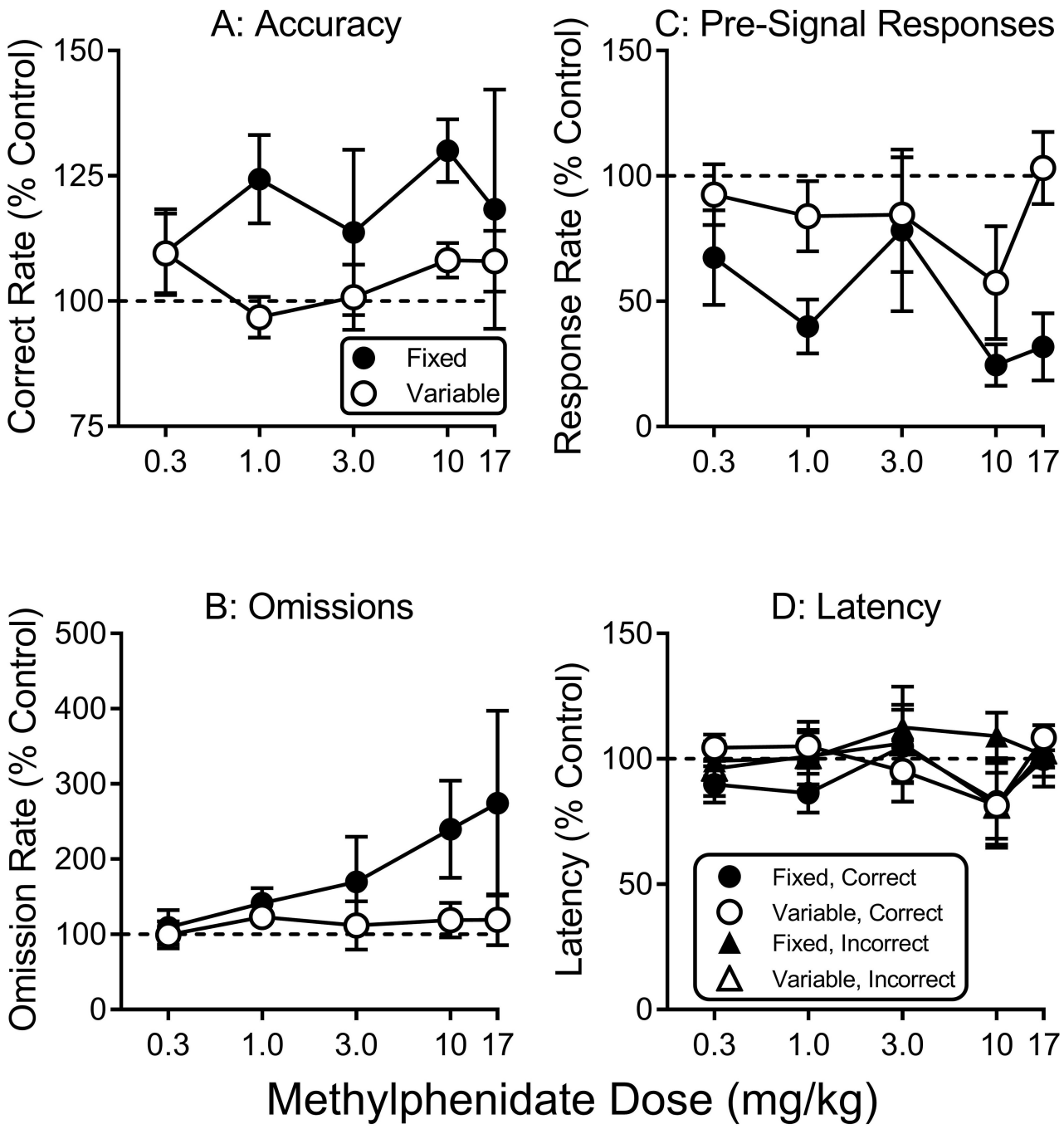

Figure 2.

Effects of methylphenidate on performances under the 5CSRT procedure with a fixed (filled circles or triangles) and variable (open circles or triangles) pre-signal period. Vertical bars about the points represent 1 SEM. Horizontal axes: Methylphenidate dose in mg/kg body weight. Panel A: Accuracy of performance displayed as percent of trials in which a correct response occurred divided by that same percentage obtained during control sessions (x100). Panel B: Rate of omissions displayed as percent of trials in which a response was not emitted divided by that same percentage obtained during control sessions (x100). Panel C:

Rate of pre-signal responses displayed as percent of trials in which a response was emitted before the signal divided by that same percentage obtained during control sessions (x100). Panel D: Latency, as time from signal onset to response, divided by latency obtained during control sessions (x100).

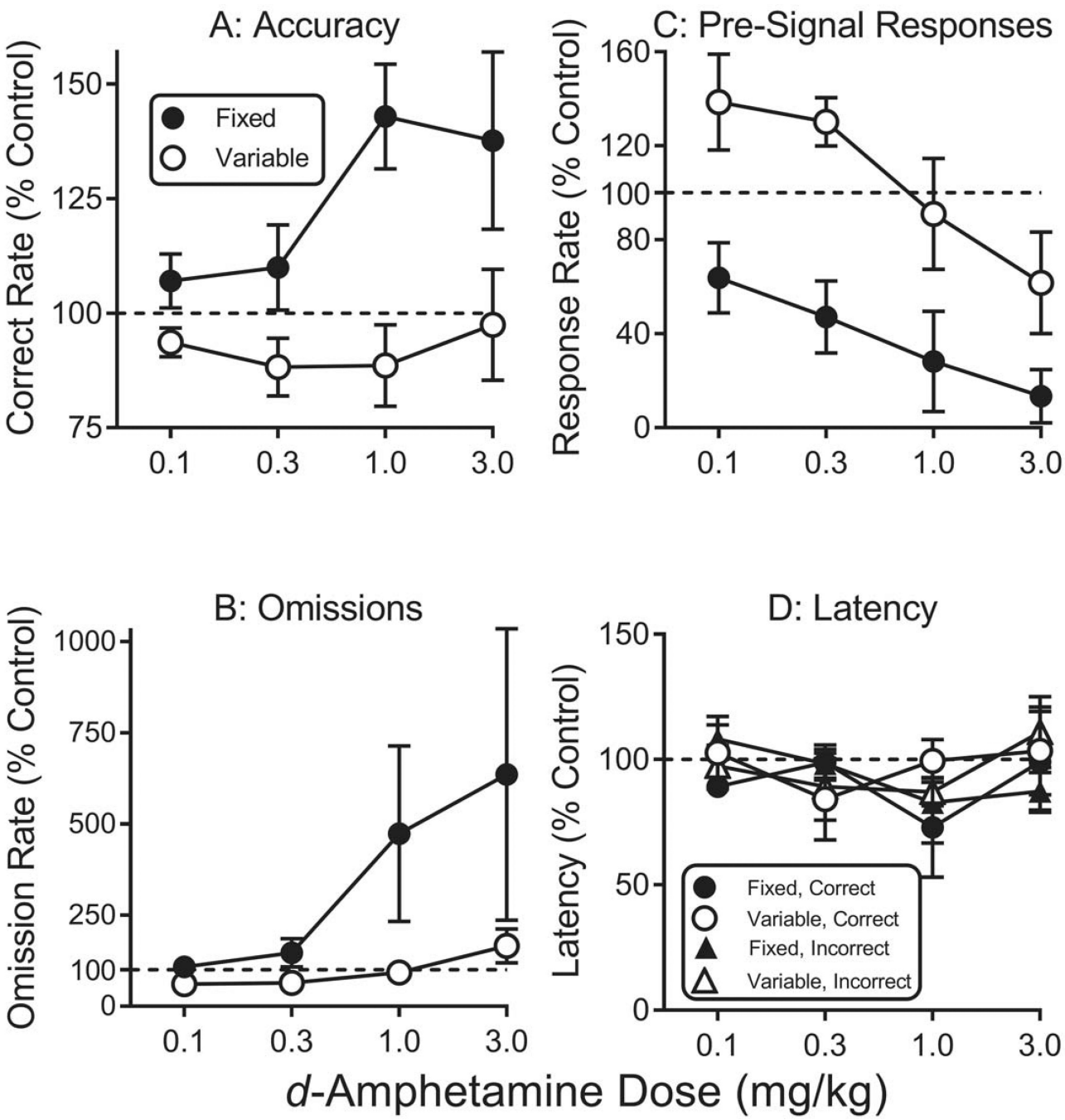

Figure 3.

Effects of *d*-amphetamine pretreatments on performances under the 5CSRT procedure with a fixed (filled circles or triangles) and variable (open circles or triangles) pre-signal period. Horizontal axes: *d*-amphetamine dose in mg/kg body weight. All other details as in Figure 2.

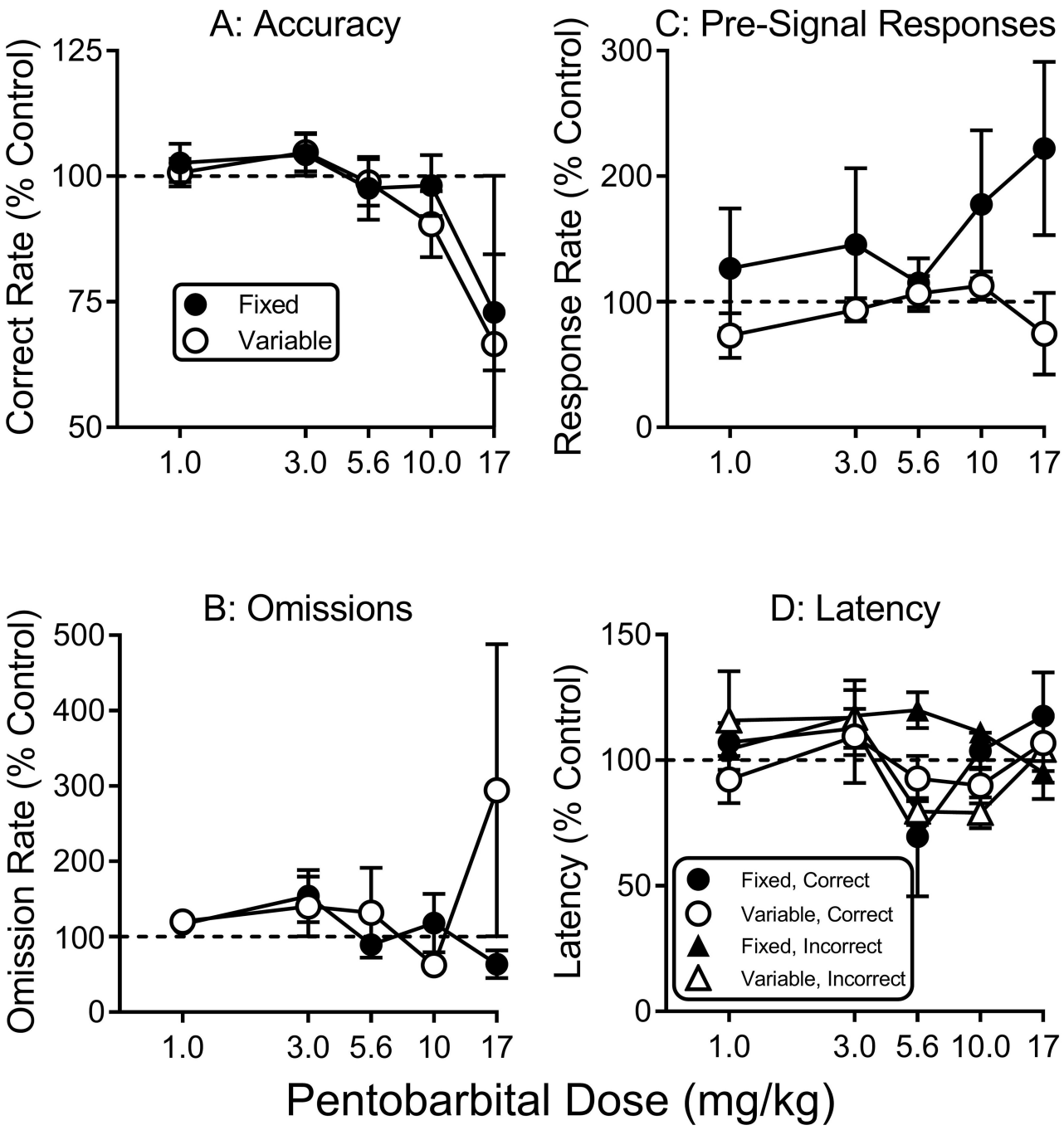

Figure 4.

Effects of pentobarbital pretreatments on performances under the 5CSRT procedure with a fixed (filled circles or triangles) and variable (open circles or triangles) pre-signal period. Horizontal axes: Pentobarbital dose in mg/kg body weight. All other details as in Figure 2.

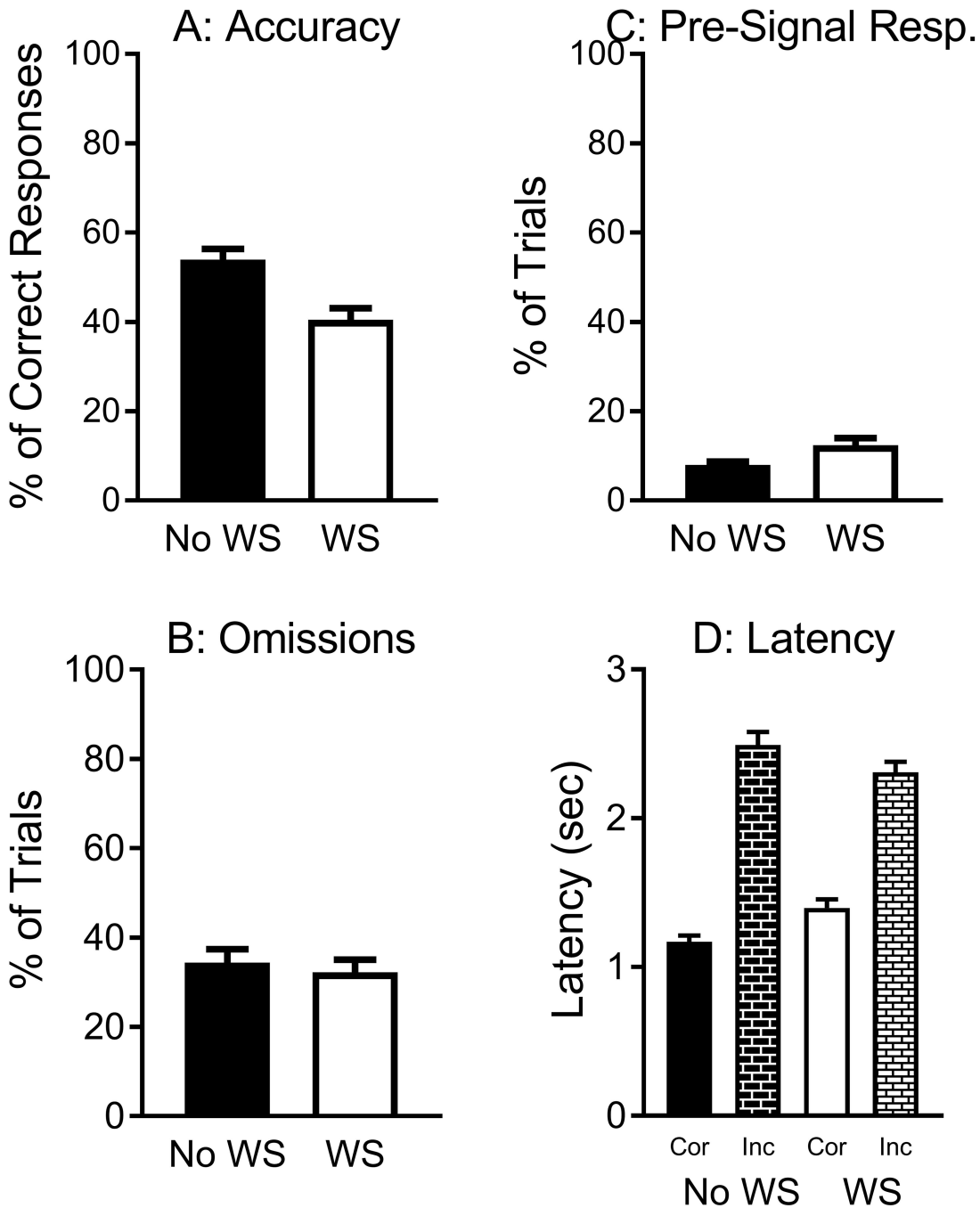

Figure 5.

Performances in the absence of drug treatments (average of control sessions during tests of drugs) under the 5-CSRT procedure without (black or black pattern bars) and with (white or white pattern bars) a “warning” stimulus during the pre-signal period. The measures of performance are described in the Methods section. Vertical bars about the points represent 1 SEM.

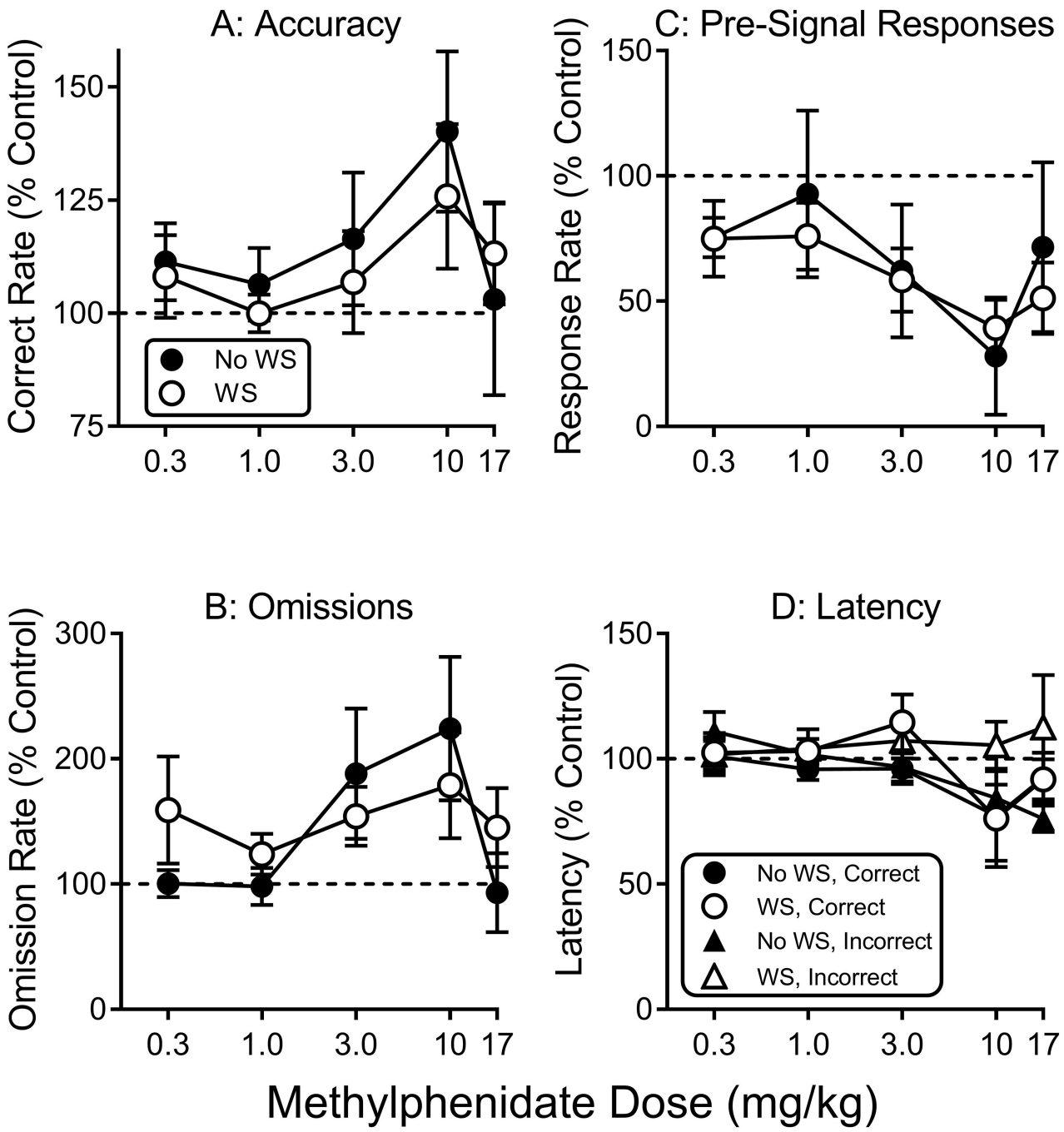

Figure 6.

Effects of methylphenidate pretreatments on performances under the 5CSRT procedure without (filled circles or triangles) and with (open squares or triangles) a warning stimulus during the pre-signal period. Horizontal axes: Methylphenidate dose in mg/kg body weight. All other details as in Figure 2.

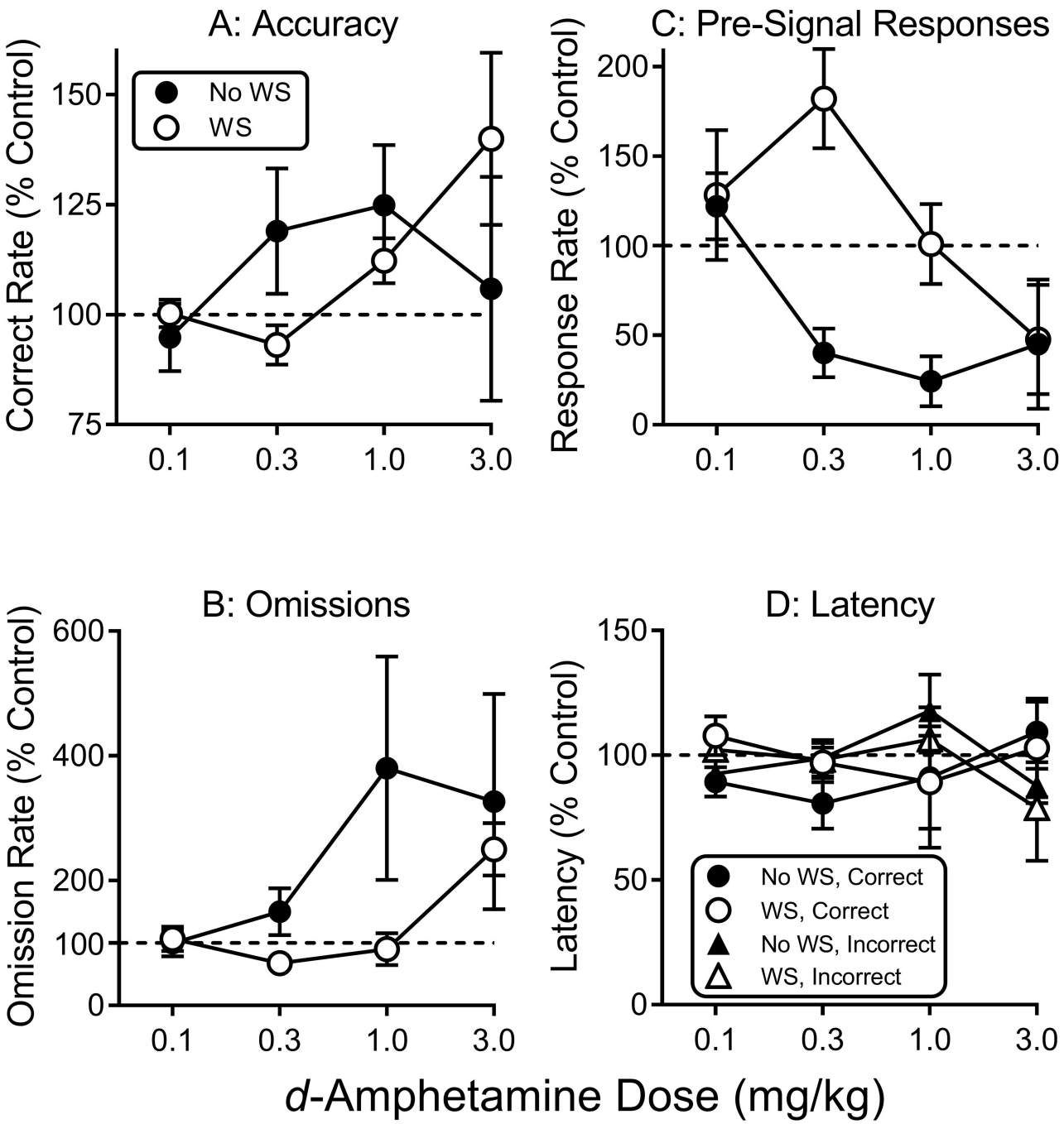

Figure 7.

Effects of *d*-amphetamine pretreatments on performances under the 5CSRT procedure without (filled circles or triangles) and with (open squares or triangles) a warning stimulus during the pre-signal period. Horizontal axes: *d*-amphetamine dose in mg/kg body weight. All other details as in Figure 2.

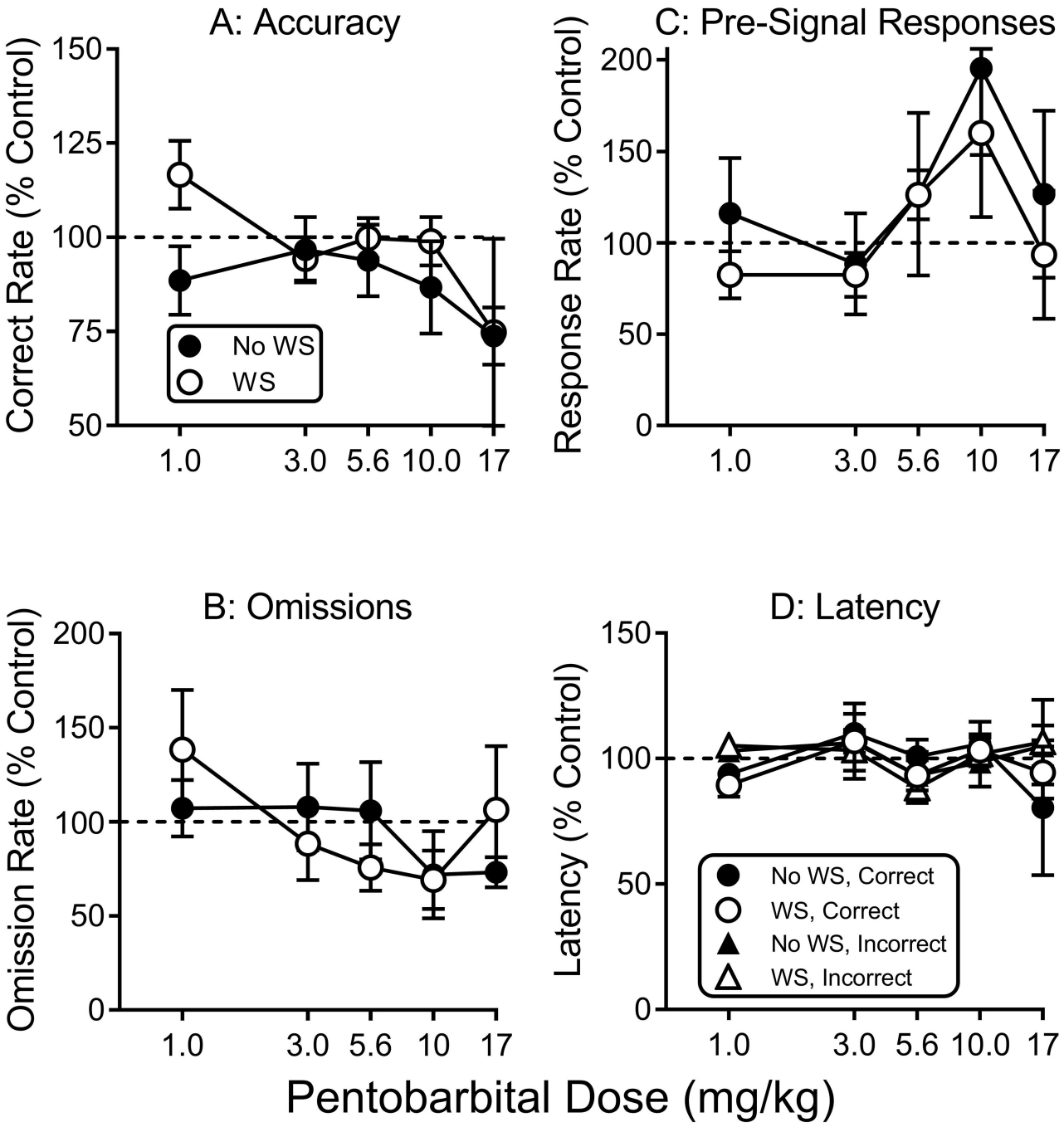

Figure 8.

Effects of pentobarbital pretreatments on performances under the 5CSRT procedure without (filled circles or triangles) and with (open squares or triangles) a warning stimulus during the pre-signal period. Horizontal axes: Pentobarbital dose in mg/kg body weight. All other details as in Figure 2.