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Effects of dopamine D1 receptor blockade in the prelimbic prefrontal cortex or lateral dorsal striatum on frontostriatal function in Wistar and Spontaneously Hypertensive Rats

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is associated with dysfunctional prefrontal and striatal circuitry and dysregulated dopamine neurotransmission. Spontaneously Hypertensive Rats (SHR), a heuristically useful animal model of ADHD, were evaluated against normotensive Wistar (WIS) controls to determine whether dopamine D1 receptor blockade of either prelimbic prefrontal cortex (plPFC) or lateral dorsal striatum (IDST) altered learning functions of both interconnected sites. A strategy set shifting task measured plPFC function (behavioral flexibility/executive function) and a reward devaluation task measured IDST function (habitual responding). Prior to tests, rats received bilateral infusions of SCH 23390 (1.0 µg/side) or vehicle into plPFC or IDST. Following vehicle, SHR exhibited longer lever press reaction times, more trial omissions, and fewer completed trials during the set shift test compared to WIS, indicating slower decision-making and attentional/motivational impairment in SHR. After reward devaluation, vehicle-treated SHR responded less than WIS, indicating relatively less habitual responding in SHR. After SCH 23390 infusions into plPFC, WIS expressed the same behavioral phenotype as vehicle-treated SHR during set shift and reward devaluation tests. In SHR, SCH 23390 infusions into plPFC exacerbated behavioral deficits in the set shift test and maintained the lower rate of responding in the reward devaluation test. SCH 23390 infusions into IDST did not modify set shifting in either strain, but produced lower rates of responding than vehicle infusions after reward devaluation in WIS. This research provides pharmacological evidence for unidirectional interactions between prefrontal and striatal brain regions, which has implications for the neurological basis of ADHD and its treatment.

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Keywords

Attention Deficit Hyperactivity Disorder; Behavioral Flexibility; Dorsal Striatum; Dopamine D1 Receptors; Executive Function; Prefrontal Cortex; Reward Devaluation

1. Introduction

The prelimbic prefrontal cortex (plPFC) in rats is critical for executive functions such as working memory, decision-making and behavioral flexibility [1]. Strategy set shifting is a common procedure for evaluating behavioral flexibility and other executive functions. Animals are required to attend to relevant stimuli, ignore irrelevant stimuli and shift the allocation of attention between strategy sets. Furthermore, this procedure is useful for evaluating many aspects of learning requiring behavioral flexibility, such as discrimination and reversal learning as well as intra-dimensional and extra-dimensional shifts [1]. Lesions and dopamine D1 receptor blockade of plPFC impair set shifting [2–4].

Among its connections, the plPFC projects focally to medial (mDST) and diffusely to lateral (lDST) dorsal striatum [5]. The DST is thought to be important for the development and maintenance of incentive-based learning and mediates performance of instrumental actions during reward-related tasks by two distinct learning processes [6]. The first process, goal-directed learning, is where actions are performed with regard to their consequences and behavior is flexible. The second process, habit learning, is attained after extensive training, with behavior now inflexible and actions no longer dependent on outcome. Goal-directed and habitual behaviors are measured with reward devaluation procedures (e.g., through aversion or satiation), depending on whether rats are tested during early stages of training or are over-trained, respectively. Such procedures provide important evidence that rats form detailed representations of reinforcement and that altering those representations changes the incentive value of the reinforcement. Lesions of the mDST disrupt acquisition and expression of goal-directed behavior [7,8], whereas lesions of the lDST disrupt habitual control of behavior [8, 9]. Information on whether PFC mediates habitual responding (e.g., [7]) or whether DST mediates set shifting (e.g., [10]) is incomplete.

Given that in rats direct plPFC projections are widespread in DST [5] and DST input feeds back indirectly to its cortical origins [11], we manipulated these two interconnected brain sites to assess frontostriatal function in Spontaneously Hypertensive Rats (SHR) and the normotensive Wistar (WIS) control strain. SHR exhibit an ADHD phenotype characterized by hyperactivity, inattention and impulsivity [12,13] and by deficits in working memory, set shifting, and habit learning (14, 15, 16). In the current study, we determined whether dopamine D1 receptor blockade in either plPFC or lDST of WIS and SHR altered learning functions of both sites in which the D1 receptor plays a critical role in mediating effects of dopamine on synaptic plasticity and cognitive functioning [2,17].

2. Materials and Methods

2.1. Subjects

Experimentally naïve male rats of the WIS (CrI(WI)BR) and SHR (CrI(SHR)BR) strains were approximately 60 days old (276–300g for WIS and 205–240g for SHR) upon arrival from Charles River Laboratories (Wilmington MA, USA for WIS and Portage MI, USA for SHR). Rats were housed individually in wedge-shaped clear plastic cages in a temperature- (21–23 °C) and light- (08:00 h on, 20.00 h off) controlled vivarium. After arrival, rats were accustomed for 72 hours to the vivarium, where they had ad libitum access to food and water. Rats began mild food restriction at least 5 days before starting the experiment to establish motivation to lever press for food pellets. Rats received 16 g of food per day to maintain body weight at ~90% of the free-feeding body weight that was adjusted over the course of the experiment. Rats were maintained in accordance with the NIH Guide for Care and Use of Laboratory Animals. The Boston University Institutional Animal Care and Use Committee approved research protocols.

2.2. Apparatus

Experimental chambers (ENV-008CT Med Associates, St. Albans VT, USA) were used for all behavioral sessions. Each chamber was outfitted with two retractable levers, a stimulus light above each lever, a house light and a food receptacle. Connected to the food receptacle was a pellet dispenser, which delivered 45 mg food pellets. A sound-attenuating cubicle (Med Associates), with an exhaust fan to provide ventilation, enclosed each chamber. A PC-compatible computer programmed in Medstate Notation and connected to an interface (Med Associates) controlled experimental events.

2.3. Surgery and Histology

For implantation of guide cannulae, rats received 0.05 mg/kg subcutaneous buprenorphine as a preoperative analgesic and then were anesthetized with an intraperitoneal injection of 80 mg/kg ketamine plus 8 mg/kg xylazine. Guide cannulae (22 gauge; Plastics One, Roanoke VA, USA) were bilaterally implanted into the pIPFC (anteroposterior [AP] + 3.2 mm, lateral [L] $\pm$ 1.4 mm at a 15° angle, dorsoventral [DV] –2.9 mm) or IDST (AP –0.8 mm, L $\pm$ 4.0 mm, DV –3.5 mm). Guide cannulae were positioned 1 mm above the intended site and placements were measured from bregma. Guide cannulae and four stainless steel anchoring screws were attached to the skull and permanently embedded in dental acrylic. Two 28-gauge obturators (Plastics One) were used to occlude guide cannulae between infusions. Rats were allowed at least 7 days of recovery from surgery before initiation of the study. Upon completion of each experiment, rats were given an overdose of sodium pentobarbital, and then perfused intracardially with 0.9% saline and 10% formalin solutions. Brains were removed, post-fixed in 10% formalin for 4 h, and then stored in 30% sucrose at 4 °C for 3 days. Forty- μ m coronal sections were collected using a cryostat. Sections were mounted on gelatin-coated slides and stained to verify guide cannulae placements.

2.4. Microinfusion Procedure

Rats received bilateral infusions of the dopamine D1 receptor antagonist SCH 23390 (1.0 µg/0.5 µl/side) or 0.9% saline vehicle (0.5 µl/side) into the plPFC or IDST 5 min before the set shift and reward devaluation test session. This dose of SCH 23390 is behaviorally active and does not decrease lever press responding nonspecifically [18]. The infusion cannula extended 1 mm beyond the guide cannula tip and was left in place for 1 min following each infusion to allow adequate diffusion of drug into surrounding brain tissue.

2.5. Strategy Set Shifting Task Procedures

To determine plPFC function, the operant version of the strategy set shifting task [3] was adapted for use in the present study. A 15-sec delay, rather than 0-sec delay, version of the task was used, as it better reveals performance differences between SHR and control strains. With a 0-sec delay, SHR do not exhibit behavioral deficits during various task phases relative to WIS or Wistar-Kyoto controls, whereas with a 15-sec delay, behavioral deficits are observed in SHR [16]. The task was divided into three phases: habituation, initial set formation and set shift. Habituation procedures were used to train rats to lever press within 10 sec of lever insertion into the chamber to earn a chocolate-flavored food pellet (BioServ, Frenchtown NJ, USA) on each of 100 discrete trials and to establish a lever position bias.

For the initial set formation phase, rats were required to press the lever opposite its lever position bias (left or right), regardless of which stimulus light was illuminated to earn a food pellet (egocentric spatial response discrimination). Each trial began with both levers retracted and the chamber in darkness for 20 sec. One stimulus light (selected pseudorandomly) then was illuminated, and 3 sec later the houselight was turned on and both levers were inserted into the chamber. Correct lever presses resulted in food pellet delivery after a 15 sec delay. Levers were retracted after a lever was pressed (correct or incorrect) or if 10 sec elapsed without a lever press (trial omission). Following a correct lever press, the stimulus light remained illuminated for 4 sec, and the house light remained illuminated until 4 sec following food pellet delivery. After an incorrect lever press or an omitted trial, the stimulus light and house light were extinguished immediately. Trials continued until criterion performance of 10 consecutive correct responses were achieved [3,16]. Sessions for the initial set formation phase were a maximum of 2 hr in length, and if criterion was not reached, sessions continued on subsequent days until criterion was reached.

The next day after reaching criterion, rats underwent a shift to a discrimination for which the rat was required to press the lever that had the stimulus light illuminated above it (selected pseudorandomly) within 10 sec of lever insertion, regardless of the lever position bias (visual cue discrimination). The same trial contingencies as used for initial set formation phase were used for the set shift phase, except that the set shift phase was conducted as a single 2 hr test session and was preceded by drug or vehicle infusions. Each rat received a total of two intracranial infusions, one for the set shift test and one for the devaluation test (see below), in order to minimize potential tissue damage from multiple intracranial infusions. A fixed 2-hr test session was used because SCH 23390 is cleared from the injection site 2–3 hr post-infusion [19].

2.6. Devaluation by Specific Satiety Procedures

To determine IDST function, the devaluation by specific satiety task [9] was adapted for use in the present study. An abbreviated version was used in that lever pressing for a devalued food was the only instrumental action assessed. In [9], lever-pressing responses were differentially sensitive to outcome devaluation in 6-hydroxydopamine vs. sham-lesioned rats during both extinction and reward tests, whereas chain-pulling responses were not. As devalued lever pressing better revealed group differences than devalued chain pulling after dopamine depletion of the nigrostriatal system, we anticipated that the use of lever pressing alone would be sufficient to detect outcome devaluation differences in WIS vs. SHR strains and after vehicle vs. SCH 23390 treatments. All rats were trained initially to lever press during sessions under a continuous reinforcement schedule. One lever (counterbalanced across treatment groups) was inserted into the chamber at the beginning of the 1-hr sessions and retracted at the end. Each lever press resulted in the immediate delivery of a grape-flavored food pellet (BioServ) and sessions continued until rats reached criterion performance of 100 lever presses within 1 hr. During the next two sessions of training, food pellets were delivered under a variable interval (VI) 20 sec schedule (reward available every 20 sec on average and delivered after the next lever press). Following the VI 20 sec schedule, rats were trained under a VI 45 sec schedule in daily 1hr sessions for a total of 28 sessions. This schedule and procedure was used to maintain high numbers of responses while maintaining sensitivity to outcome devaluation after extended training [9].

The next day after the 28th session, all rats received a single 10 min test session under the VI 45 sec schedule of food pellet delivery (reward test) that was preceded by drug or vehicle infusions. One hr prior to the test session, rats were given ad libitum access to grape-flavored food pellets in their home cages to induce satiety.

2.7. Experiment 1: Effects of SCH 23390 in prelimbic prefrontal cortex

One group of rats with cannulae aimed at the plPFC underwent set shifting procedures first, followed by reward devaluation procedures next, with 5–7 days between procedures. Immediately prior to the 2-hr set shift test session, rats were infused bilaterally with either SCH 23390 (WIS n=7; SHR n=8) or vehicle (WIS n=8; SHR n=8). Immediately prior to the 10-min reward devaluation test session, the same rats were infused bilaterally with either SCH 23390 (WIS n=6; SHR n=8) or vehicle (WIS n=8; SHR n=8). One SCH 23390-treated WIS died prior to the devaluation procedure.

2.8. Experiment 2: Effects of SCH 23390 in lateral dorsal striatum

A second group of rats with cannulae aimed at the IDST underwent set shifting procedures first, followed by reward devaluation procedures next, with 5–7 days between procedures. Immediately prior to the 2-hr set shift test session, rats were infused bilaterally with either SCH 23390 (WIS n=9; SHR n=9) or vehicle (WIS n=11; SHR n=10). Immediately prior to the 10-min reward devaluation test session, a subset of rats infused with SCH 23390 for the set shift test was infused bilaterally with SCH 23390 (WIS n=5; SHR n=5) for the reward devaluation test, and all rats infused with vehicle for the set shift test were infused bilaterally with vehicle (WIS n=11; SHR n=9) for the reward devaluation test. One vehicle-treated WIS died prior to the devaluation procedure. The remaining subset of rats given SCH 23390

during the set shift test (WIS $n=4$; SHR $n=3$) was trained under the VI 45 sec schedule for 28 sessions; on test day they received vehicle infusions, but did not undergo prefeeding in order to determine response rates under a no devaluation/no drug treatment condition.

2.9. Data analyses

The dependent measures evaluated for each phase of the strategy set shifting task were: trials completed to reach criterion (initial set formation phase) or trials completed during the 2 hr test (set shift phase), proportion of correct trials, number of omitted trials and average lever press reaction time. Omitted trials did not count toward number of trials completed to reach criterion or to the number of trials completed, and did not factor into the calculation of average lever press reaction time. For the set shift phase, error subtypes (perseverative, regressive and never reinforced) were tabulated [3] and each error subtype was expressed as the proportion of total errors made. Perseverative and regressive errors were recorded when a rat pressed a lever on trials for which that same lever was correct during the initial set and for which the stimulus light was illuminated above the opposite lever. Errors were scored as perseverative when a rat pressed the incorrect lever on six or more trials per block of eight trials. Once a rat made five or fewer incorrect choices in a block of eight trials for the first time, the incorrect lever choices in subsequent blocks were then scored as regressive errors. At this point, the rat was using the original strategy less than 75% of the time. Never-reinforced errors were recorded when a rat pressed a lever on trials for which that same lever was incorrect during the initial set and for which the stimulus light was illuminated above the opposite lever (i.e., a choice that was not reinforced during either the initial set or set shift phase). Regressive and never-reinforced errors are used as an index of the ability to maintain and acquire a new strategy, respectively, whereas perseverative errors are an index of how well the previously acquired strategy is suppressed [1].

Dependent measures evaluated for the reward devaluation task were: number of baseline responses (1 hr total and first 10 min) and number of responses during the 10 min test (expressed as percentage of 10 min baseline responses). A percentage of baseline measure was used because of the 3-fold range in baseline responses of individual rats within each group in both experiments. Each dependent measure in Experiments 1 and 2 was analyzed by a two-factor (strain $\times$ treatment) or three-factor (strain $\times$ treatment $\times$ error subtype) ANOVA followed by Tukey tests, which control for type 1 error with multiple comparisons. Prior to analysis, the proportion of correct trials and error subtypes in the set shifting task was arcsine transformed, as data ranged between 0 and 1. The percentage of baseline responses in the reward devaluation task was square root transformed, as the non-transformed data were not normally distributed and did not pass the equal variance test.

3. Results

3.1. Experiment 1: Effects of SCH 23390 in prelimbic prefrontal cortex

3.1.1. Set Shifting Task—During the initial set formation phase (no drug pretreatments; Figure 1, left panels) strains differed in trial omissions and reaction time, but not in trials to reach criterion or proportion of correct trials. Overall, SHR omitted more trials ($F [1,27] = 4.3$, $p = 0.05$) and had longer reaction times ($F [1,27] = 9.0$, $p = 0.006$) than WIS. No other

factors were significant for this phase. During the set shift phase (with drug pretreatments; Figure 1, right panels), main effects of strain and treatment as well as a strain $\times$ treatment interaction ($F [1,27] = 4.4, p = 0.05$) were found for number of trials completed. Overall, SHR completed fewer trials than WIS ($F [1,27] = 10.1, p = 0.004$) and fewer trials were completed after SCH 23390 than vehicle treatment ($F [1,27] = 23.7, p = 0.001$). Within both WIS and SHR strains, SCH-23390-treated rats completed fewer trials than vehicle-treated rats ($p = 0.001$ and 0.05 , respectively). Analysis of trial omissions also revealed main effects of strain and treatment as well as a strain $\times$ treatment interaction ($F [1,27] = 4.0, p = 0.05$). Overall, SHR omitted more trials than WIS ($F [1,27] = 9.1, p = 0.006$) and more trials were omitted after SCH-23390 than vehicle treatment ($F [1,27] = 24.4, p = 0.001$). The treatment difference was observed in both WIS ($p = 0.001$) and SHR ($p = 0.05$). Moreover, main effects of strain and treatment were found for reaction time. Overall, SHR exhibited longer reaction times than WIS ($F [1,27] = 9.9, p = 0.004$) and reaction times were longer after SCH 23390 than vehicle treatment ($F [1,27] = 13.1, p = 0.001$). Despite the above performance deficits in SHR and after SCH 23390, no significant strain or treatment effects were seen in the proportion of correct trials completed during the set shift phase.

Three-factor ANOVA of errors during the set shift phase revealed only a main effect of error subtype ($F [2,54] = 135.5, p = 0.001$). The rank order of magnitude was regressive errors $>$ never reinforced errors $>$ perseverative errors. Consequently, each error subtype was analyzed separately using two-factor ANOVA to examine differences between strains and treatments (Figure 2, upper panel). Analysis of regressive errors showed a main effect of treatment ($F [1,27] = 3.9, p = 0.05$), with fewer regressive errors made after SCH 23390 than vehicle. Further analysis revealed that this treatment effect was due mainly to differences between SCH 23390- and vehicle-treated SHR ($p = 0.04$). Treatments in WIS did not differ. Also, a trend for a main effect of strain was found ($F [1,27] = 3.5, p = 0.07$), with SHR tending to make fewer regressive errors than WIS overall. No significant strain or treatment differences were observed for perseverative or never-reinforced errors during the set shift phase, though there was a tendency for SCH 23390-treated WIS to emit more perseverative errors than vehicle-treated WIS ($p = 0.09$).

3.1.2. Reward Devaluation Task—After 28 sessions of VI 45 sec training, no statistical differences were found between strains for baseline responses/hr (no drug pretreatments; Figure 3, left panel, white and black bars). Analysis of responses during the first 10 min of these sessions, which are used as the baseline values for the 10-min devaluation test, also revealed no strain differences (Figure 3, left panel, stacked gray bars).

During the devaluation test (with drug pretreatments; Figure 3, right panel), a main effect of strain was found, with SHR making fewer responses than WIS ($F [1,26] = 4.9, p = 0.04$). In addition, there was a strain $\times$ treatment interaction ($F [1,26] = 4.7, p = 0.04$). Post-hoc tests showed that after reward devaluation, vehicle-treated SHR made fewer responses than vehicle-treated WIS ($p = 0.004$), but responses in SCH 23390-treated SHR and WIS did not differ ($p = 0.98$). Furthermore, the treatments differed within the WIS strain ($p = 0.03$), with SCH 23390 reducing response rates to levels observed in vehicle- and SCH 23390-treated SHR.

3.2. Experiment 2. Effects of SCH 23390 in lateral dorsal striatum

3.2.1. Set Shifting Task—During the initial set formation phase (no drug pretreatments; Figure 4, left panels), strains differed in trial omissions and reaction time, but not in trials to reach criterion or proportion of correct trials completed. Overall, SHR omitted more trials than WIS ($F [1,27] = 6.2, p = 0.02$) and had longer reaction times than WIS ($F [1,27] = 13.5, p = 0.001$). No other factors were significant for this phase. During the set shift phase (with drug pretreatments; Figure 4, right panels), main effects of strain were found for number of trials completed, trial omissions and reaction times. Overall, SHR completed fewer trials ($F [1,27] = 24.8, p = 0.001$), omitted more trials ($F [1,27] = 25.1, p = 0.001$) and exhibited longer reaction times ($F [1,27] = 5.5, p = 0.03$) than WIS. No significant treatment differences were found for these measures. Furthermore, there were no significant strain or treatment differences for the proportion of correct trials completed for the set shift phase.

Three-factor ANOVA of errors during the set shift phase revealed only a main effect of error subtype ($F [2,42] = 158.0, p = 0.001$). As in Experiment 1, the rank order of magnitude was regressive errors > never reinforced errors > perseverative errors. Consequently, each error subtype was analyzed separately using a two-factor ANOVA to examine differences between strains and treatments (Figure 2, lower panel). Main effects of strain were found for regressive errors and never reinforced errors; SHR made fewer regressive errors ($F [1,21] = 7.0, p = 0.01$) and more never reinforced errors ($F [1,21] = 26.1, p = 0.001$) than WIS. There were no significant treatment differences in these measures and no strain or treatment differences in perseverative errors.

3.2.2. Reward Devaluation Task—Similar to Experiment 1, no statistical differences were found between strains for baseline responses/hr or responses for the first 10 min (no drug pretreatments; Figure 5, left panel). During the devaluation test (with drug pretreatments; Figure 5, right panel), a trend for a main effect of treatment was found ($F [1,26] = 3.1, p = 0.09$), with fewer responses after SCH 23390 than vehicle. However, further analysis revealed that vehicle-treated SHR made fewer responses than vehicle-treated WIS ($p = 0.02$) and that SCH 23390-treated WIS made fewer responses than vehicle-treated WIS ($p = 0.03$). After SCH 23390 treatment, SHR did not differ from WIS or from its own vehicle control treatment.

3.2.3. No Devaluation/No Drug Treatment Condition—A subset of WIS and SHR received vehicle infusions and was tested under conditions where no reward devaluation was implemented on the test day after the 28 sessions of VI 45 sec training. Performance did not change significantly on test day relative to baseline; responses during the first 10 min were maintained at high rates (368 ± 68 vs. 342 ± 43 for WIS and 350 ± 51 vs. 348 ± 37 for SHR). These findings indicate that though the specific satiety procedure used in Experiments 1 and 2 resulted in low levels of responding compared to baseline, this procedure was sufficient to detect strain and treatment differences.

3.3. Histology

Only rats whose cannulae placements were histologically verified as positioned bilaterally in pIPFC and IDST were used in data analyses. Final group sizes are the numbers indicated in

sections 2.7 and 2.8. The atlas of Paxinos and Watson [20] was used for verification. Figure 6A depicts verified infusion sites in plPFC (n= 31) and IDST (n=39). Four rats in experiment 1 were excluded from the data analysis, as cannulae placements were outside the accepted anatomical range for the plPFC. Representative low magnification photomicrographs of guide cannulae tracks for plPFC and IDST placements are depicted in Figure 6B.

4. Discussion

The current investigation shows disrupted frontostriatal cognitive function in SHR, a heuristically useful animal model of ADHD. More importantly, blocking dopamine D1 receptors in plPFC disrupted cognitive function of both plPFC and IDST; conversely, this manipulation in IDST disrupted cognitive function of IDST, but not plPFC. Notably, SCH 23390-treated WIS expressed the same behavioral phenotype as vehicle-treated SHR. This research has implications for functional connectivity between prefrontal and striatal brain regions and for the neurological basis of ADHD and its treatment.

4.1. Strain differences during set shifting and reward devaluation tasks

During initial set and set shift phases, SHR showed slower decision-making (longer lever press reaction times) and weaker motivation and/or attention for task learning (more trial omissions and fewer completed trials at test) than WIS, suggesting that SHR have executive function impairment [21]. Previous research in adolescent rats shows that SHR have these same behavioral deficits in the strategy set shifting task compared to WIS under relatively difficult (15-sec delay), but not easy (0-sec delay), task conditions [16]. Other research indicates that SHR exhibit robust deficits in sustained attention and working memory compared to Wistar-Kyoto controls as task difficulty increases [14; 22]. Our results also mirror human data in which individuals with ADHD show slower reaction times, more attentional and motivational lapses, and dysfunctional reward-related decision-making compared to healthy controls during tests of executive function (23–27). Because speed of learning in the initial set (trials to criterion) and accuracy of learning in the initial set and the set shift (proportion of correct trials) did not differ between SHR and WIS, SHR appear capable of reinforcement-based learning and do not exhibit behavioral flexibility deficits.

Set shifting tasks conducted in mazes or operant chambers allow detailed analysis of error subtypes that elucidate specific contributions to behavioral flexibility impairment. Generally, rats made more regressive and never reinforced errors than perseverative errors. Regressive errors arise from proactive interference and reflect a natural tendency to revert to the original reinforced strategy that was learned during initial set formation after being reinforced at least 25% of the time during the set shift phase [3]. A never reinforced error involves a failed attempt at using a novel strategy [3]. SHR made fewer regressive errors (Experiments 1 and 2) and more never-reinforced errors (Experiment 2) than WIS. These results suggest that performance of SHR during the set shift phase was not related to failure to suppress performance based on earlier contingencies, but to difficulties in attempting to learn new contingencies that were likely due to their observed motivational and/or attentional deficits.

After extended training and reward devaluation, responding was lower in SHR compared to WIS under control conditions. This finding suggests that responding was relatively less habitual in SHR than WIS after reward devaluation. Prior to reward devaluation, both strains displayed similarly high rates of responding throughout 28 sessions of VI 45 sec training, indicating both strains were equally capable of exhibiting reinforcement-based goal-directed behavior. Performance of SHR before and after devaluation is consistent with performance in the ambiguous T-maze task in which SHR did not show the normal progression from using place strategies (goal-directed) early in training to using response strategies (habit) after 24 days of training [15]. SHR also failed to reach criterion levels of learning in the win-stay (habit learning) task [14]. It is unlikely that the lower rate of lever pressing in SHR than WIS during the reward devaluation test was due to greater food satiety in SHR during the pre-feeding phase as there were no strain differences in the rate of responding during the no devaluation/no drug treatment control test condition. If SHR were more easily satiated than WIS, then rates of responding would have been lower in SHR than WIS during this control test. Past research supports similar rates of food satiety in SHR and WIS, as assessed by home cage consumption tests and by operant tests conducted under VI 20 and VI 50 schedules [28, 29]. Furthermore, infusion of 1 µg/side SCH 23390 into the pLPFC or IDST influences neither responding reinforced by sucrose pellets nor motor activity [30, 31], suggesting that this dose of SCH 23390 infused into these regions does not impact satiety or the capacity to lever press. Anecdotally, rats from each strain in the present study did not consume most of the pellets they earned during the reward devaluation test, suggesting that lever presses were emitted more out of habit than hunger. As responding was relatively less habitual in SHR than WIS, this finding is consistent with the idea that SHR have increased sensitivity to reward devaluation. While engaged in delayed discounting, which is described as devaluation of rewards over time [32], individuals with ADHD choose small immediate rewards over large delayed rewards compared to healthy controls [33]. Reduced ability to delay gratification in the discounting task suggests that individuals with ADHD, like SHR, have greater sensitivity to reward devaluation.

4.2. Role of dopamine D1 receptors during set shifting and reward devaluation tasks

When shifting from response to visual cue discriminations, D1 receptor blockade of pLPFC induced behavioral deficits in WIS (fewer completed trials, more trial omissions and longer lever press reaction times) and further exacerbated these same deficits in SHR. Performance in SCH 23390-treated WIS was similar to performance in vehicle-treated SHR. D1 receptor blockade of IDST did not alter any behavioral measure during set shifting, suggesting that IDST does not influence pLPFC function. Proportion of correct trials and perseverative errors were not significantly affected by SCH 23390 infusions into pLPFC in either strain. This pattern of results suggests that D1 receptor blockade of the pLPFC influenced decision-making and motivation and/or attention during set shifting, but not behavioral flexibility.

Past research demonstrated behavioral flexibility deficits in rats after infusion of 1.0 µg SCH 23390 into the pLPFC [2]. The task used was a maze version of the strategy set shifting task and SCH 23390-induced impairments (more trials to criterion and perseverative errors) were observed when rats shifted from a response to visual cue discrimination. Although other indices of executive function performance were not measured in that study, the previous

results conflict with current results regarding behavioral flexibility deficits. It may be more difficult to impact behavioral flexibility with D1 receptor blockade of the pLPFC in the operant version than in the maze version of the task, given the different response requirements (press a lever vs. traverse arms of the maze). Interestingly, infusion of the D1 agonist SKF 81297 into pLPFC does not influence behavioral flexibility when rats shift from a response to visual cue discrimination in the same maze version of the task, suggesting that the relationship between D1 receptors in pLPFC and behavioral flexibility is not straightforward [34]. The current results add to this growing complexity. Nonetheless, the current results support executive function impairment in SHR and after SCH 23390 treatment in both SHR and WIS. Thus, low levels of prefrontal D1 receptor stimulation may contribute to executive function deficits in a variety of neurological disorders, including ADHD.

Blocking D1 receptors in IDST after reward devaluation produced a profile whereby responding was relatively less habitual in WIS after SCH 23390 treatment compared to vehicle treatment. Responses in WIS after SCH 23390 were reduced to a level observed in vehicle- and SCH 23390-treated SHR. These findings suggest increased sensitivity to reward devaluation after SCH 23390 treatment in WIS. Consistent with this effect, rats with 6-hydroxydopamine lesions of nigrostriatal neurons showed increased sensitivity to reward devaluation compared to sham-operated rats [9]. Others observed that IDST is vital for reward-related stimuli to elicit responding [35], and our findings suggest this may depend not only on D1 receptor activation in IDST, but also in pLPFC. D1 receptor blockade of both IDST and pLPFC increased sensitivity to reward devaluation, suggesting that the pLPFC influences cognitive function of the IDST. Moreover, SCH 23390 infusions into pLPFC or IDST did not further enhance sensitivity to reward devaluation in SHR. This finding, coupled with executive function deficits in SHR after vehicle infusions into pLPFC or IDST, supports the idea that SHR may inherently suffer from hypodopaminergic activity in frontostriatal networks, particularly in PFC [36]. The degree to which different densities of D1 receptors in pLPFC and IDST of SHR vs. WIS may have contributed to the observed strain differences in the effects of SCH 23390 (more pronounced effects in WIS than SHR) is not clear. With respect to D1 receptors, only a single study has directly compared SHR and WIS and found similar D1 receptor mRNA expression in DST and ventral tegmental area; PFC was not examined [37]. A direct comparison of D1 receptor protein densities in SHR vs. WIS has not been reported. However, the present findings support the view that behavioral disturbances in ADHD result from an imbalance in dopaminergic systems within frontostriatal networks (reviewed in [38]). Future pharmacological studies determining the effects of D1 receptor agonist infusions into pLPFC and IDST, either alone or in combination with SCH 23390, would provide complementary evidence for the role of D1 receptors in these regions in the pathophysiology of ADHD.

4.3. Implications for functional connectivity in frontostriatal regions and ADHD

Although pLPFC and IDST are interconnected sites, blocking D1 receptors only in pLPFC resulted in behavioral changes in both set shifting and reward devaluation tasks. These findings corroborate nonhuman primate work showing disrupted set shifting after dopamine depletion in PFC, but not DST [10]. Differences in cognitive function control in rats by

pPFC vs. IDST may relate to direct monosynaptic input from pPFC to IDST, but indirect polysynaptic input from IDST to pPFC [5, 11]. Direct feed-forward projections from pPFC to IDST may allow for increased electrical and chemical signaling strength capable of functionally influencing neural activity downstream as a means of top-down control. An opposing bottom-up feedback network from IDST sends inhibitory projections to normally active neurons of the pallidum and substantia nigra that inhibit activity in thalamic nuclei. Finally, the thalamus completes the circuit by sending excitatory projections back to PFC neurons of origin [11]. A relay of communication through multiple inputs and from other afferent sources may explain the lack of bottom-up influence of IDST on pPFC cognitive function.

Notably, in healthy human volunteers, functional connectivity between PFC and DST is linked to executive function performance (working memory task), and activation within IDST (posterior putamen) that extends into globus pallidus is linked to habitual responding [39, 40]. While posterior putamen is recruited when responding is habitual, this site does not show functional connectivity with PFC [41]. Importantly, compared to age-matched controls, children with ADHD show weaker functional connectivity between PFC and putamen [42] and stronger functional connectivity between putamen and anterior thalamus, which provides feedback to PFC [43]. The current findings with site-selective SCH 23390 infusions in WIS and SHR provide pharmacological evidence for top-down functional connectivity between prefrontal and striatal brain regions, and establish an essential link between neuroanatomy and cognitive function. As WIS expressed an ADHD phenotype (executive function deficits and increased sensitivity to reward devaluation) after blocking D1 receptors in pPFC, it is possible that frontostriatal deficits in ADHD arise from primary PFC dysfunction. This basic idea is supported by structural connectivity studies in ADHD individuals [44]. Our findings extend this view to suggest that D1-mediated dopamine neurotransmission within PFC may be critical for functional connectivity between prefrontal and striatal brain regions. Future imaging studies determining functional connectivity between pPFC and IDST in SHR and WIS would provide support for this view.

Methylphenidate, the most widely prescribed stimulant medication for ADHD, is effective at reducing hyperactivity and other motor dysfunctions as well as at improving behavioral flexibility and other executive functions [45–47]. Of interest is that low, therapeutically relevant doses of methylphenidate in rats preferentially activate dopamine and norepinephrine efflux within PFC compared to subcortical regions [48, 49]. In SHR, low dose methylphenidate improves set shifting and habit learning deficits [14,16] and increases dopamine transporter function in mPFC, but not DST or orbitofrontal cortex [50]. At higher doses, methylphenidate also targets striatal and accumbens neurons [51–53], which could lead to undesirable motor and motivational side effects. Based on the present study, ADHD medications that specifically target PFC may be safer, while at the same time remaining effective for relieving frontostriatal dysfunction.

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References

1. Floresco SB, Magyar O. Mesocortical dopamine modulation of executive functions: beyond working memory. *Psychopharmacology*. 2006; 188:567–585. [PubMed: 16670842]
2. Ragozzino ME. The effects of dopamine D(1) receptor blockade in the prelimbic-infralimbic areas on behavioral flexibility. *Learn Mem*. 2002; 9:18–28. [PubMed: 11917003]
3. Floresco SB, Block AE, Tse MT. Inactivation of the medial prefrontal cortex of the rat impairs strategy set-shifting, but not reversal learning, using a novel, automated procedure. *Behav Brain Res*. 2008; 190:85–96. [PubMed: 18359099]
4. Floresco SB, Zhang Y, Enomoto T. Neural circuits subserving behavioral flexibility and their relevance to schizophrenia. *Behav Brain Res*. 2009; 204:396–409. [PubMed: 19110006]
5. Mailly P, Aliane V, Groenewegen HJ, Haber SN, Deniau JM. The rat prefrontostriatal system analyzed in 3D: evidence for multiple interacting functional units. *J Neurosci*. 2013; 33:5718–5727. [PubMed: 23536085]
6. Balleine BW, O'Doherty JP. Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology*. 2010; 35:48–69. [PubMed: 19776734]
7. Balleine BW, Dickinson A. Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology*. 1998; 37:407–419. [PubMed: 9704982]
8. Yin HH, Knowlton BJ, Balleine BW. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *Eur J Neurosci*. 2004; 19:181–189. [PubMed: 14750976]
9. Faure A, Haberland U, Conde F, El Massioui N. Lesion to the nigrostriatal dopamine system disrupts stimulus-response habit formation. *J Neurosci*. 2005; 25:2771–2780. [PubMed: 15772337]
10. Crofts HS, Dalley JW, Collins P, Van Denderen JC, Everitt BJ, Robbins TW, Roberts AC. Differential effects of 6-OHDA lesions of the frontal cortex and caudate nucleus on the ability to acquire an attentional set. *Cereb Cortex*. 2001; 11:1015–1026. [PubMed: 11590111]
11. Balleine BW, Liljeholm M, Ostlund SB. The integrative function of the basal ganglia in instrumental conditioning. *Behav Brain Res*. 2009; 199:43–52. [PubMed: 19027797]
12. Sagvolden T, Metzger MA, Schiorbeck HK, Rugland AL, Spinnangr I, Sagvolden G. The spontaneously hypertensive rat (SHR) as an animal model of childhood hyperactivity (ADHD): changed reactivity to reinforcers and to psychomotor stimulants. *Behavioral and Neural Biology*. 1992; 58:103–12. [PubMed: 1360797]
13. Sagvolden T, Johansen EB, Aase H, [1] VA. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behav Brain Sci*. 2005; 28:397–419. [PubMed: 16209748]
14. Kantak KM, Singh T, Kerstetter KA, Dembro KA, Mutebi MM, Harvey RC, Deschepper CF, Dwoskin LP. Advancing the spontaneous hypertensive rat model of attention deficit/hyperactivity disorder. *Behav Neurosci*. 2008; 122:340–357. [PubMed: 18410173]
15. Wells AM, Janes AC, Liu X, Deschepper CF, Kaufman MJ, Katak KM. Medial temporal lobe functioning and structure in the spontaneously hypertensive rat: comparison with Wistar-Kyoto normotensive and Wistar-Kyoto hypertensive strains. *Hippocampus*. 2010; 20:787–797. [PubMed: 19623608]
16. Harvey RC, Jordan CJ, Tassin DH, Moody KR, Dwoskin LP, Katak KM. Performance on a strategy set shifting task during adolescence in a genetic model of attention deficit/hyperactivity disorder: Methylphenidate vs. atomoxetine treatments. *Behav Brain Res*. 2013; 244:38–47. [PubMed: 23376704]
17. Lovinger DM. Neurotransmitter roles in synaptic modulation, plasticity and learning in the dorsal striatum. *Neuropharmacology*. 2010; 58:951–961. [PubMed: 20096294]
18. Mashhoon Y, Tsikitas LA, Katak KM. Dissociable effects of cocaine-seeking behavior following D₁ receptor activation and blockade within the caudal and rostral basolateral amygdala in rats. *Eur J Neurosci*. 2009; 29:1641–1653. [PubMed: 19419427]

19. Caine SB, Coffin VL, Koob GF. Effects of the Dopamine D-1 antagonist SCH 23390 microinjected into the accumbens, amygdala or striatum on cocaine self-administration in the rat. *Brain Res.* 1995; 692:47–56. [PubMed: 8548319]
20. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. 6. London: Academic Press; 2009.
21. Goldman-Rakic PS. The prefrontal landscape; implications of functional architecture for understanding human mentation and the central executive. *Philos Trans R Soc London B Biol Sci.* 1996; 351:1445–53. [PubMed: 8941956]
22. Jentsch JD. Impaired visuospatial divided attention in the spontaneously hypertensive rat. *Behav Brain Res.* 2005; 157:323–330. [PubMed: 15639183]
23. Seidman LJ, Biederman J, Faraone SV, Weber W, Mennin D, Jones J. A pilot study of neuropsychological function in girls with ADHD. *J Am Acad Child Adolesc Psychiatry.* 1997; 36:366–373. [PubMed: 9055517]
24. Reeve WV, Schandler SL. Frontal lobe functioning in adolescents with attention deficit hyperactivity disorder. *Adolescence.* 2001; 36:749–765. [PubMed: 11928880]
25. Hervey AS, Epstein JN, Curry JF, Tonev S, Eugene Arnold L, Keith Conners C, Hinshaw SP, Swanson JM, Hechtman L. Reaction time distribution analysis of neuropsychological performance in an ADHD sample. *Child Neuropsychol.* 2006; 12:125–140. [PubMed: 16754533]
26. Drechsler R, Rizzo P, Steinhausen HC. The impact of instruction and response cost on the modulation of response-style in children with ADHD. *Behav Brain Funct.* 2010; 6:31. [PubMed: 20525316]
27. Epstein JN, Langberg JM, Rosen PJ, Graham A, Narad ME, Antonini TN, Brinkman WB, Froehlich T, Simon JO, Altaye M. Evidence for higher reaction time variability for children with ADHD on a range of cognitive tasks including reward and event rate manipulations. *Neuropsychology.* 2011; 25:427–441. [PubMed: 21463041]
28. Dommert EJ, Rostron CL. Appetitive and consummative responding for liquid sucrose in the spontaneously hypertensive rat model of attention deficit hyperactivity disorder. *Behav Brain Res.* 2013; 238:232–42. [PubMed: 23117093]
29. Orduña V, García A, Hong E. Choice behavior in spontaneous hypertensive rats; variable vs. fixed schedules of reinforcement. *Behav Processes.* 2010; 84:465–9. [PubMed: 20060441]
30. Sun W, Rebec GV. The role of prefrontal cortex D1-like and D2-like receptors in cocaine-seeking in rats. *Psychopharmacology (Berl).* 2005; 177:315–23. [PubMed: 15309375]
31. Gao J, Li Y, Zhu N, Brimijoin S, Sui N. Roles of dopaminergic innervation of nucleus accumbens shell and dorsolateral caudate-putamen in cue-induced morphine seeking after prolonged abstinence and the underlying D1- and D2-like receptor mechanisms in rats. *J Psychopharmacol.* 2013; 27:181–91.
32. Tesch AD, Sanfey AG. Models and methods in delay discounting. *Ann N Y Acad Sci.* 2008; 1128:90–94. [PubMed: 18469217]
33. Scheres A, Sumiya M, Thoeny AL. Studying the relation between temporal reward discounting tasks used in populations with ADHD: a factor analysis. *Int J Methods Psychiatr Res.* 2010; 19:167–176. [PubMed: 20812292]
34. Floresco SB, Magyar O, Ghods-Sharifi S, Vexelman C, Tse MT. Multiple dopamine receptor subtypes in the medial prefrontal cortex of the rat that regulate set-shifting. *Neuropsychopharmacology.* 2006; 31:297–309. [PubMed: 16012531]
35. Corbit LH, Janak PH. Inactivation of the lateral but not medial dorsal striatum eliminates the excitatory impact of Pavlovian stimuli on instrumental responding. *J Neurosci.* 2007; 27:13977–13981. [PubMed: 18094235]
36. Russell VA. Hypodopaminergic and hyponoradrenergic activity in prefrontal cortex slices of an animal model for attention-deficit hyperactivity disorder- the spontaneously hypertensive rat. *Behav Brain Res.* 2002; 130:191–196. [PubMed: 11864734]
37. Roessner V, Sagvolden T, Dasbanerjee T, Middleton FA, Faraone SV, Walaas SI, Becker A, Rothenberger A, Bock N. Methylphenidate normalizes elevated dopamine transporter densities in an animal model of the attention-deficit/hyperactivity disorder combined type, but not to the same

- extent in one of the attention-deficit/hyperactivity disorder inattentive type. *Neuroscience*. 2010; 167:1183–91. [PubMed: 20211696]
38. Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2011; 69:e145–157. [PubMed: 21550021]
 39. Tricomi E, Balleine BW, O'Doherty JP. A specific role for posterior dorsolateral striatum in human habit learning. *Eur J Neurosci*. 2009; 29:2225–32. [PubMed: 19490086]
 40. Quide Y, Morris RW, Shepherd AM, Rowland JE, Green MJ. Task-related fronto-striatal functional connectivity during working memory performance in schizophrenia. *Schizophr Res*. 2013; 150:468–75. [PubMed: 24016726]
 41. de Wit S, Watson P, Harsay HA, Cohen MX, van de Vijver I, Ridderinkhof KR. Corticostriatal connectivity underlies individual differences in the balance between habitual and goal-directed action control. *J Neurosci*. 2012; 32:12066–12075. [PubMed: 22933790]
 42. Posner J, Rauh V, Gruber A, Gat I, Wang Z, Peterson BS. Dissociable attentional and affective circuits in medication-naïve children with attention-deficit/hyperactivity disorder. *Psychiatry Res*. 2013; 213:24–30. [PubMed: 23664625]
 43. Mills KL, Bathula D, Costa Dis TG, Iyer SP, Fenesy MC, Musser ED, Stevens CA, Thurlow BL, Carpenter SD, Nagel BJ, Nigg JT, Fair DA. Altered cortico-striatal-thalamic connectivity in relation to spatial working memory capacity in children with ADHD. *Front Psychiatry*. 2012; 3:1–17. [PubMed: 22347194]
 44. Makris N, Buka SL, Biederman J, Papadimitriou GM, Hodge SM, Valera EM, Brown AB, Bush G, Monuteaux MC, Caviness VS, Kennedy DN, Seidman LJ. Attention and executive systems abnormalities in adults with childhood ADHD: A DT-MRI study of connections. *Cereb Cortex*. 2008; 18:1210–1220. [PubMed: 17906338]
 45. Mehta MA, Goodyer IM, Sahakian BJ. Methylphenidate improves working memory and set-shifting in AD/HD: relationships to baseline memory capacity. *J Child Psychol Psychiatry*. 2004; 45:293–305. [PubMed: 14982243]
 46. Chamberlain SR, Robbins TW, Winder-Rhodes S, Muller U, Sahakian BJ, Blackwell AD, Barnett JH. Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. *Biol Psychol*. 2011; 69:1192–1203.
 47. Rapoport JL, Inoff-Germain G. Responses to methylphenidate in Attention-Deficit/Hyperactivity Disorder and normal children: update 2002. *J Attention Disord*. 2002; 6:S57–60.
 48. Kuczenski R, Segal DS. Exposure of adolescent rats to oral methylphenidate: preferential effects on extracellular norepinephrine and absence of sensitization and cross-sensitization to methamphetamine. *J Neurosci*. 2002; 22:7264–7271. [PubMed: 12177221]
 49. Berridge CW, Devilbiss DM, Andrzejewski ME, Arnsten AF, Kelley AE, Schmeichel B, Hamilton C, Spencer RC. Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biol Psychol*. 2006; 60:1111–1120.
 50. Somkuwar SS, Darna M, Kantak KM, Dwoskin LP. Adolescence methylphenidate treatment in a rodent model of attention deficit/hyperactivity disorder: dopamine transporter function and cellular distribution in adulthood. *Biochem Pharmacol*. 2013; 86:309–316. [PubMed: 23623751]
 51. Kuczenski R, Segal DS. Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: relative roles of dopamine and norepinephrine. *J Pharmacol Exp Ther*. 2001; 296:876–883. [PubMed: 11181919]
 52. Carboni E, Silvagni A. Experimental investigations on dopamine transmission can provide clues on the mechanism of the therapeutic effect of amphetamine and methylphenidate in ADHD. *Neural Plast*. 2004; 11:77–95. [PubMed: 15303307]
 53. Heal DJ, Cheetham SC, Smith SL. The neuropharmacology of ADHD drugs in vivo: insights on efficacy and safety. *Neuropharmacology*. 2009; 57:608–618. [PubMed: 19761781]

Highlights

- Frontostriatal cognitive functions were disrupted in SHR compared to WIS
- SCH23390 infusions in prelimbic PFC worsened executive function in SHR
- SCH23390 infusions in prelimbic PFC impaired executive function in WIS
- SCH23390 infusions in lateral DST did not alter executive function in SHR or WIS
- SCH 23390 infusions in both sites produced relatively less habitual responding in WIS

Figure 1.

Performance on the strategy set shifting task in adult WIS and SHR before and after manipulation of the pIPFC. Values are the mean $\pm$ SEM number of trials to criterion or trials completed in the 2 hr test, proportion of correct trials, number of trial omissions, and lever press reaction time (sec) during formation of the initial set (left; without drug pretreatments) and the set shift (right; with drug pretreatments) phases. Treatments consisted of vehicle (VEH) or SCH 23390 (SCH). # $p < 0.05$ compared to WIS (main effect of strain); ^ $p < 0.05$

compared to VEH (main effect of treatment); * $p < 0.05$ compared to VEH within the same strain.

Figure 2.

Proportion of error subtypes (perseverative, regressive, and never reinforced) during the set shift phase after vehicle (VEH) or SCH 23390 (SCH) infusion into pIPFC or LDST of adult WIS and SHR. Values are the mean $\pm$ SEM. # $p < 0.05$ compared to WIS (main effect of strain); [^] $p < 0.05$ compared to VEH (main effect of treatment); * $p < 0.05$ compared to VEH within the same strain.

Figure 3.

Performance on the reward devaluation task in adult WIS and SHR before and after manipulation of the plPFC. Values are the mean $\pm$ SEM baseline responses (left; without drug pretreatments; white and black bars represent the entire 1 hr sessions and gray bars represent the initial 10 min of sessions) and responses during the 10-min test after reward devaluation (right; with drug pretreatments; expressed as percentage of the 10-min baseline). Treatments consisted of vehicle (VEH) or SCH 23390 (SCH). # $p < 0.05$ compared to WIS (main effect of strain); * $p < 0.05$ compared to VEH within the same strain; § $p < 0.05$ compared to WIS within the same treatment.

Figure 4.

Performance on the strategy set shift task in adult WIS and SHR before and after manipulation of the IDST. Values are the mean $\pm$ SEM number of trials to criterion or trials completed in the 2 hr test, proportion of correct trials, number of trial omissions and lever press reaction time (sec) during formation of the initial set (left; without drug pretreatments) and the set shift (right; with drug pretreatments) phases. Treatments consisted of vehicle (VEH) or SCH 23390 (SCH). # $p < 0.05$ compared to WIS (main effect of strain).

Figure 5.

Performance on the reward devaluation task in adult WIS and SHR before and after manipulation of the IDST. Values are the mean $\pm$ SEM baseline responses (left; without drug pretreatments; white and black bars represent the entire 1 hr sessions and gray bars represent the initial 10 min of sessions) and responses during the 10-min test after reward devaluation (right; with drug pretreatments; expressed as percentage of the 10-min baseline). Treatments consisted of vehicle (VEH) or SCH 23390 (SCH). * $p < 0.05$ compared to VEH within the same strain; § $p < 0.05$ compared to WIS within the same treatment.

Figure 6.

(A) Coronal drawings of the pPFC (left) and IDST (right) depicting bilateral infusion sites in Experiments 1 and 2. Black circles represent the location of the infusion injector tips for individual rats and each placement is shown at the midpoint of its AP extent. Numbers indicate the distance anterior or posterior to bregma in mm. (B) Representative low magnification photomicrograph of a pPFC (left) and IDST (right) guide cannulae placement.