

Staying on task versus taking cocaine: Individual differences in drug cue-evoked  
competition for attention

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## ABSTRACT

Drug-related cues in the environment have been shown to dominate the attention of drug users, therefore eliciting the users' drug-seeking and drug-taking behavior. Because of the motivational properties these cues can offer (incentive salience), it is extremely difficult for drug users to suppress their attention from these cues. However, inability to control attentional processing in order to resist these cues is another factor seen in addiction that may also make it difficult to suppress attention away from drug cues, eventually leading to relapse. A population of animals known as sign-trackers (STs) show this increased propensity to attribute incentive salience to reward cues, along with impairments in attentional control, when compared to their more goal-oriented counterparts (goal-trackers, GTs). These combined impairments are the reason STs are thought to be especially vulnerable to addiction-like behaviors. The aim of the present study was to investigate whether STs, compared to GTs, would be more likely to be distracted by a cue formerly associated with a cocaine reward while performing a task that highly demands attention. To accomplish this, we used a dual task paradigm that combined a sustained attention task (SAT) with an intermittent access (IntA) self-administration paradigm, while using a discriminative stimulus (DS+; tone) to signal cocaine availability. We used three different drug-related distracters (tone (DS+) only, tone (DS+)+cocaine, and non-contingent cocaine delivery), and we saw no differences between STs and GTs in SAT performance when any of the three distracters were presented during the dual task. Additionally, SAT performance was not affected by the presentation of only the DS+ (without cocaine onboard), suggesting that a cue previously associated with cocaine availability was not enough to distract the animals away from

SAT. On the contrary, cocaine onboard was sufficient to cause the animals to disengage from SAT, as we saw a dramatic decrease in SAT performance when the animals self-administered cocaine (during DS+ presentation) and when it was passively infused (no DS+; non-contingent cocaine). These findings, although not what we expected based on previous reports that STs have lesser control over their attentional performance, suggest that a highly routine cognitive task that demands attention may protect against drug cue-induced cocaine-seeking behavior in rats previously exposed to cocaine.

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I must disclose that I did not complete all the work in this research report. Since I have worked in the Sarter lab for the past two years, I have been a key contributor in every aspect of this research project. However, my thesis work involved the non-contingent cocaine group, which alone took almost 1 year to complete. In order for my contribution to be properly evaluated, I must frame it within the full story. Thus, I will report data from all three experimental groups rather than only my findings from the non-contingent group. I have been given full permission to do so by Dr. Kyle Pitchers, Ph.D, since this is his data to report.

## **PERSONAL ACKNOWLEDGEMENTS**

I would like to personally thank Dr. Martin Sarter, Ph.D and Dr. Kyle Pitchers, Ph.D for all of the countless hours they put in to guide and support me throughout the writing of this thesis, as well as Louisa Kane, who helped with my animals whenever I needed it. This has by far been one of the most challenging and rewarding tasks I have ever taken on, and I am grateful to be able to carry all that I have learned throughout this process with me throughout the rest of my career. Lastly, I want to especially thank my family and friends who were always there to support and encourage me when I needed it the most.

## INTRODUCTION

There are cues present in the environment of an addict that are often associated with his or her respective drug-seeking and drug-taking behavior. These cues can attract the attention and subsequently elicit behavior of the addict because they bias the individual's attention and offer motivational properties (incentive salience) (Saunders & Robinson, 2011). In rats, there is evidence of individual variation by which animals attribute incentive salience to reward cues, including food and drug cues. Two general types of variation in this propensity based on their conditioned responses have been identified, termed sign-trackers (ST) and goal-trackers (GT). The ST and GT phenotypes are determined using a Pavlovian Conditioned Approach paradigm (PCA; see Methods) in which a reward (food pellet; unconditioned stimulus, US) is paired with a lever (conditioned stimulus, CS), eventually leading to one of two main conditioned responses (CR). Upon presentation of the CS (lever), animals that are more prone to interact with the cue (lever-CS), or "sign," are called STs, whereas GTs move towards the food receptacle, or "goal," with relatively no lever-CS interaction. STs approach the lever because they have a greater propensity to attribute incentive salience to the cue, itself, whereas GTs do not, despite knowing that the cue is predictive of reward (Flagel, Akil, & Robinson, 2009). It was found that a greater susceptibility of incentive salience attribution to a food cue also predicted whether an animal would attribute incentive salience to a drug cue (Saunders & Robinson, 2010). As a result, it was initially hypothesized that STs are especially vulnerable to addiction-like behavior. However, more recent findings investigating the nature of the reward cue has complicated this hypothesis.

For STs and GTs, incentive salience attribution to a reward cue varies depending on the nature of the CS. For STs, discrete, localizable cues (i.e. a lever or a light source) themselves become attractive to the animal, causing the animal to attribute incentive salience to them. This incentive salience involves three factors, including biasing attention toward the cue (and eliciting approach toward it), working harder to gain access to the cue, and evoking a motivational state for reward-seeking behavior. These three factors are all demonstrated by STs (Brown & Jenkins, 1968; Robinson, Yager, Cogan, & Saunders, 2014). GTs, on the other hand, rarely interact with discrete cues and do not attribute incentive salience to them. Instead, contextual cues play an important role in reward-associated GT behavior, as it has been shown that GTs exhibit greater context-reinstatement of drug-seeking behavior compared to STs (Meyer et al., 2012; Saunders, O'Donnell, Aurbach, & Robinson, 2014). Finally, when using a diffuse or unlocalizable cue like an auditory cue (i.e. tone), all rats, even previously determined STs and GTs, learn a goal-tracking response, and this diffuse cue was found to be an equally effective conditioned reinforcer in both STs and GTs (Meyer et al., 2012). These findings with different CS modalities suggest that there are different mechanisms involved in STs' and GTs' pathways to addiction. Furthermore, as mentioned earlier, the initial hypothesis suggesting that individuals that are more prone to attribute incentive salience to reward cues (STs) must be updated since it appears that STs and GTs have different vulnerabilities to certain drug-related 'triggers' of drug-seeking and -taking. Moreover, recent reports add to the complexity of these findings since the propensity to attribute incentive salience to a drug cue may not be the only factor that makes an individual susceptible to addiction-like behavior. It may, also, be a product of how easily a person is



able to decide what to pay attention to and what to ignore (effectiveness of their attentional control processing).

Poor attentional control processes have been associated with an increased risk of addiction disorders (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013). Loos et al (2012) has shown that a certain mouse strain (BDXD16) has poor attentional control processing according to their performance in a 5-choice serial reaction time task (5CSRTT) (Loos et al., 2012). Poor attentional performance was classified as low response accuracy combined with high variability in correct response latencies within each animal, both of which were seen in BDX16 mice (Loos et al., 2012). These mice have also demonstrated an increase in cue-reinstatement of self-administration behavior compared to controls when the alcohol-conditioned cues were presented (Loos, Staal, Smit, De Vries, & Spijker, 2013), thus suggesting that reduced attentional control may indeed increase susceptibility to addiction disorders and relapse. Moreover, impairments in the attentional processing of cues combined with increased impulsivity (Loos et al., 2013), increased likelihood of attentional bias toward reward cues (Hester, Dixon, & Garavan, 2006), and inability to disengage attention from these cues (Franken, Kroon, & Hendriks, 2000), all may lead to an increased likelihood of relapse to drug use. As described above, not only has it been shown that this incentive salience given to environmental cues formerly associated with addictive substances varies greatly across a population, but attentional control processes do as well.

Previous studies with STs and GTs have demonstrated that STs have poorer control of attentional processing compared to GTs, which may contribute to an increased susceptibility to addiction-like behaviors (i.e. reinstatement of drug seeking). Paolone et

al. (2013) showed that STs demonstrate more attentional lapses during a task that requires attention as indicated by increased occurrence of periods of poor performance/task disengagement (Paolone et al., 2013). Acetylcholine (ACh) in the medial prefrontal cortex (mPFC) is a modulator of cognitive control (Paolone et al., 2013), suggesting that lower levels of ACh are associated with poorer cognitive control. As predicted, STs have attenuated levels of ACh in the medial prefrontal cortex during an attention task relative to GTs, and these attenuated ACh levels are more apparent when attention is taxed (Paolone et al., 2013). Therefore, this poorer attentional control seen in STs is suggested to be associated with difficulty in suppressing their attention from drug cues. Thus, the current study aims to investigate whether impaired attentional control, combined with attentional bias towards drug cues, are important cognitive traits in individuals susceptible to addiction-like behavior.

Previous findings (discussed above) showed that STs are more likely to attribute incentive salience to drug cues, have poorer cognitive control, and may be more impulsive (Lovic, Saunders, Yager, & Robinson, 2011). These findings led us to hypothesize that STs, more so than GTs, would struggle to maintain attentional performance when a cue formerly associated with a drug is presented during a time of high attentional demand. More specifically, STs would be more likely to disengage from an attention task when a drug cue is presented, followed by longer periods of inactivity before they re-engage in the task. Here, our objective was to determine whether there is individual variation in the ability of a cue formerly associated with cocaine to distract and/or disengage the subjects' attention from an attention-demanding task to cocaine seeking and/or taking. To achieve this, we combined a sustained attention task (SAT; see

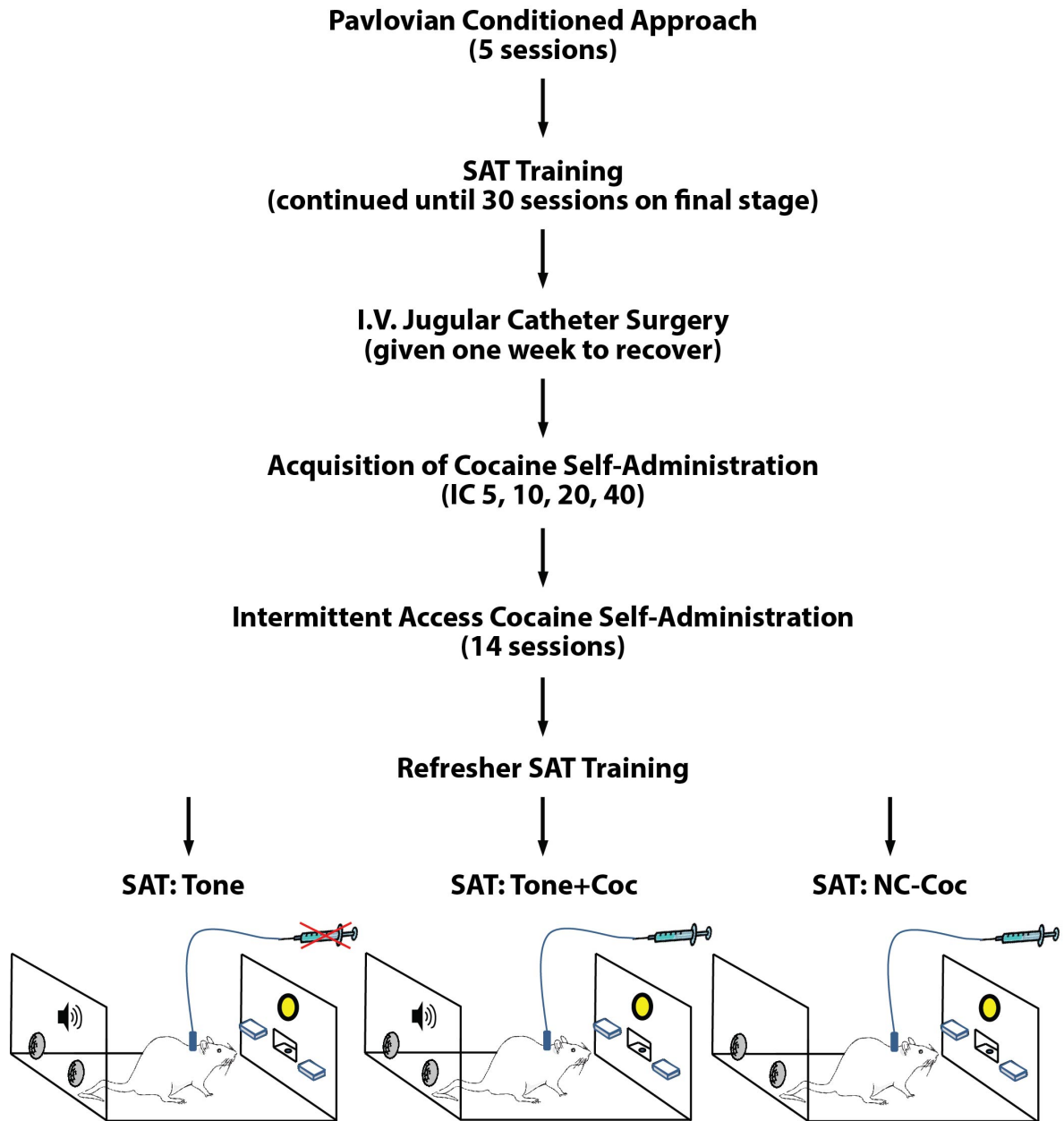
Methods) with presentation of a cue formerly associated with cocaine along with (or without) cocaine to determine whether STs or GTs are vulnerable to distraction during a cognitive task.

## MATERIALS AND METHODS

### *Subjects and Housing*

This experiment was conducted using male Sprague Dawley rats (~350 g) obtained from Envigo. The animals were housed individually in standard polycarbonate cages at a controlled temperature (23°C) and humidity level (45%) while on a 12-hour light/dark cycle (with light beginning at 0700). After arrival, rats were given 1 week to acclimate to the colony room before testing commenced. Food (rodent chow) and water were available *ad libitum* until the start of SAT training, at which point the animals were water-deprived by restricting access to a 15 min period after each operant training or practice session. Water was also provided as a reward during task performance (see below). On days not tested, water access was increased to a total of 60 min. During SAT training, food was available *ad libitum*. Starting 2 days before the first day of self-administration the animals were mildly food restricted to maintain a stable body weight throughout testing. All procedures had prior approval by the Institutional Animal Care and Use Committee (IACUC) at the University of Michigan and were conducted in AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care)-accredited laboratories.

*A summary of the experimental design is shown in Figure 1.*



**Figure 1.** Schematic illustration of the experimental design. Following Pavlovian training with a food unconditioned stimulus (US) and lever (CS), rats were classified as STs or GTs and started training on the sustained attention task (SAT). Once animals reached asymptotic performance at the task (~3 months), rats were implanted with an intravenous jugular catheter and were trained to self-administer cocaine (US) in the absence of an explicit cue. Once animals had acquired cocaine self-administration, they entered a second cocaine (US) self-administration procedure called Intermittent Access (IntA; DS+ = tone; DS- = white noise). After 14 days of IntA training, animals went back to SAT for 7 days before undergoing one of three test day conditions (independent groups of rats were used for each test day condition): Tone, Tone+Coc or Non-Contingent (NC)-Coc.

## ***Pavlovian Conditioned Approach (PCA) Training***

### *Apparatus*

To determine the phenotype of the animals (ST/GT), each animal underwent PCA training 1 week after arrival. This took place in Med Associates test chambers (29 x 24.5 floor area x 25 cm high) inside sound-attenuating cabinets with ventilation (Med Associates, Inc.; St Albans, VT, USA). The floor consisted of stainless steel rods with a tray full of corn-cob bedding to catch any waste. Included inside the chamber was a pellet dispenser connected to a pellet magazine located in the center of the front wall (2.5 cm above the floor), and an infrared sensor was used to detect animal head entries into the magazine. A retractable lever was also located 2.5 cm to the left or the right of the magazine (lever position was counterbalanced across all subjects) with a white LED illuminated behind it throughout the training. A red house light located on the back wall was also illuminated throughout each PCA session. Data collection was controlled by Med-PC software.

### *Training*

The subjects were given ~20 pellets in their home cages the day before training to familiarize themselves with the pellet. The first day of PCA is known as “pretraining,” in which the red house light was illuminated and 25 food pellets (45 mg banana-flavored pellet; #F0059; Bio-Serv; Flemington, NJ, USA) were delivered individually at a 30 second interval. The following 5 days consisted of standard PCA test sessions, in which an illuminated lever (conditioned stimulus; CS) is presented into the chamber for 8 seconds, followed by retraction of the lever paired with a single food pellet

(unconditioned stimulus; US). The lever-CS was presented on average every 60 seconds (at random intervals that varied between 30 and 150 seconds), and each session consisted of 25 trials for a total of one 35-45 minute session per day.

Repeated CS-US pairings eventually led to a conditioned response (CR), which included interaction with the lever (recorded as lever presses) and/or approach to the pellet dispenser (recorded as magazine entries). After 5 sessions, a PCA Index Score was calculated by using the following measurements: number of contacts with the lever/magazine, latency to the first lever/magazine contact, and the probability of contacting the lever/magazine on a trial. The score for each session was calculated by averaging response bias (lever presses – magazine entries/total contacts), latency score (magazine latency – lever latency/8 s), and probability difference (lever probability—magazine probability). PCA Index scores range from +1.0 (exclusively ST CRs for every trial) to -1.0 (exclusively GT CRs for every trial), and the last two scores from the last two days of PCA for each animal were averaged to give their final PCA Index Score. Only animals that fell into the +0.5 to +1.0 (ST) or -0.5 to -1.0 (GT) were used in this study—the rest were considered intermediates and were excluded from further participation.

### ***Sustained Attention Task (SAT)***

#### *Apparatus*

The SAT training took place in operant chambers similar to the ones used for PCA (MED Associates) in sound-attenuating cabinets. Inside each chamber were two retractable levers located on the front wall, a white signal light located centrally on the

front wall above the two levers, a white house light located on the rear wall, and a water-receptacle (6.0 X 6.0 cm height X width, 4.0 cm deep) located on the front wall between the levers.

### *SAT Training*

Before the beginning of training, animals were slowly weaned off of water over the course of one week. During training, animals only received water during SAT and for 15 minutes afterward (food was available *ad libitum* throughout entire experiment while water was available *ad libitum* 1 day per week.). The water-deprived rats were initially trained on a fixed-ratio 1 (FR1) schedule for obtaining water when they pressed either lever. After 5 consecutive days of this training, the animals were forced to discriminate between signal and non-signal trials. A signal trial was indicated by a 1 second illumination of the signal light on the front wall, and a non-signal trial (blank) was indicated by no illumination. Levers were presented into the operant chambers 2 seconds after a signal or non-signal event and remained there for 4 seconds, during which the animal had to press the correct lever. Data was recorded as follows (Figure 2 contains a schematic illustration of the task): if they did not press either lever before retraction, it was recorded as an omission; if it was a signal trial and they pressed the correct lever, it was recorded as a hit; if it was a signal trial and they pressed the incorrect lever, it was recorded as a miss; if it was a non-signal trial and they pressed the lever opposite to what was correct during a signal trial (correct lever), it was recorded as a correct rejection; and if it was a non-signal trial in which they pressed the lever that corresponded correctly with signal trials (incorrect lever), it was recorded as a false alarm. Levers were



immediately retracted upon response (regardless if correct or not). Water (reward, 30  $\mu$ L) was only given when the animals responded correctly (hits and correct rejections), whereas no water was given if the animals responded with misses, false alarms, or omissions. The correct levers for the animals were counterbalanced in order to eliminate selection bias, and signal and non-signal trials were presented randomly for a total of 162 trials (81 each) per training session. During this stage of SAT training, incorrect lever presses were followed with correction trials in which the trial was repeated. After three consecutive corrected trials with incorrect responses, a forced trial was presented in which the correct lever was presented in the chamber for 90 seconds or until the animal made a response (for signal trials, the light would be illuminated during this 90 seconds). During this stage, the house light was off. After animals reached an asymptotic performance of  $\geq 70\%$  correct responses on both hits and correct rejections for 4 consecutive days, they were moved up to the next step of SAT.

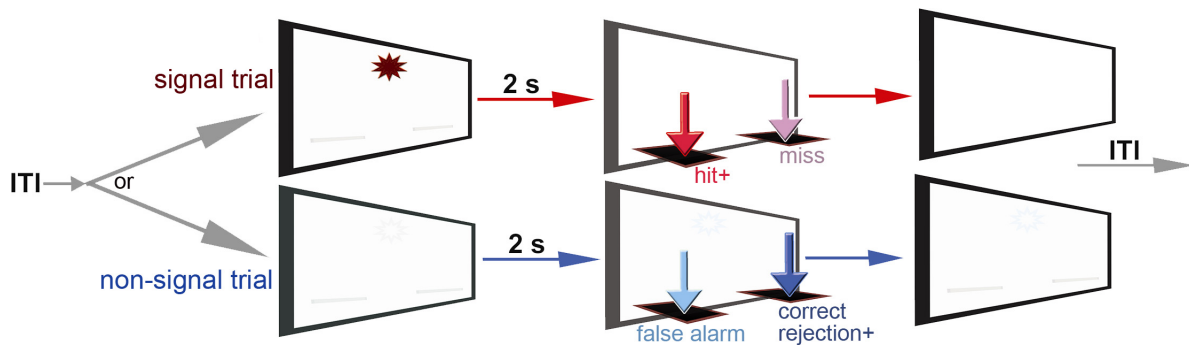
During this next phase, multiple signal durations of 500, 50, and 25 ms were presented, and there were no longer correction or forced-choice trials. Instead of having to respond for 162 trials, the SAT session lasted 40 minutes with trials occurring at  $9 \pm 3$  sec intervals. The house light was also off during this stage.

Once the animals reached asymptotic performance with  $\geq 70\%$  correct responses during the 500 ms signal duration for 4 consecutive days, they could move onto the final stage. Session parameters were exactly the same as the previous stage, except the white house light was illuminated during the entire session. The purpose of turning on the house light was to properly test the animals' ability to sustain attention on the task by requiring them to maintain their attention on the intelligence panel in order to observe

signals. The data was collected in five, 8-min blocks, and all animals stayed on this training for 30 sessions (with one day off per week).

### *SAT Score Calculation*

As an overall SAT performance measure, a SAT score can be calculated after each session. This score integrates the number of hits ( $h$ ) and false alarms ( $f$ ), as follows:  $\text{score} = (h - f) / [2(h + f) - (h + f)^2]$ . SAT scores range from +1.0 to -1.0, in which a +1.0 indicates that all responses were correct (all hits and correct rejections), while a -1.0 indicates that all responses were incorrect (all misses and false alarms). SAT score can be calculated for each signal duration, and omissions are recorded separately.



**Figure 2.** The sustained attention task (SAT) consists of randomly ordered signal (light signals 500, 50, or 25 ms long) and non-signal events, spaced by  $9 \pm 3$  s (Inter-Trial Interval; ITI). Two seconds after an event, levers are made available and animals need to respond within 4 s. Following a lever press or after 4 s, levers are withdrawn. If there is no response, the trial is considered an error by omission. Hits and correct rejections, but not misses and false alarms, are rewarded.

## ***Cocaine Self-Administration***

### *Surgery*

After completion of SAT training, animals underwent surgery for the installation of chronic indwelling intravenous catheters. They were anesthetized using isoflurane (2-5%) for a total of ~45 minutes. The catheter was placed into the right jugular vein of each animal and exited through the dorsal skin surface between the scapulae. This arrangement allowed for direct infusion of saline/drug into the bloodstream via connection to an infusion pump in the behavioral chambers (described below). After surgery, animals were given 0.05 mL of Carprofen (Rimadyl, 5 mg/kg) subcutaneously. From this day on and throughout the rest of the experiment, animals were flushed daily with 0.2 mL of saline (and Gentamicin for the first 2 weeks, 10 mg/mL) to keep catheters operational. Animals were given one week to recover from surgery before self-administration training commenced.

### *Apparatus*

Cocaine self-administration occurred in operant chambers similar to those used in PCA and SAT (MED Associates). In these chambers, levers were removed, two nose-poke ports were placed on the back wall (same wall as house light; each equipped with an infrared sensor to detect nose pokes into the ports), and a speaker for both a white noise and a tone generator was installed on the same wall as the nose poke ports in the top right corner or in the middle directly below the house light, respectively. There was also no food magazine or water-dispenser present, and a white house light was also illuminated during each session. Data collection was again controlled by Med-PC software.

### *Acquisition of Cocaine Self-Administration*

In the operant chambers, the animals' catheters were connected to tubing that was connected to an infusion pump. An active response (nose poke in the active port) resulted in an intravenous infusion of cocaine HCl (0.4 mg/kg/infusion in 25  $\mu$ L delivered over 2.6 seconds per infusion). Active ports were counterbalanced across animals to eliminate selection bias. Self-administration was done on a FR1 schedule, and after each infusion there was a 20-second timeout period where an active nose poke did not result in an intravenous infusion (active and inactive responses were still recorded during this time). The infusion criterion (IC) initially chosen was 5 infusions, meaning that the length of the session was however long it took the animals to receive 5 infusions. This criterion was chosen to ensure that all animals infused equal amounts of drug. After two consecutive days of 5 infusions, the IC was increased to 10 (for two days), then 20 (for two days), and then 40 infusions (for four days). At IC 20 and 40, the dose of cocaine was reduced to 0.2 mg/kg/infusion, which was the dose used for the remainder of the experiment. During acquisition sessions, a white house light was illuminated, and there were no discrete cues presented with cocaine infusions during the sessions.

### *Intermittent Access*

In this stage, animals were put into the same operant chambers used to acquire cocaine self-administration for 1, 4-hour session per day. Each session was divided into 30-minute blocks, where a tone (discriminative stimulus, DS+; ~78 dB) that was presented during the first 5 minutes was followed by 25 minutes of white noise (DS-; ~78

dB) for a total of 8 blocks per session. During tone presentation (DS+), a response in the active nose-poke port resulted in a cocaine infusion, while during the white noise presentation (DS-), an active response had no consequence. When drug was available, there were no drug infusion timeouts other than during an infusion, therefore animals could infuse as many times as they could nose poke. The following data was recorded: number of infusions, active and inactive responses during tone presentations, and active and inactive responses during white noise presentations. Intermittent access training continued for 14 sessions, with one day off each week.

### ***Refresher SAT Training***

Following intermittent access, the rats were put back on SAT. The first 3 days consisted of the second stage (before multiple signal durations occurred), only with the house light on to refresh task rules (signal vs non-signal) as described above. The following 4 days consisted of the last stage of SAT, only for 8, 8-min blocks (total of 64 min) rather than 5 blocks as before.

### ***Test Day: Dual Task***

#### *Apparatus*

The operant chamber arrangement used for these test days was a combination of self-administration and SAT. The SAT intelligence panel (water receptacle, cue light, levers) was located on the front wall, and nose poke ports (and house light) were located on the back wall (Figure 1).

### *Test Day Paradigms*

In paradigm 1 (*SAT: tone*), rats (n=12) underwent 12, 5-min blocks of SAT (60 min total). White noise (DS-) was present throughout the entire session except during the 3<sup>rd</sup> and 9<sup>th</sup> 5-min blocks. Specifically during these two blocks, the same DS+ that was used before during IntA was present in the background instead of the DS-. However, unlike IntA, the DS+ did not indicate that drug was available in this paradigm, meaning that an active response (nose poke in the active port) had no consequences except to distract from SAT. In paradigm 2 (*SAT: tone+cocaine*), rats (n=14) were tested in identical conditions as in paradigm 1, but an active response during either DS+ presentation resulted in a cocaine infusion (0.2 mg/kg/infusion in 25  $\mu$ L delivered over 2.6 seconds per infusion). Similar to IntA, there were no drug infusion timeouts other than during an infusion, therefore animals could infuse as many times as they could nose poke. Paradigm 3 (*SAT: NC-cocaine*, n=16) had the same general conditions as the previous 2, except instead of a presentation of the tone (DS+) during blocks 3 and 9, cocaine was passively infused (0.2 mg/kg/infusion in 25  $\mu$ L delivered over 2.6 seconds per infusion) 5 times (total of 10 infusions per session). During this stage, active responses had no consequence (similar to paradigm 1) but were recorded. Data collection included SAT performance (hits, misses, correct rejections, false alarms, and number of omissions) and drug-seeking and -taking behavior (cocaine infusions, active and inactive responses).

### ***Statistical Analysis***

Linear mixed-models (LMM) analysis was used for all repeated measures data. The best fitting model of repeated measures covariance was determined by the lowest Akaike information criterion score (West, 2006). Significant main effects and interactions were followed by planned pairwise comparison (Bonferroni t-test). Statistical significance was set at  $p < 0.05$ .

## RESULTS

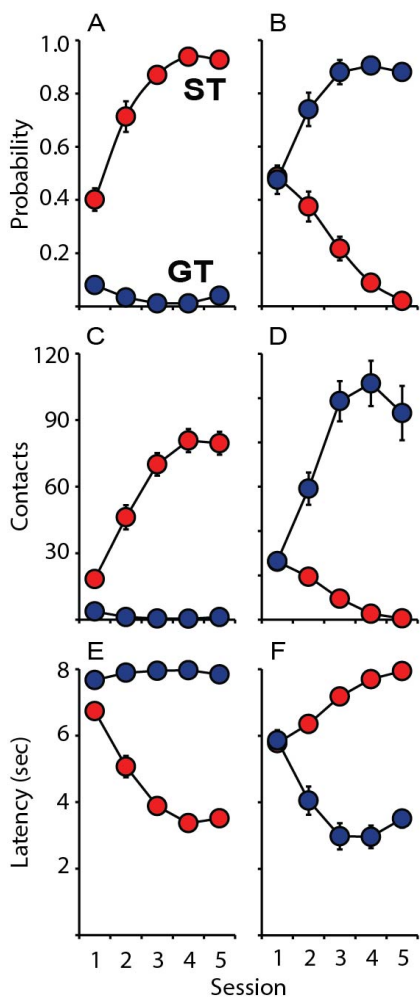
### *Pavlovian Conditioned Approach: ST/GT Classification*

Our first task was use PCA to determine which animals were STs or GTs, and that phenotype was determined based on their PCA index score (ST:  $n=24$ , range 0.618 to 0.918; GT:  $n=18$ , -0.613 to -0.946). As previously described, STs were more prone to interact with the lever, while GTs bypassed lever interaction and directed their behavior toward the food magazine. These behaviors were a part of calculating their PCA index score (see Materials and Methods; data not shown). Compared to GTs, STs exhibited an increased probability to approach the lever-CS across all 5 sessions during the 8-second CS period, (Figure 2A;  $F_{(1,40)}= 570.763, p < 0.001$ ), an increased number of lever contacts across all sessions (Figure 2C;  $F_{(1,42.753)}= 181.058, p < 0.001$ ), and decreased latency to approach the lever across all sessions (Figure 2E;  $F_{(1,44.206)}= 279.999, p < 0.001$ ). In contrast, GTs exhibited an increased probability to approach the food magazine across all 5 sessions during the 8-second CS period (Figure 2B;  $F_{(1,42.048)}= 181.058, p < 0.001$ ), an increased number of food magazine entries across all sessions (Figure 2D;  $F_{(1,41.228)}= 101.832, p < 0.001$ ), and a decreased latency to approach the food magazine across all sessions compared to STs (Figure 2F;  $F_{(1,41.279)}= 117.824, p < 0.001$ ).

### *SAT Performance*

The next stage of training was SAT (see Materials and Methods). There were no significant differences between ST and GT groups in any of the SAT measures before or after cocaine self-administration: SAT score as a function of signal duration, (see Figure

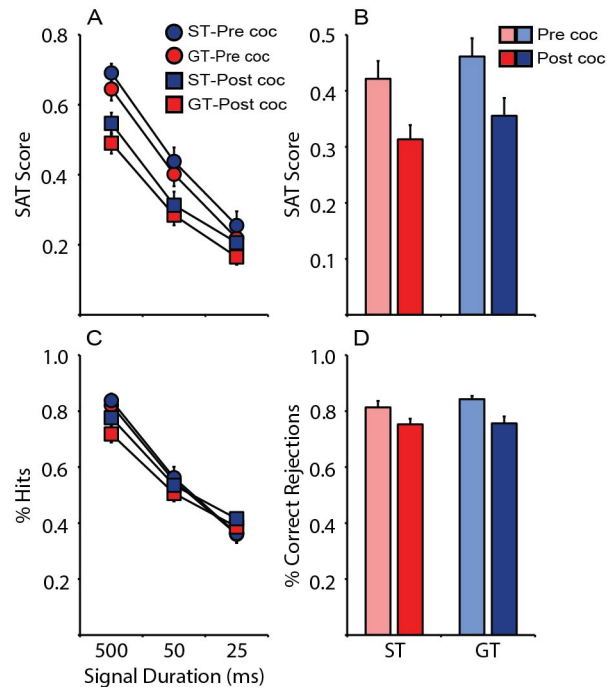




**Figure 3.** Pavlovian conditioned approach behavior towards a lever-CS vs. the location of food delivery (Food Cup) was measured over 5 training sessions to determine a sign-tracker (ST,  $n = 24$ ) or goal-tracker (GT,  $n = 18$ ) phenotype. The mean  $\pm$  SEM for (A) probability of approaching the lever-CS during the 8s-CS period, (B) probability of approaching the food magazine during the 8s-CS period, (C) number of lever contacts, (D) number of food magazine entries during the 8s-CS period, (E) latency to first lever contact after CS presentation, and (F) latency to the first food magazine entry after CS presentation. For all measures there was a significant effect of group (ST or GT), session, and a group  $\times$  session interaction ( $ps < 0.001$ ).

4A;  $F_{(1,44.779)} = 1.606$ ,  $p = 0.212$ ), SAT score averaged across all signal durations before or after cocaine self-administration separately (Figure 4B;  $F_{(1,39)} = 1.363$ ,  $p = 0.250$ ), percent hits (Figure 4C;  $F_{(1,52.364)} = .940$ ,  $p = 0.337$ ) or percent correct rejections (Figure 4D;  $F_{(1,39)} = .404$ ,  $p = 0.529$ ). The lack of ST/GT difference in SAT performance, in particular prior to cocaine self-administration, is inconsistent with the findings reported in Paolone et.al (Paolone et al., 2013). However, the poor SAT performance demonstrated in STs is primarily observed in ‘extreme’ STs (PCA index score  $> 0.90$ ). As described earlier (see Materials and Methods), the STs utilized in the current study contained a wide range of ST PCA index scores, including few extreme STs.

Previously, Briand et al (2008) showed that extended cocaine access caused prolonged impairments in cognitive function manifested by poor performance on a similar task requiring sustained attention (Briand et al., 2008). Although we used a different self-administration procedure (IntA vs Limited Access), it was found that cocaine self-administration experience caused a significant decrease (main effect) in SAT performance as indicated by: SAT score as a function of signal duration, (Figure 4A;  $F_{(1,48.455)} = 13.666, p = 0.001$ ), SAT score averaged across all signal durations before or after cocaine self-administration separately (Figure 4B;  $F_{(1,39)} = 18.049, p < 0.001$ ), and correct rejections (Figure 4D;  $F_{(1,39)} = 24.469, p < 0.001$ ) but not in hits (Figure 4C;  $F_{(1,48.455)} = 1.060, p = 0.308$ ). As expected, there was a significant main effect of signal duration on SAT score (Figure 4A;  $F_{(1,48.455)} = 13.666, p = 0.001$ ) and hits (Figure 4C;  $F_{(1,82.353)} = 524.644, p < 0.001$ ). However, we did not see a significant interaction between the two factors (Group x Coc Exp) with average SAT score (Figure 4B;  $F_{(1,39)} = 0.02, p = 0.965$ ) or correct rejections (Figure 4D;  $F_{(1,39)} = 0.758, p = 0.389$ ), or three factors (Group x Coc Exp x Signal Duration) with SAT Score ( $F_{(1,85.119)} = 0.147, p = 0.864$ ), or hits ( $F_{(1,80.309)} = 0.169, p = 0.845$ ).



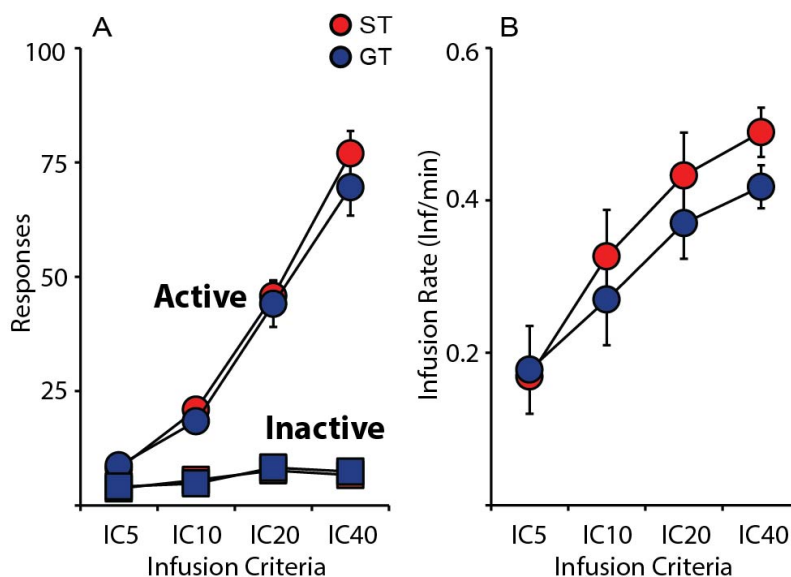
**Figure 4.** Performance of the sustained attention task (SAT) prior to and following cocaine self-administration experience. The mean  $\pm$  SEM for (A) Asymptotic SAT scores as a function of signal duration and group (500, 50, 25 ms) (B) Average SAT score for each group across all signal durations, (C) Percent hits (500, 50, 25 ms), and (D) Percent correct rejections.

## *Cocaine Self-Administration*

### *Acquisition*

Following catheter surgery (see Materials and Methods), rats were trained to acquire self-administration behavior of cocaine using 4 different infusion criteria (IC5-40). No significant main effect of group was observed in either active ( $F_{(1,43.902)} = .753, p = 0.390$ ) or inactive ( $F_{(1,43.341)} = .095, p = 0.759$ ) responses (Figure 5A). In contrast and as expected, IC did have an overall significant main effect on both active and inactive responses within ST and GT groups. As IC increased, active (Figure 5A;  $F_{(3,47.581)} = 122.926, p < 0.001$ ) and inactive responses increased (Figure 5A;  $F_{(3,44.256)} = 5.529, p =$

0.003). These results are consistent with previous reports by Saunders and Robinson (Saunders & Robinson, 2010, 2013).



**Figure 5.** Acquisition of cocaine self-administration behavior in STs and GTs. Mean  $\pm$  SEM (A) number of active and inactive responses for infusion criteria 5 and 10 (0.4 mg/kg/inf) and 20 and 40 (0.2 mg/kg/inf), and (B) number of cocaine infusion/min at each infusion criteria.

#### *Intermittent Access Cocaine Self-Administration*

Intermittent access self-administration lasted for a total of 14 sessions (see Materials and Methods). Across these 14 sessions, there was no significant main effect of group in the number of cocaine infusions (Figure 6A;  $F_{(1,39,012)} = 2.336$ ,  $p = 0.134$ ). Thus, STs and GTs received a similar amount of cocaine throughout cocaine self-administration training (Acquisition and Intermittent Access). There was a significant main effect of session as both groups escalated their cocaine intake (number of infusions) from the 1<sup>st</sup> to the 14<sup>th</sup> session (Figure 6A;  $F_{(13,39,007)} = 8.000$ ,  $p < 0.001$ ) in a quantitatively similar

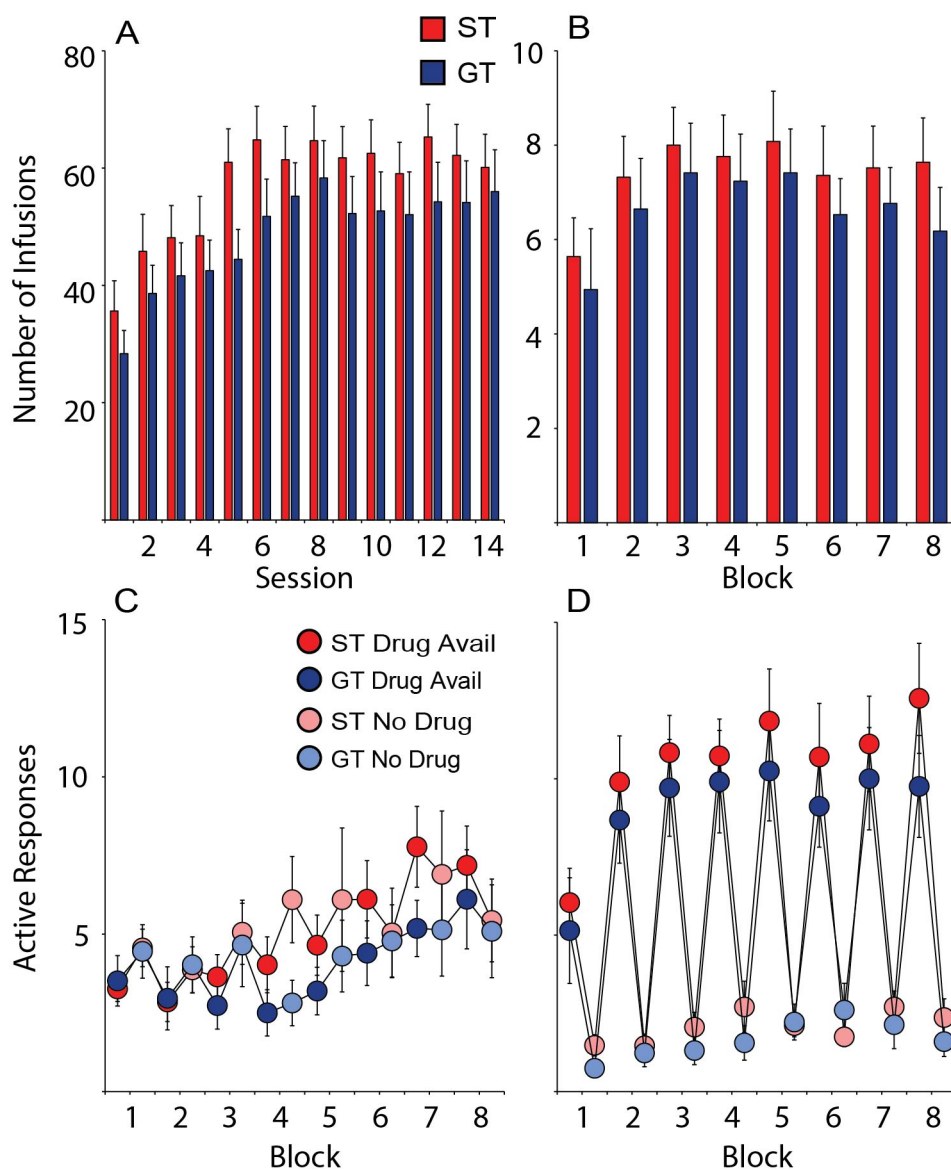
manner. It was also apparent that by session 14 there was a group difference (Figure 6B; Group:  $F_{(1,40)} = 619, p = 0.033$ ).

Figures 6C and 6D show the number of active responses during drug available and no drug available periods (averaged/5min) for sessions 1 and 14, respectively. During session 1, the animals' active responses were relatively constant during both DS+ and DS- presentation because they had not yet learned the consequences of each stimulus (DS+ meant drug available, DS- meant no drug available; Figure 6C). By session 14, it is clear that the animals learned to distinguish between the DS+ and DS- periods by a reduction in active responses during DS- periods compared to DS+ (Figure 6D). These results show that STs and GTs equally acquired intermittent access self-administration behavior with no overall group differences.

### ***Dual Task Test Day***

#### *Cocaine-Seeking Behavior*

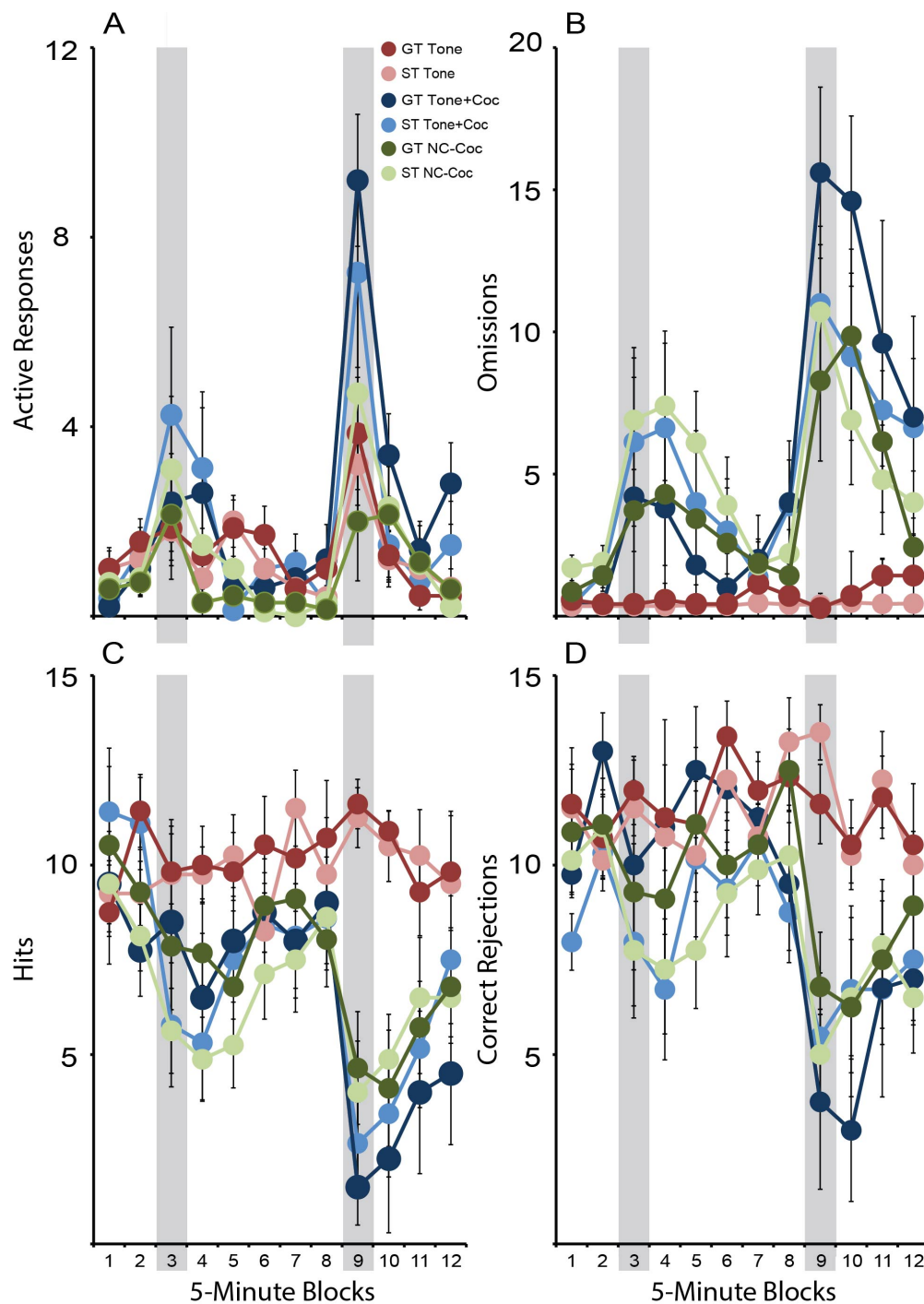
During the test day, we used the single measure of active responses to indicate cocaine-directed behavior (Figure 7A). We did not observe a significant main effect of group ( $F_{(1,37.663)} = 0.017, p = 0.897$ ) or a significant interaction between all 3 main factors ( $F_{(22,60.453)} = 0.792, p = 0.723$ ), but did see an overall effect of distracter ( $F_{(2,37.663)} = 3.559, p = 0.038$ ) and block ( $F_{(11,60.453)} = 5.989, p < 0.001$ ). Although pairwise comparisons were not permitted, there is an increase in active responses during the second presentation of the distracter on all 3 test days.



**Figure 6.** Acquisition and expression of intermittent access cocaine self-administration in STs and GTs. (A) Cocaine self-administration behavior during 14 Intermittent Access (IntA) sessions as indicated by number of total cocaine infusions. (B) Number of infusions during each block on day 14. Number of active responses per 5 min during the first day of IntA self-administration (C) and then again at the conclusion of IntA training on day 14 (D). Values represent mean  $\pm$  SEM.

### *SAT-Directed Behavior*

During the test day, we used three measures to evaluate SAT compliance and performance: trial omissions (Figure 7B), number of hits (Figure 7C) and number of correct rejections (Figure 7D). If an animal was disengaged from SAT, then we expected to see an increase in the number of omissions. We did not observe a significant main effect of group ( $F_{(1,34)} = 0.183, p = 0.671$ ) or a significant interaction between all 3 main factors ( $F_{(22,34)} = 0.792, p = 0.714$ ), but did see main effects of distracter ( $F_{(2,34)} = 6.554, p = 0.004$ ) and block ( $F_{(11,34)} = 7.233, p < 0.001$ ). The number of hits and correct rejections provided a measure of task performance on the two trials types, signal and non-signal, respectively. The presentation of the Tone distracter had no effect on task performance, while the Tone+Coc and NC-Coc distracters had a similarly stunting effect on performance. We did not observe a significant main effect of group (Hits:  $F_{(1,34)} = 0.017, p = 0.896$ ; Correct Rejections:  $F_{(1,33,939)} = 0.110, p = 0.743$ ) or significant interaction between main factors (Hits:  $F_{(22,374)} = 0.573, p = 0.940$ ; Correct Rejections:  $F_{(22,192,237)} = 1.479, p = 0.085$ ), but did see an overall effect of distracter (Hits:  $F_{(2,34)} = 10.075, p < 0.001$ ; Correct Rejections:  $F_{(2,33,939)} = 7.473, p = 0.002$ ) and block (Hits:  $F_{(11,374)} = 8.619, p < 0.001$ ; Correct Rejections:  $F_{(11,192,237)} = 9.749, p < 0.001$ ). Pairwise comparisons were not permitted, but the presentation of the Tone distracter did not alter SAT performance at all. In contrast, both Tone+Coc and NC-Coc distracters had a massive effect on performance, in particular following the second distracter presentation.



**Figure 7.** Dual task performance during all test day. The mean  $\pm$  SEM for (A) active responses, (B) SAT trial omissions, (C) number of hits, (D) number of correct rejections for STs (light colors) and GTs (dark colors) during the sustained attention task with two 5-min presentations during blocks 3 and 9 of one of 3 distracters: Tone (red: ST,  $n = 5$ ; GT,  $n = 7$ ), Tone+Coc (blue: ST,  $n = 9$ ; GT,  $n = 5$ ) or NC-Coc (green: ST,  $n = 10$ ; GT,  $n = 6$ ).



## DISCUSSION

The present experiment's main objective was to determine whether individual variation exists between STs and GTs in the propensity to be distracted from an attention task (SAT) by a drug cue formally associated with cocaine. This experiment produced the following results: (1) STs and GTs showed no individual differences in SAT performance or the effect of cocaine experience in decreasing SAT performance, IntA self-administration acquisition or expression, or propensity to be distracted by a cue formerly associated with cocaine. (2) Although the presentation of a cue formerly associated with cocaine availability (DS+;tone) alone during the dual task was enough to elicit drug-seeking behavior (active responses increased during tone presentation), the animals were not distracted enough to affect SAT performance. (3) Cocaine availability during the Tone presentation or Non-contingent cocaine was sufficient to divert attention away from SAT toward drug-seeking and drug-taking behavior during the dual task, causing a reduction in SAT performance. (4) Onboard cocaine caused a temporary disengagement from SAT altogether. In order to explain these results, I need to first address some of reasoning behind our experimental design.

The major parts of this experiment were the use of a diffuse, unlocalizable cue rather than a discrete cue, IntA rather than short or long (limited) access paradigms for self-administration, and a DS rather than a CS. It has been previously shown that when discrete, localizable cues (i.e. a lever or light) are repeatedly paired with a reward in a different location than the cue, some animals are prone to interact with the cue itself because they attribute incentive salience to it (Jenkins, Barrera, Ireland, & Woodside, 1978; Robinson et al., 2014). Since we were using a population that is prone to attributing

incentive salience to cues (STs), we wanted to eliminate that prospective difference between STs and GTs by avoiding the use of cues that are localizable and would elicit approach. Estes (1948) showed that an auditory cue can be paired with a reward to signal the reward's presentation without being localized to (Estes, 1948), and Meyer et al (2012) showed that an auditory cue was equally efficacious as a conditioned reinforcer compared to other discrete, localizable cues (Meyer et al., 2012). Therefore, we chose to use a diffuse cue rather than a localizable cue so that any difference seen between the STs' and GTs' propensity to be distracted by it would not be attributed to the fact that STs tend to interact more with the cue than GTs. Choosing an auditory cue allowed us to control for that difference.

Moving on to the self-administration paradigm, the use of IntA was chosen based on a couple of factors. The first factor was the result of a survey of experienced human cocaine users, which found that blood concentrations of cocaine typically showed a spiking pattern, with a large increase immediately after cocaine use followed by longer periods of abstinence (Zimmer, Oleson, & Roberts, 2012). This pattern of intake is contrary to what is seen in animal models of self-administration, which typically use an FR schedule with long (6 hr) or short (2 hr) access to the drug. In both of these limited access paradigms, rats typically self-administer to their preferred blood concentration and then maintain that level throughout the session (Zimmer et al., 2012). Since this stable pattern of drug intake is not typically seen in humans, Zimmer et al (2012) decided to test if this IntA paradigm causing rapid, spiking blood levels of cocaine seen in humans would increase motivation to self-administer cocaine in rats using a progressive ratio (PR) schedule self-administration paradigm, and indeed that is what they found (Zimmer

et al., 2012). Therefore, results from Zimmer et al (2012) indicate that IntA is a more appropriate paradigm to use for our current study than long or short access for a couple of reasons. The first reason is that it increases motivation to self-administer the drug while using less amount of drug overall, and the second reason is that it emulates a more human-like pattern of drug intake (Zimmer et al., 2012).

Once we determined the self-administration procedure and the cue modality, we needed to decide if the cue should be used as a conditioned stimulus (CS) or as a discriminative stimulus (DS). IntA self-administration is an operant conditioning task in which the goal is to get the animals to increase a behavior (CR) only when a cue is presented (DS) in order to get a reward (US). In a Pavlovian conditioning task, the goal is to get the animals to associate a neutral stimulus (CS) with some reward (US) to elicit a response (CR), but the reward is independent of the animals' behavior. Since our goal with IntA was to increase (or reinforce) the animals' nose-poking behavior (CR) and we were rewarding them with cocaine (US) to do so, choosing a DS that signaled cocaine was onboard (versus a CS that will not reinforce a behavior) was the best fit for our experiment. With the entire paradigm decided upon, we were able to begin the experiment.

The SAT results comparing STs and GTs from our study do not quite fit in with previous findings. We found no differences in STs and GTs, unlike the findings from Paolone et al (2013) that showed STs perform worse on SAT than GTs (Paolone et al., 2013). This poorer attentional performance was hypothesized to be due to STs' inability to increase ACh levels in the brain when attention is taxed, unlike GTs (Paolone et al., 2013). In the current study, the animals' performance did not significantly differ on SAT

across signal durations before or after cocaine self-administration experience. A possible explanation for our results could be that we did not have many “extreme” STs (PCA index > 0.90) that were pulling our results away from GTs. Therefore, it would be interesting to repeat our current study with only “extreme” STs and GTs to see if there would be more of a difference in their propensity to be distracted by the DS.

When comparing SAT scores from pre and post-cocaine self-administration, both STs’ and GTs’ performance did worsen following IntA. This finding fits with the results of Briand et al (2008), who found that prolonged cocaine access (through limited access self-administration) resulted in prolonged impairments in cognitive function, specifically from alterations in the prefrontal cortex (Briand et al., 2008). However, the decrease in SAT score from Briand et al (2008) was mostly attributed to a decreased percentage of hits (increase in misses), whereas our decreases in SAT scores were due to decreased percentage of correct rejections (increase in false alarms). This difference could be attributed to the small number of animals Briand et al (2008) tested, or they may not have had an equal distribution of STs/GTs since that was not the focus of their study, and therefore did not classify their animals as such (Briand et al., 2008). Another hypothesis to explain SAT score decrease in our study was that the animals had not been trained on SAT for a couple months prior to their short refresher training. Although they received this training to refresh their memories on the task, it may not have compared to the roughly 2 months straight of SAT training they received before self-administration. Thus, they may not have reached asymptotic performance.

Our self-administration results were also consistent with previous findings that STs and GTs do not differ in their acquisition of self-administration behavior (Saunders

et al., 2014; Saunders & Robinson, 2010). Saunders and Robinson (2010) used increasing IC in which session length was determined by how long it took the animals to reach the criterions' number of infusions, and we chose to use that as well. Therefore, our results that STs/GTs do not differ in acquisition or expression of IntA self-administration simply strengthen the results that Saunders and Robinson (2010) have put forth regarding the lack of differences seen in ST/GT behavior (Saunders & Robinson, 2010).

Although slightly different than our self-administration paradigm, Ahrens et al (2016) also examined ST/GT differences in operant conditioning responses using a DS (Ahrens, Singer, Fitzpatrick, Morrow, & Robinson, 2016). There were two main differences between their experiment and ours, in that they used a food reward rather than cocaine, and used different light illuminations as a DS instead of a tone to distinguish between rewarded and non-rewarded trials. In their study, STs and GTs showed no difference in being able to detect discrete stimuli and subsequently distinguish between reward and non-reward trials (Ahrens et al., 2016). Although they used slightly different parameters (as mentioned above), their findings are similar to ours because we also saw no differences in ST/GT ability to discriminate between auditory DS+ and DS- presentations by session 14 of IntA. Therefore, our results expand their findings by suggesting that STs/GTs have an equal ability to distinguish between auditory discriminative stimuli, as well as discriminative stimuli such as cue light illumination from their study (Ahrens et al., 2016).

The dual task results overall were not what we expected. The tone alone (cue formerly associated with drug availability) was not enough to distract the animals from SAT during the dual task as we had originally thought. It could be argued that the use of

a discriminative stimulus in our experiments is more of a contextual cue (rather than diffuse or discrete) because it only indicates that the drug is available for self-administration and is not directly associated with a cocaine infusion. However, if that were the case, then, based on findings from Saunders et al (2014) we should have seen more of an increase in active responses in GTs rather than STs (Saunders et al., 2014). Therefore, the way STs and GTs perceive a DS in association with cocaine needs to be investigated further.

Contrarily to the tone alone results, cocaine onboard was enough to distract the animals from SAT. This effect of cocaine was expected based off of results from McGaughy and Sarter 1995, where administration of a psychostimulant (amphetamine, 0.4 and 0.8 mg/kg) did affect SAT performance, manifested in part by a decreased number of hits and correct rejections (McGaughy & Sarter, 1995). In our experiment, cocaine (also a psychostimulant) onboard decreased the number of hits, correct rejections, and SAT performance in general; therefore, based on previous findings, our results are not surprising (McGaughy & Sarter, 1995). From a different perspective, our results are not surprising based on drug-priming literature stating that animals that receive a drug primer after extinction rapidly undergo reinstatement behavior (Gerber & Stretch, 1975), despite our animals not undergoing extinction. However, if this were the case, we should have seen greater “reinstatement” behavior (active nose-poking) in STs compared to GTs in the NC-coc group based of the results of Saunders and Robinson (2011) that showed STs are more prone to reinstatement behavior in response to a drug primer (similar to what the NC-coc group received), which was not what we found (Gerber & Stretch, 1975; Saunders & Robinson, 2010).

Because of the lack of research into this topic of sustained attention and drug cue distraction in STs and GTs, more research needs to be done to investigate it. Here, we have only shown that there is no difference between STs' and GTs' propensity to be distracted by the presentation of a DS+ previously associated with cocaine availability during a sustained attention task. This lack of difference seen in our experiments may be a consequence of our cognitive task, but it also may be that great demands on attention (as in SAT), or SAT's highly routine/habitual nature protect against distractibility even in the presence of drug cues. From this task alone, we showed for the first time (to our knowledge) that a natural reward combined with a routine, habitual task that demands attentional control is protective against DS+ evoked reinstatement. Therefore, behavioral resistance to distraction by drug cues may be a consequence of the routine demands on attention by the SAT. In the future, further research into the mechanisms behind this protection against distractibility in the presence of drug cues needs to be done, as it opens up a whole new area of research into sustained attention and its effect on the detection of drug cues that can be applied to addiction and relapse.

In our experiment, we were able to show that these stable demands on attention might be protective against drug cue-evoked drug-seeking and -taking. Since our paradigm failed to reveal a ST/GT difference, we hypothesize that using a less routine or habitual attention-demanding task that yields unstable natural reward may enhance the differences in the propensity to be distracted between STs and GTs. This new hypothesis needs to be tested. Overall, addictive behaviors are partly a result of executive control impairments (i.e. sustained attention), which is currently being investigated as a possible treatment target using cognitive behavioral therapy and rehabilitation (Sofuoglu, DeVito,

Waters, & Carroll, 2016). Our findings add to that knowledge behind sustained attention in relation to cues, and if further research can discover a way to integrate the routine cognitive performance task that demands attentional control from our study into future cognitive behavioral therapies, we may be one step closer to a more effective treatment in addiction and subsequent relapse.

### ***Future Directions***

As previously mentioned, using a less habitual or routine attention task for further investigation of our results may reveal ST/GT differences in propensity to be distracted by cues previously associated with cocaine. To begin this investigation, we tested alternate reward rates (50, 75, and 90% ) in SAT and found no significant effects on SAT performance between STs and GTs. Moving forward, these alternative reward rates used in the dual task from our experiment may reveal ST/GT differences in propensity to be distracted by the DS. Additional to that proposed experiment, investigation into the neurochemistry and neurobiology of STs and GTs is needed to further parse out these differences.

Very little is known about the genetic makeup of STs and GTs, and that is partly due to the lack of investigation into ST/GT genetic studies. Fitzpatrick et al (2013) showed that variation exists in the form of Pavlovian conditioned approach (PCA) behavior (sign-tracking and goal-tracking) among outbred male Sprague-Dawley rats across different vendors and colonies (Fitzpatrick et al., 2013). They used both genotyping-by-sequencing and population structure to analyze this result, and found that genetically similar strains showed similar ST/GT phenotype distributions (Fitzpatrick et



al., 2013). This study was one of the first to support the hypothesis that these ST/GT PCA behavioral differences are based, at least partially, on genetics, although environmental effects may also be responsible for some of the behavioral differences seen (Fitzpatrick et al., 2013). Despite this finding, Dickson et al (2015) recognized the difficulty of producing a ST/GT model in mice (which are essential for genetic analysis), but for the first time used different mouse strains to demonstrate robust ST and GT behavior (Dickson et al., 2015). Being able to show traits associated with addiction (i.e. incentive salience attribution to drug cues, impulsivity, poor attentional control processes) in mice with considerable genetic variability is essential to the detection of addiction-related genes that may lead to possible treatment targets (Dickson et al., 2015). Now that the different strains have been identified, further research into the genetics behind ST/GT behavior can start to explain why certain ST and GT behaviors are seen, along with their relevance to addiction. Additional to these strain differences, Dickson et al (2015) also showed that some ST/GT propensities are sex-dependent, leading us into a discussion on the lack of research that exists on sex differences in STs and GTs (Dickson et al., 2015).

Sex differences exist in relatively all phases of substance abuse in both human and animal models, in which females often escalate substance use to addiction-like behavior at a faster rate than males and also have a greater risk of relapse (Becker & Hu, 2008). However, there has been little investigation into sex differences between STs and GTs and their propensity to attribute incentive salience to drug cues. Pitchers et al (2014) attempted to discover variation in incentive salience attribution based on sex using a food cue but showed little difference between the two sexes (Pitchers et al., 2015). It is possible that males and females do not differ in this attribution of incentive salience, but

it is also likely that females do not respond to food cues like they do drug cues, as seen in males (Pitchers et al., 2015). It is difficult to make conclusions such as this regarding ST/GT sex differences and apply them to addiction vulnerability since such little research has been done. Therefore, further investigation into these sex differences may reveal individual variation that has not been previously discovered, and therefore may offer other possibilities for treatment targets to prevent addiction and subsequent relapse. Once we start discovering these behavioral and neurobiological differences, we can start manipulating them to see if cue-induced reinstatement behavior can be blocked as well as other behaviors that parallel addiction and relapse in humans. All of this may eventually allow for translation of the ST/GT model into humans that may eventually lead to possible therapeutic treatment targets for addiction and relapse.

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