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Review

Adolescent-onset vs. adult-onset cocaine use: Impact on cognitive functioning in animal models and opportunities for translation

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ABSTRACT

Animal models are poised to make key contributions to the study of cognitive deficits associated with chronic cocaine use in people. Advantages of animal models include use of a longitudinal experimental design that can control for drug use history and onset-age, sex, drug consumption, and abstinence duration. Twenty-two studies were reviewed (13 in adult male rats, 5 in adolescent vs. adult male rats, 3 in adult male monkeys, and 1 in adult female monkeys), and it was demonstrated repeatedly that male animals with adult-onset cocaine self-administration exposure had impairments in sustained attention, decision making, stimulus-reward learning, working memory, and cognitive flexibility, but not habit learning and spatial learning and memory. These findings have translational relevance because adult cocaine users exhibit a similar range of cognitive deficits. In the limited number of studies available, male rats self-administering cocaine during adolescence were less susceptible than adults to impairment in cognitive flexibility, stimulus-reward learning, and decision making, but were more susceptible than adults to impairment in working memory, a finding also reported in the few studies performed in early-onset cocaine users. These findings suggest that animal models can help fill an unmet need for investigating important but yet-to-be-fully-addressed research questions in people. Research priorities include further investigation of differences between adolescents and adults as well as between males and females following chronic cocaine self-administration. A comprehensive understanding of the broad range of cognitive consequences of chronic cocaine use and the role of developmental plasticity can be of value for improving neuropsychological recovery efforts.

1. Introduction

The testing of human subjects to examine the effects of chronic cocaine use on cognitive functioning began in earnest over 20 years ago, stemming in part from the knowledge that cocaine use produces metabolic and physiological disturbances in brain activity (Hoff et al., 1996). Nonetheless, animal models that examine this question remain necessary, owing to the fact that results have been mixed in human studies concerning the deleterious effects of chronic cocaine use in the variety of cognitive domains. The inability to replicate findings across studies has been the biggest stumbling block for establishing the degree to which chronic cocaine use may produce a broad range of cognitive deficits. As reviewed by Frazer et al. (2018), there are many mitigating factors that confound a clear understanding of the cognitive consequences of chronic cocaine use. These included differences in the amount and duration of cocaine use, differences in the use of other drugs, differences in the length of abstinence prior to cognitive testing, and differences in the presence of psychiatric co-morbidities that could confound results. As important, cross-sectional designs mainly were used and many of the non-drug-using control groups were not matched for age, education, or sex. Adding to this complexity is the fact that most studies have been conducted in participants with adult-onset cocaine use, with very few studies examining participants with adolescent-onset cocaine use. Across all age groups, the global prevalence of past-year cocaine use is estimated at 0.4%, with the rate in developed nations considerably higher (1–2%) than the global average, especially in the United States (World Drug Report, 2018). The 2019 Monitoring the Future Study found that among 8th, 10th and 12th graders in the United States, the prevalence of past-year cocaine use was 0.7%, 1.5% and 2.2%, respectively, with the rate trending upward in 10th graders and remaining relatively stable in 8th and 12th graders compared to 2016 rates (National Institute on Drug Abuse, 2020). This epidemiological evidence suggests that adolescent cocaine use is not on the decline in the United States, even among youth in the early stages of adolescent development, and is on par with global levels of past-year cocaine use. Accordingly, age of cocaine-onset is an important

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Box 1
Studies of neurocognitive functioning in adolescent vs. adult cocaine users.

Lima et al. (2019) examined associations between cocaine use severity (age of onset, duration and recent use) and cognitive functioning (**cognitive flexibility, inhibitory control, attention span, working memory, and global executive function**) in patients (18–45 years old) meeting at least 6 of the 11 DSM-5 criteria for cocaine use disorder at admission for treatment and reporting cocaine as the substance of choice. Patients were compared to controls (matched for education and IQ) and cognitive assessments were made at baseline (after a urine test became negative for cocaine metabolites; ~9 days). Self-reports of cocaine relapse and abstinence were assessed at 3 months following discharge. At baseline, cocaine patients exhibited worse attention span and working memory performance than controls, after controlling for age and sex. Correlation analyses indicated that more years of lifetime cocaine use was associated with poorer performance in the executive function task and that more days of recent cocaine use was associated with poorer inhibitory control, attention span and working memory. Severity of cocaine use disorder (sum of DSM-5 criteria) at baseline was not correlated with cognitive performance on any of the domains evaluated. Of interest, a younger age of cocaine use was associated with worse inhibitory control among patients. At follow up, patients who relapsed had a greater number of baseline DSM-5 criteria for cocaine use disorder than patients who remained abstinent. Still, none of the cognitive functions measured at baseline predicted cocaine abstinence/relapse status measured at follow up. Minimally, these findings revealed deficits in attention span and working memory after a short abstinence period (less than 2 weeks), with longer use and more recent use measured at baseline producing cognitive deficits more broadly. The inability of inhibitory control capacity at baseline in early-onset users to predict cocaine abstinence/relapse status at follow up was surprising, but suggests a need for more comprehensive experimental designs that include recruitment of subjects < 18 years old.

Vonmoos et al. (2014) addressed these issues to some extent by recruiting subjects as young as 15 and testing cognitive functioning (**working memory, declarative memory, attention, and global executive function**) at baseline and at 1-year follow up. The study controlled for abstinence duration at baseline (< 6 months), prior use of cocaine at baseline (e.g. times per week, grams per week, years of use), use of other drugs at baseline (e.g. alcohol, nicotine, cannabis, amphetamines, hallucinogens), and Axis 1 psychiatric comorbidities at baseline (except for a history of depression and attention deficit hyperactivity disorder). Cocaine users were divided into two groups: one whose cocaine use increased from baseline to 1-year follow up (cocaine increasers) and another whose cocaine use decreased from baseline to 1-year follow up (cocaine decreasers). The control group was matched for age, education, and sex. At baseline, both cocaine user groups exhibited similar amounts of cocaine use and moderate to strong impairments in working memory, declarative memory and global executive function relative to the control group, with no group differences in attention. After adjustment for test-retest effects and ADHD, cocaine increasers exhibited a further decline in working memory and declarative memory at 1-year follow up, whereas cocaine decreasers showed non-significant improvement in all four domains. These findings were among the first to demonstrate empirically that cognitive impairments were partially cocaine-induced and could be partially reversible with decreasing cocaine use. Of particular interest, cocaine decreasers showed a significant positive correlation between cocaine use onset-age (range 15–34 years old) and change in the working memory score (timepoint 2 - timepoint 1). As participants less than 18 years old had negative change scores (poorer working memory at 1-year follow up), the authors concluded that adolescent-onset cocaine use might be a risk factor for sustained working memory impairment, even with decreasing usage of cocaine. The older the cocaine use onset-age, the more positive the working memory change score was (improved working memory at 1-year follow up). A limitation of this study was that an insufficient number of younger participants were recruited to conduct group-wise comparisons in early-onset vs. late-onset individuals.

Lopes et al. (2017) published the only study to date that utilized group comparisons involving early-onset cocaine use (initiated < 18 years of age) and late-onset cocaine use (≥18 years of age). Cognitive functioning (**declarative memory, attention, global executive function, cognitive flexibility, inhibitory control, and decision making**) was assessed, with the analyses controlling for age, IQ, years of education, age of onset of substances other than cocaine (tobacco, alcohol, and cannabis) and other psychiatric co-morbidities (depression, anxiety, and childhood ADHD). Whereas years of cocaine use and the number of days of cocaine abstinence (~11 days) prior to cognitive testing did not differ statistically in the early- vs. late-onset cocaine users, early-onset cocaine users showed poorer performance than controls in working memory, sustained attention, declarative memory, and global executive function, while late-onset users presented poorer performance than controls in divided attention and general executive function. Although early-onset cocaine users had greater use of alcohol and cannabis than late-onset cocaine users, this factor did not contribute significantly to cognitive performance. It should be noted that there were no statistically significant differences in cognitive performance between early-onset vs. late-onset cocaine users, making it unclear if chronic cocaine use impacts cognitive functioning differently in adolescents vs. adults.

consideration for developing a comprehensive understanding of the broad range of cognitive consequences of chronic cocaine use, as adolescent-onset users may be at greater risk for cocaine dependence and its associated problems than adult-onset users (Chen et al., 2009; Wagner and Anthony, 2002). Only three studies involving human subjects have attempted to provide insight into whether or not chronic cocaine use has distinct effects on the various cognitive domains while assessing if adolescent-onset use differs from adult-onset use in this regard (Text Box 1). However, these studies have limitations for establishing if cognitive functioning is impacted differently with adolescent-onset vs. adult-onset cocaine use.

Animal research involving adult and adolescent subjects can overcome these methodological limitations to make key contributions to this line of inquiry. Importantly, studies that utilize the intravenous drug self-administration procedure are of greatest relevance for extrapolating animal findings to human cocaine users (Frazer et al., 2018). There are multiple advantages to using the self-administration procedure in animals to model the effects of chronic cocaine use on cognitive functioning. These include use of a longitudinal experimental design that can control for drug use history and onset-age, sex, amount of drug consumed, and duration of abstinence prior to cognitive testing. In the planning of this review, PubMed was searched from its inception through April 2020, using the search term “cocaine” or “cocaine self-administration” and combining each with a general term such as “learning and memory” or “executive function”, or by combining each with one of several specific terms such as “visual attention”, “spatial learning”, “spatial memory”, “stimulus-response habit learning”, “decision making”, “stimulus-reward learning”, “working memory”, “cognitive flexibility”, “reversal learning”, or “set-shifting”. Abstracts were screened for relevance and the accessible articles were downloaded to identify the studies for which behavioral performance on a cognitive task was measured after animals intravenously self-administered cocaine during adulthood or adolescence. This search strategy identified 22 published papers that addressed this topic and all are included in this review. The main purpose of this review is to discern from research using animal models which cognitive impairments can specifically be attributable to chronic cocaine use. This facet is unclear in human studies, given that the majority of chronic cocaine users concurrently consume other substances of abuse such as alcohol, cannabis, and nicotine (Hanlon et al., 2011) that can independently alter cognition

(Bueno-Junior et al., 2017; Kumari et al., 2003; Wesley et al., 2011, 2017). A secondary purpose of this review is to highlight some perceived research needs in this area (demarcated by *italicized text* within the manuscript), as a better alignment between animal models and clinical studies will expedite the discovery of long-term treatment options, perhaps personalized according to cocaine onset-age and sex.

2. Animal models of chronic cocaine self-administration and cognitive functioning

2.1. Experimental design considerations

Intravenous drug self-administration is an operant procedure whereby during sessions animals activate a device (e.g., lever press, nose poke, touch screen) for drug delivery into a permanently implanted intravenous catheter. In this manner, the animal controls if and when drug is delivered, much like humans who use drugs. Important considerations when using the drug self-administration procedure are the length of cocaine use history, the duration of daily sessions, the unit dose of drug delivered, the operant schedule of drug delivery, the condition used to control for drug exposure, and the duration of cocaine abstinence at start of cognitive testing. There are 22 published animal studies reviewed below (18 in rats and 4 in monkeys) that are relevant to the question of whether or not chronic cocaine self-administration produces cognitive deficits. It should be pointed out that the characteristics of the cocaine self-administration sessions varied considerably across studies (Table 1), especially the control condition for self-administered cocaine, the unit dose of cocaine, the length of cocaine use history, and the duration of cocaine abstinence prior to cognitive testing.

2.1.1. Control condition for self-administered cocaine

Some investigations listed in Table 1 used a "yoked-triad" design (first described by Dworkin and Smith, 1989) for which one rat in each grouping of 3 rats was assigned to actively self-administer cocaine while the second and third rats passively received cocaine or saline, respectively, with delivery controlled by and yoked to the timing of cocaine delivery in the rat actively self-administering cocaine. Others implemented a yoked-dyad design for which rats actively self-administered cocaine or passively received saline. Unlike a yoked-dyad design, a yoked-triad design helps to disambiguate the contribution of contingent (active) vs. non-contingent (passive) drug delivery to changes in the endpoint of interest. This is relevant because numerous animal studies have reported a variety of physiological and neurochemical distinctions between these modes of drug delivery (Broadbear et al., 1999; Bystrowska et al., 2019; Caffino et al., 2014; Crespo et al., 2002; Galici et al., 2000; Hemby et al., 1997; Kuzmin and Johansson, 1999; Mantsch and Goeders, 2000; Palamarchouk et al., 2009; Ploense et al., 2018; Pomierny-Chamiolo et al., 2015; Porrino and Lyons, 2000; Smith et al., 2003; Wilson et al., 1994), potentially influencing cognitive performance in differential ways. Other control conditions included comparison to active responding maintained by a commodity other than cocaine, comparison to non-yoked saline self-administration, comparison to short-access cocaine self-administration, to cocaine self-administration in animals of a different age group or to pre-cocaine performance, and comparison to naïve controls. When using an alternate commodity, it is critical that the response rates generated by the alternate commodity are comparable to those generated by cocaine self-administration, but this oftentimes requires the use of a different schedule of reinforcement. A common theme in most of these studies is the use of animals not exposed to cocaine as a control condition. As the control for chronic cocaine use in human studies typically involves recruitment of non-drug-using individuals (Frazer et al., 2018), the translational relevance of short-access cocaine self-administration as a control condition for long-access cocaine self-administration is not totally transparent. However, such an experimental design may be of translational value from the perspective that it addresses the question of whether or not the daily or weekly amounts of cocaine used might differentially impact cognitive functioning. Some clinical studies have reported that greater daily or weekly amounts of cocaine used was associated with poorer cognitive functioning (Bolla et al., 2000; Lima et al., 2019), but not consistently so (Mahoney III et al., 2017).

2.1.2. Unit cocaine dose

In experienced cocaine users, the peak plasma concentration of cocaine reaches 867 ng/ml 5-min after administration of a typical 100 mg (~1.4 mg/kg) intravenous dose (Barnett et al., 1981). This benchmark should be considered when conducting cocaine self-administration studies in animals. In rats, a single 1.0 mg/kg intravenous dose of cocaine produces a peak plasma concentration of 755 ng/ml 30-s after administration (Booze et al., 1997), in line with clinical observations. Pharmacokinetic studies in macaque monkeys showed that plasma concentration only nears a clinically relevant peak (600 ng/ml) 5-min after administration of four intravenous doses of 0.8 mg/kg cocaine spaced 30-min apart (Evans and Foltin, 2006; Mello et al., 2002). These findings suggest that unit doses of at least 1.0 mg/kg should be used in cocaine self-administration studies in rats and monkeys to best model the effects of chronic cocaine use on cognitive performance. Of the 22 published animal studies listed in Table 1, only 11 achieved this threshold. Unfortunately, data on unit dose consumed by chronic cocaine users are not routinely collected during the conduct of clinical studies assessing cognitive performance (Spronk et al., 2013). *This represents a missed opportunity that could assist in back translational efforts for dose selection in animal models, which in turn could advance our understanding of the cognitive consequences of chronic cocaine use in people. Another opportunity for translation is for animal studies to report weekly or monthly amounts of cocaine consumed, as these are the measures commonly reported in human studies. It should be noted, however, that reporting the amount of cocaine consumed per month may be more feasible for nonhuman primate studies, as rodent studies often utilize fewer than 30 days of self-administration.*

2.1.3. Length of cocaine use history

Some clinical studies have reported that severity of cognitive deficits was correlated with length (years) of cocaine use (Fernandez-Serrano et al., 2010a,b; Vonmoos et al., 2013). However, when this question was examined in a group-wise manner, participants with the highest cocaine use history (25 years) did not differ from participants with the lowest cocaine use history (10 years) in neuropsychological tests of sustained attention, verbal learning and memory, and working memory, with performance of both groups falling below average normative data (Mahoney III et al., 2017). The authors speculated that cognitive impairments associated with chronic cocaine use stabilize and are not exacerbated by increased length of cocaine use history. These findings mitigate a potential concern for interpreting results from the animal studies listed in Table 1, as cocaine use history ranged from 0.5 to 5 months in rats and from 6 months to 5 years in monkeys.

2.1.4. Duration of cocaine abstinence

The duration of cocaine abstinence in the preclinical studies listed in Table 1 range from 0–3 days to 1–2 weeks, 3–4 weeks and 6–12 weeks. These time points overlap with those that have been used in clinical studies to assess the effects of chronic cocaine use on cognitive functioning. With adult-onset use in human subjects, cognitive deficits measured after 3 days, 2 weeks, or 6 weeks of cocaine abstinence were reported to be quite broad, and included deficits in visuospatial function, verbal memory, concentration, set shifting, visual memory, and auditory verbal learning, visual attention, executive function, spatial processing, and immediate and delayed memory recall (Berry et al., 1993; Di Sclafani et al., 2002). With adolescent-onset use in human subjects, cognitive deficits seen after 9–11 days of cocaine abstinence also were reported to be quite broad, and included deficits in inhibitory

Table 1
Characteristics of cocaine self-administration sessions in animal studies evaluating cognitive functioning.

Studies in Chronological Order	Length of Cocaine Use History	Duration of Daily Cocaine Sessions	Unit Cocaine Dose	Schedule of Cocaine Delivery	Control for Cocaine Delivery	Abstinence Duration at Start of Cognitive Testing	Species/Age of Cocaine-Onset
Udo et al., 2004	1.5 - 2 months	2 hr	1.0 mg/kg	FR 5	yoked saline passive cocaine	0 and 4 days	Rat/adult
Kantak et al., 2005	3–5 months	2 hr	1.0 mg/kg	FR 5	yoked saline passive cocaine	0 days	Rat/adult
Dalley et al., 2005	2 months	8 hr	0.25 mg/infusion (~ 0.6 mg/kg)	FR 1	yoked saline	1 day	Rat/adult
Kerstetter and Kantak, 2007	0.75 months	2 hr	1.0 mg/kg	FR 5	yoked saline passive cocaine	2.5 weeks	Rat/adult and adolescent
Del Olmo et al., 2007	1 month	2 hr	1.0 mg/kg	FR 1	saline self-administration	3 hours	Rat/adult
Calu et al., 2007	0.5 months	3 hr	0.75 mg/kg	FR 1	naive control	4 weeks	Rat/adult
Briand et al., 2008	1 month	6 hr	0.4 mg/kg	FR 1	short access cocaine naïve control	1 day, 2 weeks, or 4 weeks	Rat/adult
George et al., 2008	3.5 months	6 hr	0.5 mg/kg	FR 1	short access cocaine naïve control	3 days	Rat/adult
Harvey et al., 2009	0.75 months	2 hr	1.0 mg/kg	FR 5	yoked saline passive cocaine	2.5 weeks	Rat/adult and adolescent
Li and Frantz, 2009	0.5 months	2 hr	0.36 mg/kg	FR 1	onset-age	1 day, 2 weeks, 4 weeks and 8 weeks	Rat/adult and adolescent
Porter et al., 2011	5-9 months	Time to earn 6 infusions	0.5 mg/kg	FR 30	water-maintained responding	3 days	Monkey/adult
Gould et al., 2012	5 years	Time to earn 15 infusions	0.1 or 0.3 mg/kg	FR 30	food-maintained responding	18 hours or 4 weeks	Monkey/adult
Porter et al., 2013	12 months	Time to earn 6 infusions	0.5 mg/kg	FR 30	water-maintained responding	12 weeks	Monkey/adult
Kantak et al., 2014	0.75 months	2 hr	1.0 mg/kg	FR 5	yoked saline passive cocaine	2.5 weeks	Rat/adult and adolescent
Mitchell et al., 2014	1 month	6 hr	1.0 mg/kg	FR 1	sucrose-maintained responding	3 weeks	Rat/adult
Kromrey et al., 2015	6 months	not reported	not reported	Not reported	food-maintained responding	8 weeks	Monkey/adult
Gobin and Schwendt, 2017	1 month	6 hr	0.35 mg/infusion (~ 1.0 mg/kg)	FR 1	30 saline infusions	6 weeks	Rat/adult
Bechard et al., 2018	1 month	6 hr	1.0 mg/infusion (~ 3.3 mg/kg)	FR 1	short access cocaine yoked-saline	1 day	Rat/adult
Li et al., 2018	0.5 months	2 hr	0.36 mg/kg	FR 1	yoked-saline	1 day and 8 weeks	Rat/adult
Gobin et al., 2019	0.75 months	6 hr	0.35 mg/infusion (~ 1.0 mg/kg)	FR 1	30 saline infusions	8 weeks	Rat/adult and adolescent
Zhukovsky et al., 2019	0.5 months	6 hr	0.25 mg/infusion (~ 0.8 mg/kg)	FR 1	short access cocaine food-maintained responding	1 week	Rat/adult
Cocker et al., 2020	0.75 months	12 hr	0.25 mg/infusion (~ 1.0 mg/kg)	FR 1	pre-drug performance	1 day, 1 week, and 4 weeks	Rat/adult

control, working memory, sustained attention, declarative memory, and global executive function (Lima et al., 2019; Lopes et al., 2017). Although the view that cocaine users have broad cognitive deficits has been questioned (Frazer et al., 2018), it is important to note that after 6 months of abstinence, cocaine users showed improvements across all the cognitive domains (Di Sclafani et al., 2002), suggesting neuropsychological recovery is possible after long-term abstinence. *Missing from animal studies is an assessment of cognitive deficits after long-term cocaine abstinence to determine whether or not there is neuropsychological recovery. From this perspective, animal research to date has relevance only to cognitive deficits associated with shorter-term cocaine abstinence in people.*

2.2. Adult cocaine self-administration experience and cognitive functioning

Most studies conducted in animal models of chronic cocaine use and cognitive functioning tested subjects experiencing cocaine for the first-time during adulthood. Reviewed below are the multiple domains of cognitive functioning that have been investigated for deficits after adult cocaine self-administration experience. *As studies almost exclusively used male subjects, an important unanswered question from the preclinical literature is whether or not there are sex differences in the multiple domains of cognitive functioning in adult animals after chronic cocaine use.*

2.2.1. Visual attention

Two studies have investigated visual attention after chronic cocaine self-administration. The first study used the 5-choice serial reaction time task (5-CSRRT) to measure visual sustained attention (Dalley et al., 2005). Adult male rats were pretrained on the 5-CSRRT and then trained to self-administer a unit dose of ~0.6 mg/kg cocaine in daily 8-hr sessions. Next, rats with a 2-month cocaine use history were tested for sustained attention over 7 days beginning after 1 day of cocaine abstinence. Rats that had self-administered cocaine exhibited reduced accuracy in sustained attention after 1 day of cocaine abstinence compared to yoked-saline control animals, an effect that was accompanied by a large increase in trial omissions. Accuracy and trial omissions returned to normal levels by the 7th day of cocaine abstinence. These results suggested a brief transient effect of chronic cocaine self-administration on sustained attention, despite prior high daily access to cocaine.

The second study measured visual sustained attention by comparing responses on signaled and non-signaled trials in an operant task (Briand et al., 2008). Adult male rats were pretrained on the sustained attention task and then trained to self-administer a unit dose of 0.4 mg/kg cocaine in daily 1-hr (short access) or 6-hr (long access) sessions. Next, rats with a 1-month cocaine use history were tested for sustained attention after either 1 day and 2 weeks (within-subject study) and 1 day or 4 weeks (between-subject study) of cocaine abstinence. After 1 day of cocaine abstinence, rats that had self-administered long access cocaine, but not short access cocaine, were impaired compared to naive control animals, exhibiting reduced performance on signaled and non-signaled trials. Impairment was still present after 2 weeks and 4 weeks of cocaine abstinence in long access animals, with reduced performance only on non-signaled trials.

Both of the above studies, using different tasks, reported profound deficits in sustained attention, a cognitive function under the control of the medial prefrontal cortex in rats (see Broersen and Uylings, 1999), after 1 day of cocaine abstinence. The first study (Dalley et al., 2005) found that sustained attention returned to normal levels after 7 days of cocaine abstinence while the second study (Briand et al., 2008) found lingering deficits in sustained attention after 2 and 4 weeks of cocaine abstinence. An important procedural difference between these two studies was than in the first study, the sustained attention task was conducted on each of the 7 days of cocaine abstinence, while in the second study, the sustained attention task was conducted either once or twice during cocaine abstinence. *This procedural difference raises the interesting possibility that cognitive training exercises for sustained attention may curtail cocaine-induced impairment in sustained attention and shorten the time to neuropsychological recovery in this domain. A past neuroimaging study* (Goldstein et al., 2007) *found that practice involving a single repetition of two identical blocks consisting of 9 trials each on a monetary sustained visual attention task produced a differential pattern of neural activation in chronic cocaine users (prefrontal cortex and cerebellum) and healthy controls (posterior brain regions), but further research is needed to determine if these neural differences help or hinder potential training-assisted improvements in sustained attention in chronic cocaine users.*

2.2.2. Spatial learning and memory

Spatial learning and memory have been examined in two studies after chronic cocaine self-administration. The first study used the win-shift radial arm maze task to measure spatial learning and memory in rats under the influence of cocaine (Kantak et al., 2005). Adult male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-hr sessions. Rats with a 4-month cocaine use history were tested for spatial learning and memory immediately after cocaine self-administration sessions, with their performance compared to rats passively receiving yoked-cocaine or yoked-saline. There were no differences in sessions to reach criterion performance or total errors among the three groups of rats. Interestingly, rats actively self-administering cocaine and those passively receiving yoked-cocaine had shorter latencies to complete the win-shift sessions at criterion compared to rats passively exposed to yoked-saline. These results suggested that while rats were under the influence of cocaine, they were able to learn a spatial navigation task, a cognitive function under control of the hippocampus in rats (see McDonald and White, 1993; Black et al., 2004), at a normal rate and once learned, they were able to complete win-shift sessions faster than rats never exposed to cocaine.

The second study used the Morris water maze task to measure spatial learning and memory in rats that were recently under the influence of cocaine (Del Olmo et al., 2007). Adult male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-hr sessions. After a 1-month cocaine use history, rats were tested for spatial learning and memory 3 h after cocaine self-administration sessions, with their performance compared to rats self-administering saline. Rats self-administering cocaine had shorter escape latencies and spent more time in the platform quadrant than rats self-administering saline, indicating facilitated spatial learning and memory in rats with recent cocaine use. Together, the reports by Kantak et al. (2005) and Del Olmo et al. (2007) demonstrated that cocaine exposure in non-abstinent or newly abstinent rats does not produce deficits in spatial learning and memory. *How spatial learning and memory would be impacted by a longer abstinence duration in animal models of chronic cocaine use is currently unknown. Interestingly, a small study of heavy chronic cocaine users demonstrated that after 2–10 days of cocaine abstinence, accuracy of spatial memory was not different from healthy control subjects* (Kelley et al., 2005). *Thus, it is possible that spatial learning and memory is spared from impairment by chronic cocaine use, but more research is needed.*

2.2.3. Habit learning

Stimulus-response habit learning has been examined in two studies after chronic cocaine self-administration. The first study used the win-stay radial arm maze task to measure habit learning in rats that were under the influence of cocaine (Udo et al., 2004). Adult male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-hr sessions. Rats with a 2-month cocaine use history were tested for habit learning immediately after cocaine self-administration sessions, with their performance compared to rats passively receiving yoked-cocaine or yoked-saline. There were no differences in sessions to reach criterion performance or total errors among the three groups of rats. Interestingly, rats actively self-administering cocaine and those passively receiving yoked-cocaine had shorter latencies to complete the win-stay sessions at criterion compared to rats passively exposed to yoked-saline.

These results suggested that while rats were under the influence of cocaine, habit learning, a cognitive function under control of the dorsal striatum in rats (see McDonald and White, 1993; Kantak et al., 2001), progressed at a normal rate. Once the task was learned, cocaine-exposed rats completed win-stay sessions faster than rats never exposed to cocaine.

The second study used a 5-choice operant chamber to measure win-stay probability during a reversal learning task (Zhukovsky et al., 2019). Adult male rats were trained to self-administer a unit dose of ~0.8 mg/kg cocaine in daily 1-hr (short access) or 6-hr (long access) sessions. After a 0.5-month cocaine use history, rats were tested after 1-week of cocaine abstinence, with their performance compared to rats self-administering food. The probability of using a win-stay (habit learning) strategy for choices during the task did not differ among long-access cocaine, short-access cocaine, and food self-administering groups. Together, the reports by Udo et al. (2004) and Zhukovsky et al. (2019) demonstrated that cocaine exposure, whether in non-abstinent or abstinent rats and whether with higher or lower daily cocaine usage, did not affect habit learning, but did enhance utilization of habits. These animal studies are in line with a recent clinical study demonstrating that newly learned behavior is under habitual control more so in chronic cocaine users than in healthy controls, suggesting increased propensity for utilization of habits in chronic cocaine users (Ersche et al., 2016). *Additional research in animal and human subjects is warranted, with the possibility that enhanced propensity for utilization of habits after chronic cocaine use could be leveraged therapeutically to instill healthier habits to replace cocaine use.*

2.2.4. Decision making

Decision making has been examined in two studies after chronic cocaine self-administration. The first study used an operant task to measure decision making for large risky rewards (Mitchell et al., 2014). Male rats first were pretrained in the risky decision-making task for food pellets during adolescence and then were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 6-hr sessions during adulthood. After a 1-month cocaine use history, rats were retested for risky decision making following 3 weeks of cocaine abstinence, with their performance compared to control rats self-administering 20% sucrose. Rats self-administering cocaine increased their choice for large risky rewards compared to their pre-cocaine baseline and to the sucrose group. The rats self-administering 20% sucrose had a similar choice for large risky rewards compared to their pre-sucrose baseline. The authors suggested that the increased propensity for risky decision-making, a cognitive function under control of the orbital prefrontal cortex in rats (see Rolls and Grabenhorst, 2008), might promote further drug use and other maladaptive behavior. In line with this view, chronic cocaine users were shown to have a greater propensity for making risky decisions during abstinence than control subjects and chose a risky option more often following a loss (Bolla et al., 2003; Bornovalova et al., 2005; Gowin et al., 2017). It was speculated that risk-taking differences in chronic cocaine users may serve as a useful biomarker for likelihood of relapse (Gowin et al., 2017).

This idea was investigated in a recent study in adult male rats tested for risky decision-making (rodent Iowa Gambling Task) prior to cocaine self-administration training (~1.0 mg/kg; 12 h extended access sessions; 19 days) and again following 1 day, 1 week, and 1 month of cocaine abstinence (Cocker et al., 2020). At the 1-week cocaine abstinence time point, rats also were evaluated for propensity to relapse in reinstatement tests of cocaine seeking induced by reexposure to the self-administration context. As abstinence duration increased, risky decision-making was progressively impaired. An analysis of individual differences found that 50% of rats had marked impairment in risky decision-making relative to baseline and that 50% of rats had no change in risky decision-making relative to baseline. Impaired rats had a greater degree of reinstatement of cocaine seeking than non-impaired rats. Furthermore, the change in the risky decision-making score between baseline and abstinence was negatively correlated with the magnitude of cocaine seeking. *As greater risky decision-making impairment predicted greater vulnerability for cocaine seeking after 1 week of abstinence, it is plausible to consider that the magnitude of reinstated cocaine seeking is a form of risky decision-making in animal studies.*

2.2.5. Stimulus-reward learning

Stimulus-reward learning has been examined in two studies after chronic cocaine self-administration. The first study used a 3-compartment conditioned cue preference task to measure stimulus-reward learning for cues associated with Froot Loops reward (Udo et al., 2004). Adult male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-hr sessions. Rats with a 1.5-month cocaine use history were tested for stimulus-reward learning immediately after cocaine self-administration sessions as well as after 1 day of cocaine abstinence, with their performance compared to rats passively receiving yoked-cocaine or yoked-saline. Whereas rats passively receiving yoked-saline showed strong preference for the Froot Loops-associated cue during both post-conditioning preference tests, rats actively self-administering cocaine or passively receiving yoked-cocaine did not exhibit a conditioned cue preference, regardless of whether or not they were under the influence of cocaine at the time of preference testing. These results suggested that chronic cocaine exposure disrupted stimulus-reward learning, a cognitive function under control of the amygdala in rats (see McDonald and White, 1993; Kantak et al., 2001).

The second study used the same 3-compartment conditioned cue preference task (Kerstetter and Kantak, 2007). Adult male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-hr sessions. After a 0.75-month cocaine use history, rats were tested for stimulus-reward learning after 2.5 weeks of cocaine abstinence, with their performance compared to rats passively receiving yoked-cocaine or yoked-saline. Again, whereas rats passively receiving yoked-saline showed strong preference for the Froot Loops-associated cue during the post-conditioning preference test, rats actively self-administering cocaine or passively receiving yoked-cocaine did not exhibit a conditioned cue preference after 2.5 weeks of cocaine abstinence. Together, these studies suggested that disrupted stimulus-reward learning began while rats were under the influence of cocaine and extended at least throughout the early abstinence period. A study tangently related to stimulus-reward learning in people found that facial emotional recognition, a cognitive function that involves a neural network encompassing the amygdala and orbital prefrontal cortex, was impaired In chronic cocaine users compared to healthy controls (Ersche et al., 2015). *Given the importance of the amygdala in the processing of reward-related cues and the results of animal model testing, assessment of stimulus-reward learning in chronic cocaine uses represents a new avenue of human investigation that is needed.*

2.2.6. Working memory

2.2.6.1. Studies in rats. Five studies in rats have investigated working memory after chronic cocaine self-administration. The first study used the delayed win-shift radial arm maze task (visual and olfactory versions) to measure working memory while rats were under the influence of cocaine (Kantak et al., 2005). Adult male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-hr sessions. The same rats were tested first in the visual version of the task (3-month cocaine use history) and then in the olfactory version of the task (5-month cocaine use history) immediately after cocaine self-administration sessions. Performance was compared to rats passively receiving yoked-cocaine or yoked-saline. For the visual version of the delayed win-shift task, there were no differences in sessions to reach criterion performance, total errors, or the latency to complete sessions at criterion among the three groups of rats. These results suggested that while rats were under the influence of cocaine, visually-guided working memory was intact. In contrast, odor-guided working memory was impaired selectively in rats actively self-administering cocaine. Rats

self-administering cocaine required more sessions to reach criterion performance and made more errors than rats passively receiving yoked-cocaine or yoked-saline.

The second study used the delayed win-shift radial arm maze task (olfactory version) to measure odor-guided working memory during cocaine abstinence (Harvey et al., 2009). Adult male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-hr sessions. After a 0.75-month cocaine use history, rats were tested for odor-guided working memory after 2.5 weeks of cocaine abstinence, with their performance compared to rats passively receiving yoked-cocaine or yoked-saline. While there were no between-group differences in sessions to reach criterion performance, rats actively self-administering cocaine made more errors and took longer to complete daily delayed win-shift sessions than rats passively receiving yoked-cocaine or yoked-saline. Together, these studies suggested that disruption in odor-guided working memory began while rats were under the influence of cocaine and extended at least throughout the early cocaine abstinence period. The different outcomes for the effects of self-administered cocaine in the visual and olfactory versions of this working memory task may relate to the fact that the visual version is more under control of the medial prefrontal cortex and the olfactory version is more under control of the orbital prefrontal cortex (see Di Pietro et al., 2004). Clinical studies have shown that chronic cocaine users are particularly sensitive to disruption in tasks requiring intact orbital prefrontal cortex functioning after recent use (Grant et al., 2000; Simon et al., 2002).

The third study used the delayed match-to-sample and delayed nonmatch-to-sample operant tasks to measure visually-guided working memory during cocaine abstinence (Gobin and Schwendt, 2017). Adult male rats were trained to self-administer a unit dose of ~1.0 mg/kg cocaine in daily 6-hr sessions. After a 1-month cocaine use history, rats were tested for visually-guided working memory. After 6 weeks of cocaine abstinence, performance of rats actively self-administering cocaine was compared to rats passively receiving saline infusions. There were no between-group differences in accuracy in the delayed match-to-sample and nonmatch-to-sample versions of the task across all delay lengths (0 s, 10 s, 20 s, and 30 s).

The fourth study also used the delayed nonmatch-to sample task to measure visually-guided working memory during cocaine abstinence (George et al., 2008). Adult male rats were trained to self-administer a unit dose of 0.5 mg/kg cocaine in daily 1-hr (short access) or 6-hr (long-access) sessions. After a 3.5-month cocaine use history, rats were tested for visually-guided working memory after 3 days of cocaine abstinence, with their performance compared to naïve control rats. In the delayed nonmatch-to sample task, performances across groups were normal at the 10 s delay. Increasing the delay from 10 s to 70 s and 130 s produced working memory impairments in the long-access cocaine self-administration group compared to the short-access group and the naïve controls.

The fifth study used the delayed match-to-sample and delayed nonmatch-to-sample operant tasks to measure visually-guided working memory during cocaine abstinence (Gobin et al., 2019). Adult male rats were trained to self-administer a unit dose of ~1.0 mg/kg cocaine in daily 6-hr sessions. After a 0.75-month cocaine use history, rats were tested for visually-guided working memory. After 2 months of cocaine abstinence, performance of rats actively self-administering cocaine was compared to rats passively receiving saline infusions. Cocaine-trained rats exhibited lower accuracies than saline-trained rats in the delayed match-to-sample, version of the task across all delay lengths (0 s, 2 s, 4 s, 8 s, 12 s, 18 s, and 24 s). There were no between-group differences in the delayed nonmatch-to-sample version of the task.

Taken together, the five rats studies suggest that working memory under control of the orbital prefrontal cortex (odor-guided working memory) is more sensitive to disruption by chronic cocaine self-administration than working memory under control of the medial prefrontal cortex (visually-guided working memory), with disruptions occurring in the latter with long daily access to cocaine over a prolonged period of time prior to testing.

2.2.6.2. Studies in monkeys. Four studies in monkeys have investigated working memory after chronic cocaine self-administration. Each of the four studies used the delayed match-to-sample touchscreen task to measure visually-guided working memory during cocaine abstinence. In the first study (Porter et al., 2011), adult male monkeys were pretrained in the touchscreen task and then trained to self-administer a unit dose of 0.5 mg/kg cocaine in daily sessions for up to 6 drug infusions. Monkeys with a 5- to 9-month cocaine use history were tested for working memory, with their performance compared to control monkeys whose responding was maintained by water. Monkeys trained to self-administer cocaine had decreased working memory accuracy in a delay-dependent manner relative to their own baseline (differences at 10 s, 20 s and 40 s delays but not a 0 s delay), whereas working memory accuracy in control monkeys did not differ between baseline and the water self-administration period across delays.

The second study used the same experimental design as above, but added an appetitive distractor (an audiovisual compound stimulus present during self-administration sessions) or a novel distractor (an audiovisual compound stimulus not previously experienced) on certain blocks of the delayed match-to-sample task (Porter et al., 2013). Adult male monkeys were trained to self-administer a unit dose of 0.5 mg/kg cocaine in daily sessions for up to 6 drug infusions. Monkeys with a 12-month cocaine use history were tested for working memory after 12 weeks of cocaine abstinence, with their performance compared to control monkeys whose responding was maintained by water. Monkeys trained to self-administer cocaine had decreased working memory accuracy at the 10 s and 20 s delays during novel distractor blocks, but not during appetitive distractor blocks, relative to non-distractor blocks. Working memory accuracy in control monkeys did not differ during the novel or the appetitive distractor blocks relative to the non-distractor blocks.

In the third study (Gould et al., 2012), adult male monkeys were co-trained in the touchscreen (morning sessions) and self-administration (afternoon sessions) tasks. Monkeys self-administered a unit dose of 0.1 or 0.3 mg/kg cocaine in daily sessions for up to 15 drug infusions. Monkeys with a 5-year cocaine use history were tested for working memory after 18 h and 3–4 weeks of cocaine abstinence, with their performance compared to control monkeys whose responding was maintained by food. Working memory accuracy in monkeys trained to self-administer 0.1 mg/kg cocaine did not differ from control monkeys across delays after 18 h of abstinence; these data were designated as baseline performance. When the cocaine unit dose was increased to 0.3 mg/kg, working memory was impaired relative to baseline during the first 5 of 10 sessions following 18 h of abstinence. Following 3–4 weeks of cocaine abstinence, working memory improved relative to baseline for the medium and long delays. Control monkeys did not differ from baseline under any of the conditions.

In the fourth study (Kromrey et al., 2015), adult female monkeys were trained to self-administer cocaine (unit dose not reported) in daily sessions (session duration not reported). Monkeys with a 6-month cocaine use history were tested for working memory after 8 weeks of cocaine abstinence, with their performance compared to control monkeys whose responding was maintained by food. Female monkeys trained to self-administer cocaine or food had decreased working memory accuracy in a delay-dependent manner, but there were no between-group differences across delays (short, medium and long).

Taken together, the four monkey studies indicated that visually-guided working memory is disrupted in male monkeys but not in female monkeys, suggesting potential sex differences for disruption by cocaine in this cognitive domain. The impairments observed in male monkeys on this visually-guided task likely is related to a long cocaine use history, and in this respect, the findings in monkeys were consistent with the findings concerning the conditions needed in rats (a long cocaine use history and testing early in cocaine abstinence) to observe

impairment in visually-guided working memory. A unique aspect of the monkey research was the improvement in visually-guided working memory after 3–4 weeks of cocaine abstinence, suggesting neuropsychological recovery from the impairments that were detected early in cocaine abstinence in both rats and monkeys. However, impairments were still observed in monkeys after 12 weeks of cocaine abstinence if a novel attentional distractor was presented during the visually-guided working memory task. The authors (Porter et al., 2013) suggested that an attentional challenge can uncover a latent vulnerability for working memory impairment during cocaine abstinence. The findings in animals are consistent with a body of work conducted in chronic cocaine users, with multiple studies showing working memory impairment early in cocaine abstinence (Spronk et al., 2013).

2.2.7. Cognitive flexibility

2.2.7.1. Studies in rats. Four studies in rats have investigated cognitive flexibility after chronic cocaine self-administration, utilizing either set-shifting or reversal learning tasks. The first study used set-shifting in a 2-lever operant task to measure cognitive flexibility during cocaine abstinence (Kantak et al., 2014). Adult male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-hr sessions. Rats with a 0.75-month cocaine use history were tested for set-shifting and its reversal after 2.5 weeks of cocaine abstinence, with their performance compared to rats passively receiving yoked-cocaine or yoked-saline. During the initial discrimination phase, there were no between-group differences in the number of sessions to reach criterion performance, proportion of correct to total trials completed, number of errors, number of trial omissions, and lever press reaction times. During the extradimensional set-shift phase, rats actively self-administering cocaine had a higher proportion of correct to total trials completed and made fewer errors than rats passively receiving yoked-cocaine and yoked-saline. During the reversal phase, rats actively self-administering cocaine and passively receiving yoked-cocaine needed fewer sessions to reach criterion performance and made fewer errors than rats passively receiving yoked-saline. Considering this set of findings, it is unlikely that chronic cocaine use actually improved aspects of cognitive flexibility during abstinence, but may reflect instead weakened memory/poor retention of the previously learned set, resulting in less proactive interference leading to better performance on subsequent sets. The smaller number of perseverative + regressive errors in rats actively self-administering cocaine during set-shifting and its reversal is in line with the view that proactive interference was reduced by chronic cocaine in this group of rats. If cognitive flexibility had been impaired then a greater number of perseverative + regressive errors would have been observed (Floresco et al., 2008).

The second study used reversal learning in a spatial navigation plus maze task to measure cognitive flexibility during cocaine abstinence (Bechard et al., 2018). Adult male rats were trained to self-administer a unit dose of ~3.3 mg/kg cocaine in daily 1-hr (short access) or 6-hr (long-access) sessions. After a 1-month cocaine use history, rats were tested for reversal learning following 1 day of cocaine abstinence, with their performance compared to rats passively receiving yoked-saline. During the initial discrimination phase and the reversal-learning phase, there were no between-group differences in trials to reach criterion performance and total errors. These findings suggested an absence of cognitive flexibility impairment during abstinence after long-access and short-access cocaine self-administration.

The third study used reversal learning in an odor-guided go-no go discrimination task to measure cognitive flexibility during cocaine abstinence (Calu et al., 2007). Adult male rats were trained to self-administer a unit dose of 0.75 mg/kg cocaine in daily 3-hr sessions. After a 0.5-month cocaine use history, rats were tested for reversal learning after 4 weeks of cocaine abstinence, with their performance compared to naïve controls. During the initial discrimination phase, there were no between-group differences in the number of trials needed to learn and retain the discrimination. During the reversal learning phase, rats trained to self-administer cocaine required more trials than naïve controls to reach criterion performance, indicating an impairment in cognitive flexibility during cocaine abstinence.

The fourth study used reversal learning in 5-choice operant task to measure cognitive flexibility during cocaine abstinence (Zhukovsky et al., 2019). Adult male rats first were assessed for reversal learning and then were trained to self-administer a unit dose of ~0.8 mg/kg cocaine in daily 1-hr (short access) or 6-hr (long access) sessions. After a 0.5-month cocaine use history, rats were re-tested for reversal learning after 1 week of cocaine abstinence, with their performance compared to control rats whose responding was maintained by food. Rats self-administering cocaine under the long-access condition failed to improve reversal learning performance between the first and second assessments as did the other groups. Compared to the short-access cocaine and food control groups, the long-access cocaine group needed more trials and made more errors to reach criterion performance during the retest, indicating an impairment in cognitive flexibility during cocaine abstinence. Taken together, the four rats studies suggested that cognitive flexibility, a cognitive function under control of the medial prefrontal cortex and orbital prefrontal cortex in rats (see Floresco, 2013; Winter et al., 2009), was either unaffected (Bechard et al., 2018; Kantak et al., 2014) or impaired (Calu et al., 2007; Zhukovsky et al., 2019) by chronic cocaine self-administration.

2.2.7.2. Studies in monkeys. Four studies in monkeys have investigated cognitive flexibility after chronic cocaine self-administration, utilizing either set-shifting or reversal learning tasks. In the first study (Porter et al., 2011), adult male monkeys were pretrained in the touchscreen task and then trained to self-administer a unit dose of 0.5 mg/kg cocaine in daily sessions for up to 6 drug infusions. Monkeys with a 5- to 9-month cocaine use history were tested for reversal learning after 3 days of cocaine abstinence, with their performance compared to control monkeys whose responding was maintained by water. During the initial discrimination, there were no between-group differences in trial accuracy. However, during the reversal-learning phase, monkeys trained to self-administer cocaine exhibited decreased accuracy compared to the control group, indicating an impairment in cognitive flexibility during cocaine abstinence.

The second study used the same experimental design as above, but added an appetitive distractor (an audiovisual compound stimulus present during self-administration sessions) or a novel distractor (an audiovisual compound stimulus not previously experienced) during the reversal learning task (Porter et al., 2013). Adult male monkeys were trained to self-administer a unit dose of 0.5 mg/kg cocaine in daily sessions for up to 6 drug infusions. Monkeys with a 12-month cocaine use history were tested for reversal learning after 12 weeks of cocaine abstinence, with their performance compared to control monkeys whose responding was maintained by water. During the initial discrimination, sessions accuracy in the presence of either the novel or appetitive distractor did not differ from baseline in either the cocaine group or the water control group. During the reversal-learning phase, monkeys self-administering cocaine had less accurate performance in the presence of the novel and appetitive distractors compared to baseline. These distractors did not influence performance in the water control group relative to baseline. These findings indicated that an attentional challenge can uncover a latent impairment in cognitive flexibility during cocaine abstinence.

In the third study (Gould et al., 2012), adult male monkeys were co-trained in the touchscreen (morning sessions) and self-administration (afternoon sessions) tasks. Monkeys self-administered a unit dose of 0.1 or 0.3 mg/kg cocaine in daily sessions for up to 15 drug infusions. Monkeys with a 5-year cocaine use history were tested for set-shifting and its reversal after 18 h of cocaine abstinence, with their performance compared to control monkeys whose responding was maintained by food. During the initial discrimination phase, there were no between-group differences in trials to criterion performance and number of

errors. During the extradimensional set-shift and reversal phases, monkeys self-administering cocaine needed more trials to reach criterion performance and made more errors than food control monkeys, indicating an impairment in cognitive flexibility during cocaine abstinence.

In the fourth study (Kromrey et al., 2015), adult female monkeys were trained to self-administer cocaine (unit dose not reported) in daily sessions (session duration not reported). Monkeys with a 6-month cocaine use history were tested for reversal learning after 8 weeks of cocaine abstinence, with their performance compared to control monkeys whose responding was maintained by food. During the initial discrimination phase, there were no between-group differences in trials to criterion performance, number of errors, or number of trial omissions. During the reversal-learning phase, female monkeys self-administering cocaine needed more trials to reach criterion performance and made more errors and trial omissions than food control monkeys, indicating an impairment in cognitive flexibility during cocaine abstinence. Taken together, the four monkey studies demonstrated that cognitive flexibility is impaired in both males and females, suggesting there may be no sex differences in how chronic cocaine use disrupts this cognitive function.

The impairments observed in monkeys were observed in some, but not all studies in rats. The different outcomes for cognitive flexibility in the rat studies can be due several factors, one notably being the level of task difficulty. In the rat studies that showed no cognitive flexibility impairment (Bechard et al., 2018; Kantak et al., 2014), a relatively simple response discrimination was used for the extradimensional set-shift and reversal learning phases (press the right or left lever; turn into the right or left arm), possibly rendering cognitive flexibility less susceptible to cocaine-induced impairment. In the rat studies that showed impairments in cognitive flexibility (Calu et al., 2007; Zhukovsky et al., 2019), a relatively more complex discrimination was used for reversal learning (use of predictive odor cues to decide whether or not to lick at a tube; use of spatial orientation to decide which of two lit apertures was correct), possibly rendering cognitive flexibility more susceptible to cocaine-induced impairment. Consistent with this view, each of the 4 studies in monkeys used a relatively complex discrimination (reversal of delayed match-to-sample) to test for cognitive flexibility and found impairments.

There are three other factors to consider for the different effects of cocaine self-administration on cognitive flexibility in rats: cocaine use history, cocaine abstinence duration, and duration of daily cocaine access. Cocaine use history is unlikely to be an important factor because the range was narrow across rat studies (0.5–1 month). Differences in cocaine abstinence duration in rats (1–7 days for cognitive flexibility impairment and 2.5 to 4 weeks for no cognitive flexibility impairment) suggest that impairment may be associated only with the very early stages of cocaine abstinence. The results in monkeys refute this possibility, as impairment in cognitive flexibility in monkeys was observed after 18 h, 3 days, 8 weeks and 12 weeks of cocaine abstinence. Differences in duration of daily cocaine access in rats (6 h sessions for cognitive flexibility impairment and 2–3 h sessions for no cognitive flexibility impairment) suggest that disruption could be associated with high daily cocaine intake, but the results in monkeys again refute this possibility. Impairments in cognitive flexibility in monkeys were observed with limited daily cocaine access (time to earn a maximum of 6–15 infusions) of low cocaine unit doses (0.3–0.5 mg/kg), albeit over a prolonged period of time (9 months to 5 years). What is clear from these studies is that if the task is relatively challenging, then the ability of adult animals to respond flexibly to changing environmental contingencies to maximize positive outcome is impaired by chronic cocaine self-administration. These findings in animals are consistent with a body of work conducted during early abstinence in chronic cocaine users, with multiple studies showing cognitive flexibility impairment (Spronk et al., 2013).

2.3. Adolescent cocaine self-administration experience and cognitive functioning

There are 5 animal studies that have examined the effects of adolescent cocaine self-administration on cognitive functioning. Summarized below are the domains of cognitive functioning that have been investigated for deficits thus far in animals: stimulus-reward learning, working memory, cognitive flexibility, and decision making. *As these studies were conducted in male rats, an important unanswered question from the preclinical literature is whether or not there are sex differences in the multiple domains of cognitive functioning in adolescent animals after chronic cocaine use.*

2.3.1. Stimulus-reward learning

This study used the 3-compartment conditioned cue preference task to measure stimulus-reward learning for cues associated with Froot Loops reward (Kerstetter and Kantak, 2007). Adolescent male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-h sessions from post-natal day 37–59. Rats (now emerging adults) then were tested for stimulus-reward learning after 2.5 weeks of cocaine abstinence, with their performance compared to rats passively receiving yoked-cocaine or yoked-saline. In rats actively self-administering cocaine or passively receiving yoked-cocaine or yoked-saline during adolescence, there were no between-group differences in preference for the Froot Loops-associated cue during the post-conditioning preference test.

2.3.2. Working memory

This study used the delayed win-shift radial arm maze task (olfactory version) to measure odor-guided working memory during cocaine abstinence (Harvey et al., 2009). Adolescent male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-h sessions from post-natal day 37–59. Rats (now emerging adults) then were tested for working memory after 2.5 weeks of cocaine abstinence, with their performance compared to rats passively receiving yoked-cocaine or yoked-saline. Rats actively self-administering cocaine during adolescence needed more trials to reach criterion performance, made more total errors, and took longer to complete delayed win-shift sessions than rats passively receiving yoked-cocaine or yoked-saline during adolescence.

2.3.3. Cognitive flexibility

This study used set-shifting in a 2-lever operant task to measure cognitive flexibility during cocaine abstinence (Kantak et al., 2014). Adolescent male rats were trained to self-administer a unit dose of 1.0 mg/kg cocaine in daily 2-hr sessions from post-natal day 37–59. Rats (now emerging adults) then were tested for set-shifting and its reversal after 2.5 weeks of cocaine abstinence, with their performance compared to rats passively receiving yoked-cocaine or yoked-saline. During the initial discrimination phase and the extradimensional set-shift phase, there were no between-group differences in the number of sessions to reach criterion performance, proportion of correct to total trials completed, number of errors, number of trial omissions, and lever press reaction times. During the reversal phase, rats that passively received yoked-cocaine during adolescence had slower lever press reaction times and made more trial omissions than rats that passively received yoked-saline or actively self-administered cocaine during adolescence, indicating greater difficulty in staying on task after non-contingent cocaine exposure.

2.3.4. Decision making

Although reinstatement of cocaine-seeking behavior is not a traditional measure of decision making, Section 2.3.4 highlighted the plausibility of considering the magnitude of reinstated cocaine seeking as a form of risky decision-making in animal studies. Two studies have examined reinstatement of cocaine seeking in male rats with

adolescent-onset cocaine self-administration experience (starting on post-natal day 35) and comparing them to rats with adult-onset cocaine self-administration experience (starting on post-natal day 83). By comparing reinstated cocaine seeking following adolescent-onset vs. adult-onset self-administration experience, a relative measure of risky decision-making capacity associated with adolescent cocaine use can be gleaned. In both studies, 0.36 mg/kg cocaine was self-administered in daily 2 h sessions for 2 weeks before undergoing cocaine abstinence. In the first study (Li and Frantz, 2009), rats underwent cue-induced reinstatement testing after 1 day, 2 weeks, 1 month, and 2 months of cocaine abstinence. Adult and adolescent rats self-administered similar amounts of cocaine, but relative to adults, rats with adolescent-onset self-administration experience made fewer responses during cue-induced reinstatement tests following 1 month and 2 months of cocaine abstinence. In the second study (Li et al., 2018), rats underwent cue-induced reinstatement testing after 1 day and 2 months of cocaine abstinence. As in the earlier study, adult and adolescent rats self-administered similar amounts of cocaine. Relative to adults, rats with adolescent-onset self-administration experience made fewer responses during cue-induced reinstatement tests following 1 day and 2 months of cocaine abstinence. These findings suggest that risky decision-making capacity might be relatively intact in rats chronically self-administering cocaine during adolescence.

Review of this limited number of animal studies examining the effects of adolescent-onset cocaine self-administration on later cognitive functioning revealed that the domains of stimulus-reward learning, cognitive flexibility, and risky decisions-making were intact, whereas working memory was impaired. In the only clinical study that specifically evaluated a group of early-onset cocaine users (< 18 years of age), poorer performance compared to age-matched controls were reported for working memory, sustained attention, and declarative memory, but not for cognitive flexibility, decision making, divided attention, and verbal fluency (Lopes et al., 2017). *The correspondence between the animal work and human work in early-onset cocaine users, though striking, advocate for a greater consideration of the level of task difficulty used by investigators, especially for those tasks showing negative findings in both human and animal studies. In addition, there is a need for evaluating additional cognitive domains, such as declarative memory and sustained and divided attention, in young animals to obtain a broader translational perspective.*

3. Integration of findings from animal studies

3.1. Adolescent vs. adult animals

The top portion of Table 2 summarizes what is known to date on the effects of adolescent vs. adult cocaine self-administration exposure on cognitive functioning in abstinent animals. The findings show that cocaine-induced changes in cognitive functioning may be protected by developmental plasticity in some instances and made worse by developmental plasticity in other instances.

The findings concerning stimulus-reward learning in rats with adolescent cocaine exposure (Section 2.3.1) stand in stark contrast to rats with adult cocaine exposure (Section 2.2.5). During abstinence, adult rats with the same cocaine exposures as the adolescent rats (active and passive) failed to condition to the Froot Loops-associated cue during the post-conditioning preference test. These findings suggested that stimulus-reward learning was impaired when chronic cocaine use was initiated during adulthood, but not adolescence. The lack of conditioning to the Froot-Loops-associated cue in rats exposed to cocaine in adulthood may have resulted from a cocaine-induced devaluation of natural rewards (Yin and Knowlton, 2002). Adolescent rats are less sensitive to cocaine-induced devaluation of natural rewards than adult rats (Schramm-Sapyta et al., 2006), which may help to protect the younger rats from later impairment in stimulus-reward learning. It may be important in this regard that during stimulus-reward learning, the amygdala interacts with the medial prefrontal and the orbital prefrontal cortex to encode reward-based associative learning (Rudebeck et al., 2017). Amygdalar-prefrontal circuits undergo remarkable development during adolescence (Cunningham et al., 2002), a process that may underlie the greater motivation of adolescent rats to obtain larger rewards than adult rats (Stolyarova and Izquierdo, 2015). *Clearly, further research is necessary to more fully understand why amygdala-related reward learning is spared after adolescent cocaine self-administration experience and if this outcome extends to early-onset cocaine users.*

Regarding the odor-guided working memory task, only rats with cocaine self-administration exposure during adolescence showed deficits in all three indices of learning during abstinence (more trials to reach criterion performance, more total errors, and more time to complete the odor-guided delayed win-shift sessions; Section 2.3.2) and only rats with cocaine self-administration exposure during adulthood showed deficits in two of the three indices of learning during abstinence (more total errors and more time to complete odor-guided delayed win-shift sessions; Section 2.2.6). From this perspective, it appears that chronic cocaine self-administration impairs working memory performance to a greater extent in rats with adolescent exposure than adult exposure. This age-related difference may be related to an increased vulnerability of the younger rats to cocaine-induced dysfunction of the prefrontal cortex, a later-to-develop brain region in adolescents (Casey et al., 2008). Hippocampal-prefrontal circuits are known to be important for both spatial and non-spatial working memory (Wall and Messier, 2001). During the delay period, the hippocampus and prefrontal cortex become more strongly synchronized as the prefrontal cortex preferentially shifts from encoding retrospective information

Table 2
Summary of findings on the effects of chronic cocaine self-administration on cognitive functioning in animals.

Study type	Cognitive function	Adult-onset	Adolescent-onset	Number of studies showing the effect of chronic cocaine self-administration
Adult vs. adolescent	Cognitive Flexibility	Intact, with reduced proactive interference	Intact	1 of 1
	Working Memory	Impaired	Impaired	1 of 1
	Stimulus-Reward Learning	Impaired	Intact	1 of 1
	Decision Making	Impaired	Intact	2 of 2
Adult	Cognitive Flexibility	Impaired		6 of 8
	Working Memory	Impaired		7 of 9
	Stimulus-Reward Learning	Impaired		2 of 2
	Decision Making	Impaired		2 of 2
	Habit Learning	Intact, with faster speed of performance		2 of 2
	Spatial Learning & Memory	Intact, with faster speed of performance		2 of 2
	Visual Attention	Impaired		2 of 2

(past events) to prospective information (future events) during a working memory task (Myroshnychenko et al., 2017).Studies involving chronic cocaine self-administration in adult male rats found decreased neurogenesis in the hippocampus (Sudai et al., 2011) and decreased structural plasticity in the prefrontal cortex (Radley et al., 2015), with each change associated with worse performance in tasks measuring working memory during cocaine abstinence. *It will therefore be useful in future studies to discern if neurogenesis and other forms of structural plasticity in hippocampal-prefrontal circuits are reduced to an even greater extent after adolescent-onset compared to adult-onset cocaine self-administration experience. A greater reduction in the functioning of these circuits after early use of cocaine might help explain the greater cocaine-induced impairment in odor-guided working memory found in adolescent vs. adult rats self-administering cocaine* (Harvey et al., 2009) *and the greater duration of cocaine-induced working memory impairment found in early-onset vs. late-onset cocaine users* (Vonmoos et al., 2014).

For cognitive flexibility, rats with cocaine and saline exposures during adolescence (Section 2.3.3) needed more trials to reach criterion performance and made more total errors during the initial discrimination phase, and also omitted more trials during the reversal phase in comparison to the rats with the same exposures during adulthood (Section 2.2.7). Collectively, these findings suggested that emerging adult rats in general found the initial set more difficult to learn and the reversal set more difficult to stay on task than the fully adult rats, perhaps reflecting the relative immaturity of the entire extent of the prefrontal cortex in adolescents (Casey et al., 2008). Cocaine did not produce cognitive flexibility deficits in the adult-onset groups and did not produce a further decline in cognitive flexibility in the adolescent-onset groups. Other types of deficits were noted during task testing. The adult rats self-administering cocaine uniquely exhibited behaviors consistent with memory impairment during the set-shift and reversal set (effects not observed in the younger rats) and the adolescent rats passively receiving yoked-cocaine uniquely had greater difficulty staying on task during the reversal set (effects not observed in the older rats). As previously mentioned, it is possible that the 2-lever operant task used to measure cognitive flexibility in the Kantak et al. (2014) report may not have been challenging enough to reliably detect cognitive flexibility deficits. Along these lines, if the above task was made more difficult by imposing a 15 s delay between a correct lever press and delivery of the food pellet reward, then the expected deficits in cognitive flexibility were revealed in an animal model of Attention Deficit Hyperactivity Disorder (Harvey et al., 2013). Without the 15 s delay, adolescent rats with the ADHD-like phenotype did not exhibit the expected deficits in cognitive flexibility. There are several reports showing that chronic cocaine self-administration impairs cognitive flexibility in adult animals when task demands are sufficiently challenging (Section 2.2.7). *Consequently, there is a need to assess cognitive flexibility with more challenging task demands in animals with adolescent-onset cocaine self-administration experience. Recent reports indicated that cognitive flexibility depends on activity in hippocampal-prefrontal circuits and prefrontal-striatal circuits* (Avigan et al., 2020; Marquardt et al., 2019). *As maturation of this circuitry underlying cognitive flexibility has a distinct developmental trajectory* (Calabro et al., 2020), *there is an expectation that cognitive flexibility might be more greatly impaired after adolescent-onset cocaine use than adult-onset cocaine use. It is possible that the task demands for cognitive flexibility in early-onset cocaine users in the* Lopes et al. (2017) *study were insufficiently challenging enough to detect differences from age-matched control subjects, or perhaps tasks demands were too challenging such that even age-matched control subjects had difficulties with this task.*

Lastly, risky decision-making capacity might be relatively intact in rats chronically self-administering cocaine during adolescence vs. adulthood based on findings showing less cue-induced reinstatement of cocaine seeking in the younger rats (Section 2.3.4). The greater expression levels of *arc* mRNA in nucleus accumbens and of *bdnf* mRNA in medial prefrontal cortex of rats with adolescent-onset vs. adult-onset self-administration experience may contribute to this difference and suggest that ongoing plasticity in the younger animals may attenuate some enduring effects of chronic cocaine use on risky decision-making (Li et al., 2018). Another study found that spine density in the orbital prefrontal cortex peaked in early adolescence (post-natal day 31) and then declined 18% by early adulthood (post-natal days 56–61) in wild-type mice (Gourley et al., 2012). Compared to wild-type mice, arginine kinase knockout mice had a sustained spine loss and narrower spine heads during adolescence and exhibited pronounced deficits in an instrumental decision-making task, possibly through disruption of amygdalar-orbital prefrontal circuits. Notably, repeated cocaine administration in wild-type mice, but not arginine kinase knockout mice, between post-natal days 31–35 enlarged the width of spine heads by 15% in non-pruned orbital prefrontal cortex neurons, supporting a view that cocaine-induced plasticity in the orbital prefrontal cortex of adolescent mice may help protect against cocaine-induced impairment in decision-making. *Based on these latter two reports, future research needs to address if the nucleus accumbens, medial prefrontal cortex, orbital prefrontal cortex, and amygdala functionally connect to subserve decision making. It may not be a coincidence that these brain regions identified in animal studies as important for decision making overlap with brain sites that form a large-scale brain network referred to as the Salience Network, a network implicated in both decision making and drug addiction in people* (Menon, 2015). *It will be important to discern what the state of the Salience Network is in adults and adolescents and to investigate why decision making might be spared after adolescent-onset cocaine use but not after adult-onset cocaine use in both animal models and human populations.*

3.2. Adult animals

The bottom portion of Table 2 summarizes the effects of chronic cocaine self-administration on cognitive functioning from the studies conducted in adult animals. Cocaine-induced changes were broad and were observed across rat and monkey models. Some of the findings bear further comment.

3.2.1. Negative findings

For cognitive flexibility assessments, chronic cocaine self-administration produced impairment during cocaine abstinence in 6 of 8 studies. An explanation for these negative findings may relate to the task used in these two reports (Bechard et al., 2018; Kantak et al., 2014), specifically not being challenging enough to detect cognitive flexibility deficits (see Section 2.2.7). Working memory impairments also were reported in 7 of 9 studies. One of the negative reports used female monkeys (Kromrey et al., 2015), suggesting potential sex differences in how chronic cocaine self-administration impacts working memory. The other negative report used a visually-guided working memory task in rats (Gobin and Schwendt, 2017), but these rats may not have had a long enough cocaine use history to detect working memory impairment in the visually-guided task (see Section 2.2.6). *These negative findings in animal studies help to establish the boundary conditions under which chronic cocaine use may impact cognitive function.*

3.2.2. Abstinence vs. intoxication

Four cognitive functions were evaluated while rats were either abstinent or under the influence of cocaine at the time of testing: odor-guided working memory (Harvey et al., 2009; Kantak et al., 2005), stimulus-reward learning (Kerstetter and Kantak, 2007; Udo et al., 2004), habit learning (Udo et al., 2004; Zhukovsky et al., 2019), and spatial learning and memory (Del Olmo et al., 2007; Kantak et al., 2005). For odor-guided working memory and stimulus-reward learning, impairments began while rats were under the influence of cocaine and continued at least throughout the early cocaine abstinence period (see Sections 2.2.5 and 2.2.6). For habit learning and spatial learning and memory, facilitation of the speed to complete sessions was observed whether rats were under the influence of cocaine or had undergone

short-term cocaine abstinence (see Sections 2.2.2 and 2.2.3). *These findings suggest that at least some changes in cognitive function associated with chronic cocaine use may not require an abstinence period for expression, which helps to refine the timeline of their origin.*

4. Translational relevance of animal models

Chronic cocaine use is thought to produce a broad range of cognitive deficits in people. An early meta-analysis found that chronic cocaine use produced general impairment in the domains of attention, memory, and global executive functioning (Jovanovski et al., 2005). These findings were further refined in a meta-analysis conducted 8 years later (Spronk et al., 2013). Regarding executive function, chronic cocaine use produced deficits in sustained attention, response inhibition, decision making, working memory, and cognitive flexibility. The deficits in these domains of executive function following chronic cocaine use are recapitulated in cocaine self-administration studies in adult animals, establishing the translational relevance of the animal models. An important lesson from the animal work is that negative findings in executive function domains may reflect task demands that are too easy to detect deficits, which then present as normal function. This may be especially important to consider when attempting to study sex differences. There is only a single report that examined female animals (monkeys) and which assessed visuospatial working memory and cognitive flexibility (Kromrey et al., 2015). No deficits were found in the working memory task, while reversal-learning was impaired in the cognitive flexibility task (Table 2). *The question - are there sex differences in the ability of chronic cocaine use to impair working memory, or was the working memory task not difficult enough to detect deficits - requires further research to obtain an answer. It is important to note that there have been no studies that have assessed if men and women differ in working memory or any other executive function following chronic cocaine use. Women have been enrolled in multiple studies alongside men, but sex as a variable has yet to be explored as an independent variable. Further animal research can help address this question while controlling for other important factors (longitudinal experimental design, drug use history, amount of drug consumed, and duration of abstinence prior to cognitive testing) while manipulating task difficulty.*

Regarding learning and memory processes, several studies demonstrated that abstinent cocaine users showed deficits in verbal memory (De Oliveira et al., 2009; Fox et al., 2009), but not in spatial learning and memory (Kelley et al., 2005; Tau et al., 2014) or stimulus-response habit learning (Ersche et al., 2008; Kumar et al., 2019; Vadhan et al., 2008). The lack of deficits in habit learning and spatial learning and memory are consistent with the findings in adult animals (Table 2). *Animal studies do show robust deficits in stimulus-reward learning in adult rats self-administering cocaine* (Table 2). *This may be a particularly important finding, as this type of associative learning is critical for determining how environmental cues come to motivate and guide future behavior* (Bucker and Theeuwes, 2018). *Stimulus-reward learning has not been investigated in chronic cocaine users, so it may be vital that such assessments are performed.*

There are only a limited number of studies that have assessed cognitive functioning in early-onset (adolescent) cocaine users. One study (Lopes et al., 2017) reported a pattern of deficits in early-onset users (deficits in sustained attention, working memory, verbal memory, and global executive function) that was broader in scope than the pattern observed in adult-onset users (deficits in divided attention and global executive function). The other study (Vonmoos et al., 2014) reported a positive correlation between cocaine use onset-age (range 15–34 years old) and working memory change scores, indicating that adolescent-onset cocaine use might be a risk factor for sustained working memory impairment. *The impairment in working memory found in rats with adolescent-onset cocaine self-administration exposure is especially pertinent, as the deficit was greater in this cohort compared to rats with adult-onset cocaine self-administration exposure* (Table 2). *These findings reinforce the translational relevance of animal work for understanding the cognitive consequences of chronic cocaine use at a younger age.*

5. Conclusions

The close correspondence between animals and humans concerning the effects of chronic cocaine use on cognitive functioning suggests that animal models can help fill an unmet need for investigating important but yet-to-be-fully-addressed research questions in people. An advantage of using animal models is the degree of control over experimental variables that can help disambiguate many of the confounds inherent in studies with human subjects. Major research priorities include investigations to further determine potential differences in cognitive functioning between adolescents and adults as well as between males and females following chronic cocaine use. Another major research priority pertains to uncovering the brain mechanisms that underlie the protective and exacerbating effects of developmental plasticity for cognitive function after chronic cocaine use. Several other research needs were identified, including assessment of long-term cocaine abstinence studies in animal subjects, assessment of stimulus-reward learning in human subjects, assessing of varying task demands in animal and human subjects, assessment of a wider range of cognitive functions after early-onset cocaine use in animals, assessment of cognitive functions while subjects (animal and human) are under the influence of cocaine vs. during abstinence, and assessment of the benefits of cognitive training in animal and human subjects. A comprehensive understanding of the broad range of cognitive consequences of chronic cocaine use and the role of developmental plasticity can be of value for improving neuropsychological recovery efforts.

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