Behavioural Brain Research 348 (2018) 241–262

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

The long-term effects of cocaine use on cognitive functioning: A systematic critical review

Kirsten M. Frazer[a,*], Qwynten Richards[a], Diana R. Keith[b]

[a] Department of Psychology, Columbia University, 1190 Amsterdam Ave., New York, NY 10027, USA
[b] Department of Psychiatry, University of Vermont Medical Center, 1 South Prospect Street, Burlington, VT 05401, USA

ARTICLE INFO

Keywords:
Cocaine
Cognitive functioning
Clinical significance
Norms
Control groups

ABSTRACT

Background: The predominant view of chronic cocaine use maintains that it causes a broad range of cognitive deficits. However, concerns about the possibly deleterious impact of cocaine on cognitive functioning have yet to be thoroughly vetted. This review addresses the impact of cocaine use on such cognitive domains as executive function, memory, language, and psychomotor speed. Additionally, relevant neuroimaging data is considered to understand the neural basis underlying cocaine-related effects on cognitive functioning.

Methods: We searched PubMed, Google Scholar, and Embase using the search terms "cocaine and cognition," "cocaine and cognitive functioning," and "cocaine and cognitive deficits or impairment." To meet inclusion criteria we evaluated only cognitive and neuroimaging studies describing the long-term effects of cocaine on cognitive functioning published from 1999 to 2016.

Results: The majority of studies reported statistically significant differences between cocaine users and non-drug-using controls in brain structures, blood-oxygen-level dependent signals, and brain metabolism. However, differences in cognitive performance were observed on a minority of measures. Additionally, the majority of studies were not compared against normative data.

Conclusions: The current evidence does not support the view that chronic cocaine use is associated with broad cognitive deficits. The view that cocaine users have broad cognitive deficits is inaccurate based upon current evidence, and the perpetuation of this view may have negative implications for treatment programs and development of public policies.

1. Introduction

Cocaine use disorders continue to be a public health concern. Previous reports indicate that 1.5 million people in the U.S. have used cocaine in 2014, and 913,000 met DSM criteria for cocaine use disorder during the same period [1]. Cocaine use is associated with multiple negative outcomes and health problems [2], including purported broad cognitive deficits [3–5]. Recent data, however, show that national estimates likely misrepresent the extent of cocaine use [6].

Though inconsistencies pervade the literature, reports have documented deleterious effects associated with cognitive functioning in numerous domains including attention, working memory, executive functioning [7–10], psychomotor speed [11,12], social functioning including decreased empathy [13], and social interactions [13,14]. For example, in terms of cognitive flexibility, Woicik et al. [15] found that individuals with cocaine dependence showed poorer cognitive flexibility during the Wisconsin Card Sorting Task (WCST) when compared to non-drug-using controls. While several other studies using this task reported similar findings [16–18], a large number did not replicate the results (e.g., [19,20,122]), suggesting that the observed differences between cocaine users and controls may be specific to a set of experimental conditions and not broadly generalizable.

Prior reviews attempting to parse effects of cocaine concluded that cocaine use causes a broad range of cognitive deficits [21]. However, many concerns regarding methodological and data interpretation issues remain unaddressed. *One* such concern is that researchers assume that statistically significant differences are also clinically significant. This concern is applicable to the cocaine literature, where the vast majority of research compares the cognitive performance of cocaine users to that of non-drug-using controls. Conclusions about impairments are then drawn based upon statistically significant differences with respect to a limited number of tasks. However, when determining whether an individual's performance is impaired, a fundamental requirement is that the performance be compared against a normative baseline that takes into consideration that individual's demographic information (i.e., age, education, sex). *Another concern* is that cocaine users tend to use other

* Corresponding author.
E-mail address: kmf2143@columbia.edu (K.M. Frazer).

https://doi.org/10.1016/j.bbr.2018.04.005
Received 12 December 2017; Received in revised form 3 April 2018; Accepted 4 April 2018
Available online 16 April 2018
0166-4328/

psychoactive drugs. Studies often include cocaine users who report extensive use of other drugs (e.g., [9,14,22]), thus making it difficult to disentangle the contributions of other drug use to the effects of cocaine, especially when the control group reports limited or no drug use.

Experimental work on cocaine use is intrinsically difficult. Most of the literature on cocaine use in humans considers the long-term effects of repeated use that are typically assessed when the drug is no longer in the body (i.e., behavioral assessment is completed after cocaine users have provided negative urine samples). If it were the case that some level of a drug was present in a participant's system or if there was some degree of withdrawal, this could explain the variability in cognitive performance. The empirical evidence on the cognitive consequences of regular cocaine use is mixed. Because ethical considerations prohibit researchers from repeatedly administering doses of cocaine to drug naïve individuals (i.e., those with no prior history of cocaine use), a default approach to determining possible detrimental effects on cognitive performance involves studying both the cognitive performance and the brain of abstinent cocaine abusers.[1]

While the non-human literature is beyond the scope of this paper, we briefly discuss some of the relevant contributions. The animal literature regarding this topic is mixed. Although a large number of preclinical studies indicates that acute cocaine withdrawal is associated with PFC-related cognitive deficits, it is unclear whether these deficits are transient or permanent [23–25]. In particular, studies in rodents and primates have shown deficits in learning and memory that can persist for up to three months after chronic cocaine exposure [26–28]. However, similar to the studies on neurotoxicity, these studies utilize dosing regimens that are not relevant to the natural ecology. Further, all of the above studies utilized experimenter-administered rather than self-administered cocaine. This is problematic, as data indicate that self-administration differentially affects brain neurochemistry and behavior when compared to non-contingent administration [29–32].

Previous systematic reviews have compared the acute and long-term effects of cocaine [21], the magnitude of neurocognitive differences between cocaine abusers and non-drug-using controls [33], and the effect of abstinence duration on cognitive dysfunction [34]. However, importantly, until now no review has sought to determine (a) the clinical significance of findings associated with long-term cocaine use, (b) whether study methodologies control for important variables, and (c) whether results corroborate the conclusions suggesting impairment in chronic cocaine users.

The goal of this review is to critically evaluate the literature on cognitive functioning in cocaine users. *First*, we will provide a brief overview of cocaine neuropharmacology. *Second*, we evaluate the long-term effects of chronic cocaine use on cognition by reviewing evidence from (a) cognitive test batteries in abstinent cocaine users, (b) Magnetic Resonance Imaging (MRI) studies investigating brain structure sizes in abstinent cocaine users without cognitive testing, (c) MRI studies that have administered both imaging and cognitive testing, (d) functional MRI (fMRI) studies investigating neuronal activity in abstinent cocaine abusers with cognitive testing included, and lastly (e) Positron Emission Tomography (PET) studies investigating brain metabolism in abstinent cocaine abusers with cognitive testing included. This review will point to important gaps in our knowledge following an evaluation of the diverse methodologies and findings that have emerged from recent research on the impact of chronic cocaine use on human cognition.

2. Methods

To select papers for consideration in this review, we searched PubMed, Google Scholar, and Embase using the search terms *cocaine and cognition*, *cocaine and cognitive functioning*, and *cocaine and cognitive deficits and cocaine and cognitive impairment*. In all searches we applied the limits *human laboratory* in order to exclude papers examining the effects of cocaine in animals and prenatal cocaine exposure in children. The long-term effect studies describe the cognitive performance in individuals with a history of cocaine use compared to non-drugs-using controls. Participants with a history of recreational use or with a history of abuse and/or dependence have been included. We define abstinence as a participant not using cocaine for a minimum of 72 h. For the purposes of this paper, we are considering all sample sizes of 18 or fewer to be mentioned in caveats as small sample sizes. We arrived at this number by conducting an a priori power analysis. For the level of significance of 0.05 and 80%, the lowest sample size required was 18.8 individuals in each group. For 90% power, the required sample size was 25.3 individuals for each group based on a previously observed global cognitive index effect size ($d = 0.74$) [35] This justifies our cutoff of 18 participants in each group as a small sample size.

The majority of studies in this review used neuropsychological testing alone. Magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) are two techniques that have been most widely used to study the brain impact of long-term cocaine use. We also included studies using other neuroimaging techniques such as positron emission tomography (PET) and electroencephalogram (EEG). To meet inclusion criteria we critically evaluated only neuroimaging and neuropsychological studies describing the long-term effects of cocaine on cognitive functioning published from 1999 to 2016. We note that Jovanovski et al. [33] and Spronk et al. [21] reviewed studies from 1987 to 2002 and 2003 to 2013 respectively, here we provide a broader and updated analysis and critique of the research.

3. Cocaine neuropharmacology

Over the past few decades, a large body of research has contributed to the understanding of the neural mechanisms of cocaine-related effects. While a comprehensive review of cocaine neuropharmacology is beyond the scope of this review, a brief overview will provide the reader with insight into the mechanisms of action of cocaine in the brain and a context for the discussion of the cognitive effects of the drug [36,37].

Cocaine is a stimulant with complex effects on the brain. Acute administration of cocaine increases synaptic dopamine (DA), norepinephrine (NE), and serotonin (5-HT) by binding to their respective transporters and blocking neurotransmitter reuptake. The majority of research however, has focused on the role of cocaine in enhancing DA transmission in the mesocorticolimbic dopamine pathway, thought to mediate the reinforcing properties of the drug [38–40].

Cocaine-induced increases in synaptic DA lead to enhanced signaling through D1 and D2 receptors, which activate intracellular signaling pathways coupled with G proteins [41]. (For a review, see Ref. [42]). In this signaling cascade, G proteins activate (or inhibit) cyclic AMP-dependent protein kinase (PKA), inducing phosphorylation of transcriptional regulators. This in turn initiates the production of cFos, an immediate early gene that codes for a transcription factor thought to mediate long-term changes in neural functioning. These immediate early genes trigger a number of short-term neuroplastic changes, including altered functioning of pre- and post-synaptic voltage-gated ion channels, vesicle release machinery, receptor expression, and glutamatergic neurotransmission [43–47]. Together, these transient changes increase PFC excitability and neurotransmission, which are thought to mediate the acute cognitive effects of cocaine.

3.1. Toxicity

Traditionally, it has been theorized that impairment is caused by neurotoxicity [48]. Despite some indications of cocaine-induced

[1] The term *abusers*, as used throughout this article conforms to the definitions of substance abuse and dependence in the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV-TR) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10). DSM-IV-TR and ICD-10 terminology are used to avoid terminology that has multiple meanings.

increases in free radicals and oxidative stress there is little evidence in rodent models, for example, that these increases lead to broad tissue damage or neurotoxicity. Cocaine does not produce any long-term depletion of DA or other catecholamine neurotransmitters in the striatum, cortex, hypothalamus, and hippocampus [49,50]. Converging evidence supports these results, showing that other markers of monoamine system integrity are not affected by binge cocaine administration [51–53]. Absence of neurotoxicity in rodents was noted even when cocaine was repeatedly administered in an environment with high ambient temperatures, conditions which increase amphetamine neurotoxicity [54]. Consequently, data collected in rodent models are inconsistent with the predominant view that chronic cocaine use causes a broad range of cognitive deficits in humans. This is particularly noteworthy when considering that all of the studies cited above administered large, bolus doses of cocaine repeatedly to drug-naïve animals, which has been shown to amplify neurotoxic effects in amphetamines [55]. These dosing regimens have been criticized as lacking ecological validity, since humans escalate drug use slowly over time. Indeed, research on amphetamines has shown that the neurotoxicity induced by this type of dosing regimen can be prevented when animals are initially exposed to several days of escalating doses [56–58]. Thus, null results when using such an extreme dosing regimen provide evidence for a lack of cocaine-induced neurotoxicity.

3.2. Prefrontal cortex neuroplastic changes

It has been argued that cocaine-related cognitive deficits are mediated by permanent neuroplastic changes in prefrontal cortex (PFC) circuitry rather than cell damage/neurotoxicity [59]. Again, data collected in animals have been mixed. Chronic exposure to cocaine activates a number of neurochemical compensatory mechanisms, which are not completely understood. In rodent models of extended cocaine exposure, changes in PFC functioning have been noted in D1/D2 receptor availability, glucose metabolism, glutamatergic and endocannabinoid signaling, and synaptic excitability [60–64]. These changes in functioning are accompanied by some differences in cognitive flexibility, learning, and memory [65–67]. However, similar to the foregoing studies on neurotoxicity in rodents, most studies utilize dosing regimens that are not relevant to the natural ecology. For example, one study administered 30 mg/kg cocaine hydrochloride (intraperitoneal injection) daily to drug-naïve rats for 2 weeks prior to testing [68]. This would be equivalent to giving 2100 mg (or 2.1 g) cocaine daily to a drug-naïve human who weighs 70 kg (i.e., 150 pounds), for a total dose of almost 30 g of cocaine over a 2-week period. For comparison, one observational study noted that heavy, chronic cocaine users (mean duration of use = 7 years) reported self-administering an average of 9.6 g every 2 weeks [69]. Thus, researchers who use animal models to investigate cocaine-induced neurological and cognitive deficits typically utilize dosing regimens in drug-naïve animals that are approximately 3 times larger than those observed in self-administering cocaine-dependent humans. Furthermore, the majority of the above studies utilized experimenter-administered rather than self-administered cocaine. This approach is less than ideal because data indicate that neurochemical consequences of cocaine administration varies depending upon whether a drug was contingently or non-contingently administered [29,30,32,70,71]. When drug administration is contingent upon the animal emitting a behavioral act, there appears to be a certain degree of protection against drug-related neurotoxicity.

Longitudinal studies investigating the cognitive effects of extended cocaine self-administration in primates show similar, albeit less-striking results. Porter et al. [72] examined the effect of chronic cocaine use on cognitive functioning in rhesus macaques. At baseline, age- and performance-matched monkeys were assigned to self-administer cocaine or water for nine months. Cognitive assessments were administered weekly during a 72-hour drug free period. During maintenance of self-administration, monkeys who received cocaine showed marked disruptions in reversal learning and working memory on drug-free days. As testing occurred 3 days after the most recent exposure, the cognitive deficits were likely related to short-term withdrawal. In a follow-up study (Porter et al. [73]), the authors found that performance in the cocaine self-administration group completely normalized by 3 months of abstinence. However, the introduction of novel and appetitive distractors disrupted performance in the cocaine, but not control group.

While independent studies have determined the long-term effects of chronic cocaine self-administration on brain and behavior, the most rigorous study designs combine imaging methods with cognitive-behavioral tasks. When assessed longitudinally in a primate model, this combination of data can provide compelling, ecologically valid evidence for the breadth and duration of cocaine-induced cognitive deficits. However, to date, only a single study has included this rigorous methodology. In a second follow-up study utilizing the same animals, Porter et al. [74] examined PET imaging and working memory in animals that had been drug-free for 20 months (animals previously self-administered cocaine or water for 1 year). There were no differences in task performance between the two groups, although cocaine-experienced monkeys showed significantly greater metabolic activity in the cerebellum during the task.

Considered together, converging evidence suggests that the compensatory neuroplastic changes associated with chronic cocaine exposure likely create conditions where cognitive performance is normalized during acute intoxication, declines during withdrawal, and recovers gradually over the course of abstinence.

Thus, preclinical research does not support the theory that chronic cocaine use is associated with neurotoxicity or permanent changes in PFC network functioning that can cause cognitive impairment. In light of (a) the lack of evidence from animal research for permanent deficits and (b) the methodological and data interpretation issues that may inflate the deleterious impact of drugs of abuse on cognition, it is crucial that the effects of cocaine use on cognitive functioning be examined with a critical eye.

4. Review of the long-term effects of cocaine on human cognition

4.1. Comprehensive neuropsychological testing of abstinent cocaine abusers

This section will discuss studies conducted by researchers who employed neuropsychological testing only to assess the cognitive functioning of recreational cocaine users and individuals with cocaine use disorders.

Some researchers have focused their efforts on investigating the cognitive functioning of cocaine abusers as compared to controls by using neuropsychological testing to that end. Unlike most of the studies that employ neuroimaging methods, which entail a single test assessing a few specific domains, it is feasible for researchers conducting studies using neuropsychological testing to administer several different tests assessing various domains.

Fernandez-Serrano et al. [75] examined whether there were performance differences between individuals with cocaine dependence and non-drug-using individuals on neuropsychological tasks of inhibition and perseveration. These researchers administered the Stroop and Go/No-Go tests measuring impulsivity as well as the Revised Strategy Application and Probabilistic Reversal tests measuring perseveration. They found that the cocaine-dependent individuals showed significantly more inhibition and perseveration, and thus they concluded that those individuals have deficits in control. Unlike previous researchers, they used multiple measures to assess each domain of interest. However, there still was a discrepancy between the two groups in terms of years of education. The non-drug-using controls completed significantly more years of education than did the cocaine-dependent individuals (17 vs. 11.87 years). Even though Fernandez-Serrano et al. [75] statistically controlled for years of education, normative comparisons should have been included as well. Given that completed years of formal education

Table 1
Studies that have Included Neuropsychological Test Batteries Only.

Investigators	Domains tested	Participants	Period of abstinence	Cognitive findings	Caveats
Albein-Urios et al. [7]	*Response Inhibition* (Stroop)	Cocaine users met DSM-IV criteria for dependence (CDI): N = 29	Minimum of 15 days	↓ Response inhibition (Stroop)	Cognitive data not compared against normative data set.
	(UPPS-P trait impulsivity)	Gamblers met DSM-IV criteria for pathological Gambling (PG): 23		↑ Scores on UPPS-P Negative and Positive Urgency	Thus, the clinical importance of findings could not be determined
	Working Memory (N-back)	Controls: (CON) N = 20		↓ Delay discounting in PG compared to CDI and CON ↓ Working memory	Groups not matched on age
Bolla et al [11]	*Executive functioning* (Verbal/Nonverbal cancellation test, Digit symbol substitution, TMT-A, TMT-B, Stroop, WCST)	Cocaine users met DSM-III criteria for dependence: N = 30	28 days	↓ Executive function	Cognitive data not compared against normative data set
	Visuoperception (Rey Complex Figure, Block Design and Judgment of Line orientation)	Controls: N = 21		↓ Visuoperception Cocaine group outperformed controls on Block Design test	Cocaine users housed inpatient for 30 days before testing compared to controls participants tested as outpatients
	Psychomotor speed (CALCAP)			↓ Psychomotor	
	Intelligence (Shipley, WAIS-R)			↔ Language	
	Language (Controlled oral verbal fluency)			↑ Verbal memory	
	Verbal memory (WMS-R, RAVLT)			↓ Visual memory (only Symbol Digit Paired Associate Learning Test)	
	Visual memory (Rey-Osterrieth Complex Figure, Symbol Digit Paired Associate Learning Test)				
Colzato et al. [82]	*Response Inhibition* (Stop-signal task)	Recreational cocaine users: N = 13	2 days	↓ Response inhibition	Cognitive data not compared against normative data set.
		Cocaine-free controls: N = 13			Thus, the clinical importance of findings could not be determined
					The influence of marijuana and MDMA use not controlled
					Small number of participants studied
Colzato et al. [77]	*Executive function* (WCST) (dots-triangles task)	Study 1: Executive Function	14 days	↓ Executive function	Small amount of cocaine used by recreational polydrug users.
	Working Memory (Digit span)	Recreational cocaine polydrug users: N = 20		↔ Working memory	Thus, unable to determine whether performance on tasks are unique to cocaine use
	(Digit span)	Controls: N = 20			Did not control for education
	(N-back task)	Study 2: Working Memory			
		Recreational cocaine polydrug users: N = 20			
		Controls: N = 20			
Cunha et al. [122]	*Executive function/decision-making* (WCST) (IGT)	Cocaine users met DSM-IV criteria for dependence: N = 15	Avg 2 weeks	↔ Executive function (WCST)	Only self-report cocaine and other drug use for both groups
	Social Adjustment Scale (SAS)	Controls: N = 15		↑ Scores on SAS	Small number of participants studied
				↔ Decision-making (IGT) Cocaine group made more disadvantageous choices	Only male participants
Fernández-Serrano et al. [9]	*Set-Shifting/Executive Functioning*	Cocaine users met DSM-IV criteria for dependence: N = 42	Minimum15 days, avg 34.28 weeks	↔ Revised strategy application task	Cognitive data not compared against normative data set, thus the clinical importance of findings could not be determined
	(Reversal learning task, Revised strategy application task)	Controls: N = 65		↓ Response inhibition and perseveration	Controls had higher level of education
	Response Inhibition: (Stroop/Go/NoGo) (UPPS-P scale)	Due to missing data: CDI = 44 for Go/NoGo, Controls: N = 56 for Go/NoGo and reversal task, Controls = 63 for Stroop task		↑ Scores on trait impulsivity	The influence of drug use other than cocaine not controlled

(*continued on next page*)

Table 1 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive findings	Caveats
Filmore and Rush [125]	*Response Inhibition* (Stop Signal Task)	Cocaine users: N = 22 Controls: N = 22	Cocaine group was required to submit urine positive for cocaine, but negative for other drugs on the day of testing	↓ Response inhibition ↔ Response execution	Only one cognitive measure included The influence of drug use other than cocaine not controlled
Fox et al. [83]	*Memory*	Cocaine users met DSM-IV criteria for dependence: N = 36	Minimum 14 days	↓ Memory	Cognitive data not compared against normative data set. Thus the clinical importance of findings could not be determined
	Verbal learning	Controls: N = 36		↓ Verbal learning	Cocaine users were assessed 2 weeks after inpatient stay compared to controls who were assessed 4 days after inpatient stay
	Executive function (RAVLT)			↓ Executive function	The influence of other comorbid substance use disorders and psychiatric disorder such as anxiety not controlled
Hulka et al. [14]	*Decision-making* (Iowa Gambling Task, Delay Discounting)	Cocaine users met DSM-IV criteria for dependence (CD): N = 30	Minimum 3 days	↔ Decision-making (↓in CD)	Cognitive data not compared against normative data set, thus the clinical importance of findings could not be determined
	Social interaction (Distribution Game, Dictator Game)	Recreational cocaine users (RU): 68		↓ social interaction (CD and RU)	Controls had higher levels of education
		Controls: N = 68			The influence of comorbid ADHD not controlled The influence of drug use other than cocaine not controlled
Liu et al. [22]	*Attention* (Cocaine Stroop Task)	Cocaine users met DSM-IV criteria for dependence: non treatment seekers (NT seekers) and treatment seekers (T seekers): N = 37	Unk (urine pos at screening)	↑ Attentional bias	Cognitive data not compared against normative data set
	Inhibitory Control (IMT)	Controls: N = 32		↓ Inhibitory Control	Cocaine users included NT- seekers and T-seekers, but results were not sig for T-seekers. Sample size of NT-seekers is unclear, so unable to determine the clinical significance of findings Groups were not matched on age The influence of alcohol and marijuana use disorders not controlled The influence of nicotine not controlled
Moeller et al. [77]	*Decision-making (insight)*	Cocaine users met DSM-IV criteria for dependence: N = 42	CUD+ Median = 2.4 days	When divided into CUD + vs CUD- only CUD + had significantly ↓ performance	Cognitive data not compared against normative data set. Thus, the clinical importance of finds could not be determined
	(Probabilistic Choice Task)	Cocaine use disorder testing positive (CUD+): N = 16	CUD- Median = 31 days	CUD+ > CUD- > controls for cocaine picture probability	The influence of other comorbid substance use disorder and psychiatric disorder such as depression not controlled
	(Explicit Choice Task)	Cocaine use disorder testing negative (CUD-): N = 26 Controls : N = 23		CUD+ < CUD- < control for pleasant picture probability Cocaine related choice in CUD- was ↑ among those with impaired insight	

(*continued on next page*)

Table 1 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive findings	Caveats
Oliveira et al. [78]	*Executive function and attention* (Digit span, forward and backward) (Verbal fluency) (Stroop Color Word Test) (Cancellation Test) (Trail making A and B) (DSST)	Ex-cocaine users: N = 20	Ex-cocaine users: Minimum of 6 months	Current users: ↔ Verbal memory	Self-report data of current drug use instead of objective drug screen confirmation
	Verbal memory (Logical memory) (Verbal associated pairs)	Current cocaine users: N = 17	Current users: 1-30 days	↓ Logical memory	Small number of participants studied
		Controls: N = 18		↔ Logical memory between current users and ex-users ↔ Executive function and attention Ex-users: ↔Verbal memory ↓ Executive function and attention	
Preller et al. [79]	*Cognitive Empathy* (MET/RMET)	Cocaine users met DSM-IV criteria for dependence: N = 31	Minimum 3 days	↔ Cognitive empathy	Cognitive data not compared against normative data set. Thus the clinical importance of findings could not be determined
	Mental Perspective Taking (MASC)	Recreational cocaine users: 69 Controls: N = 68		↓ Mental perspective taking	Controls had higher level of education and were younger than the cocaine group
Preller et al. [81]	*Sensorimotor gating, response inhibition* (PPI,ASR)	Cocaine dependent users met DSM-IV criteria for dependence: N = 29	Minimum 3 days (alcohol, 24 h)	↑ PPI DCU and RCU vs controls	Cognitive data not compared against normative data set. Thus the clinical importance of findings could not be determined
	Startle reactivity, habituation (Eye-blink)	Recreational cocaine users: 64 Drug-naïve controls: N = 66		↔ startle reactivity and habituation	While recreational users were included, no normative data comparison The groups only differed on a single task No difference between DCU and RCU with regard to the task. Did not control for ADHD and depression Groups not matched on sample size, age and education.
Reske et al. [126]	*Memory and Learning* (CVLT)	Recreational cocaine users: N = 13	Unk	↔ Immediate intrusions	Performance on CVLT was not outside normative data range
		Stimulant-naïve controls: N = 48		↔ Delayed recall intrusions ↓ Cued recall intrusions	Small number of cocaine users studied
Sellaro et al. [123]	*Response conflict* (Simon task)	Recreational cocaine polydrug users: N = 17 Cocaine-free controls: N = 17	Minimum 2 days	↓ Response conflict ↑ Reaction time ↔ Percentage of errors	Cognitive data not compared against normative data set. Thus, the clinical importance of findings could not be determined No objective assessment of drug use administered Recreational cocaine polydrug users and cocaine-free controls reported consuming alcohol, marijuana and MDMA. Thus, unable to disentangle the effects of cocaine from other drug effects Small number of participants studied

(*continued on next page*)

Table 1 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive findings	Caveats
Simon et al. [12]	*Memory* (Repeated Memory Test) (Backward Digit Span) *Perceptual Speed/Psychomotor Speed*, (Digit Symbol Subtest of the Wechsler Adult Intelligence S-Revised), *Attention, Sequencing, Psychomotor Speed, Mental Flexibility* (Trail Making Test, pats A and B), (Stroop Color Word Interference Test), *Verbal Fluency (FAS)*, *Vocabulary and Abstract Thinking* *Executive Function* (WCST)	Cocaine users met DSM-IV criteria for abuse or dependence: N = 40 Cocaine users met DSM-IV criteria for abuse dependence: N = 40 Controls: N = 80	Tested positive for drug and negative for other drugs of abuse on testing day	Cocaine Abusers: ↓ Memory ↓ Attention and cognitive flexibility ↓ Vocabulary and abstract thinking ↔ Executive function Methamphetamine Abusers: ↓ Memory, but not working memory test ↓ Perceptual Speed/psychomotor speed ↓ Attention and cognitive flexibility (not sig) ↓ Vocabulary and abstract thinking ↓ Executive function	No mention of a sobriety test to rule out acute intoxication on study day Majority of cocaine group were African American
Soar et al. [124]	Cambridge Neuropsychological Test Automated Battery (CANTAB) *Spatial Working Memory* (SWM) *Executive Functioning* (IED) *Spatial Planning* (SOC) *Sustained Attention* (RVP)	Recreational cocaine users: N = 17 Controls: N = 24	Avg 7 days	↓ Spatial working memory ↓ Set-shifting/executive function ↓ Sustained attention ↔ Spatial planning	No measure of IQ Self-report data of current drug use instead of objective drug screen confirmation Small number of participants studied
Streeter et al. [83]	*Executive Function* Stroop	Cocaine users met DSM-IV criteria for dependence: N = 74 Completers: 50 Non-completers: 24	unk	Non-completers: ↔ Executive function	Did not exclude individuals with alcohol dependence The influence of other drug use not controlled
Vadhan et al. [20]	*Reward Based Decision Making* (Modified Gambling Task) *Executive function* (WCST)	Cocaine users met DSM-IV criteria for dependence: N = 22 Controls: N = 24	morning of testing	Hypothetical Condition: ↓ Card selection selection ↔ Time to complete task Cash Payment Condition: ↔ In card selection ↑ Time to complete task ↔ Executive function	Cocaine abusers had lower reported years of education, estimated IQ levels and greater depressive symptoms Did not manipulate different magnitudes of earnings and losses. Thus, unable to determine the saliency of negative and positive consequences

(*continued on next page*)

Table 1 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive findings	Caveats
Vonmoos et al. [129]	*Rapid visual processing* (RVP), *spatial working memory* (SWM), *intra/extradimensional set shifting* (IED), *paired associates learning* (PAL) (CANTAB) (RAVLT) (LNST)	Cocaine users met DSM-IV criteria for dependence: N = 30 Recreational cocaine users: N = 68 Controls: 68	Minimum 72h for urine toxicology 6 months for hair toxicology	Both cocaine dependent and recreational users: ↓ Attention (strongest effect in recreational users) ↓ Working memory (strongest effect in cocaine dependent users) ↓ Declarative memory ↓ Executive function (RAVLT) ↔ Executive function (IED)	The influence of other drug use not controlled Cocaine dependent users had fewer years of education Small cocaine sample size relative to comparison groups
Woicik et al. [15]	*Executive functioning/Set-Shifting* (WCST) *Verbal Memory and Learning* (CVLT)	Cocaine users met DSM-IV criteria for dependence or abuse: N = 107 Controls: N = 107 *subdivided according to their ability to complete all six blocks of the WCST (completers [C] versus non-completers [N]) Cocaine use disorder non-completers (CUD-N) = 54 Control non-completers (CON-N) = 17 Cocaine use disorder completers (CUD-C) = 53 Control completers (CON-C) = 90	Minimum 72h/Unk	↓ Executive Functioning/set-shifting ↓ Ability to complete WCST CUD-C ↑ perseveration compared to CON-C ↔ State motivation or words recalled on trial 1 ↓ Words recalled on trial 5	Cognitive performance was not outside normative data range Large number of cocaine users did not complete the WCST compared to controls Nineteen CUD-C participants tested negative for cocaine. Thus, conclusions about compromised neurotransmission as indexed about positive urine status cannot be made Groups were not matched on age

Abbreviations: CALCAP, California computerized assessment package; CANTAB, Cambridge Neuropsychological Test Automated Battery; COC−, Cocaine negative; COC+, Cocaine positive; CON-C, Control completers; CON-N, Controls non-completers; CUD-N, Cocaine use disorder non-completers; CUD-C, Cocaine use disorder completers; CVLT, California verbal learning test; DSST, Digit Symbol Substitution Test; DSM-III, Diagnostic and Statistical Manual of Mental Disorders 3rd; Edition; DSM-IV; Diagnostic and Statistical Manual of Mental Disorders 4rd; Edition; DSM-IV; FAS, verbal fluency test; IED, Intra/extradimensional set shifting; IGT, Iowa Gambling Task; IMT, Immediate memory task; LNST, Letter number sequencing test; MASC, Movie for the assessment of social cognition; MDMA, 3,4, methylenedioxyamphetamine; MET, Multifaceted empathy test; NT seekers, Non treatment seekers; PAL, Paired associates learning; RAVLT, Rey auditory verbal learning test; RMET, Reading the mind in the eyes test; RVP, Rapid visual processing; SAS, Social Adjustment Scale; SOC, Stockings of Cambridge; SWM, Spatial working memory; T seekers, Treatments seekers; TMT-A, Trail making test part A; TMT-B, Trail making test, part B; WAIS-II, Wechsler's adult intelligent scale II; WAIS-R, Wechsler's adult intelligent scale-revised; WCST, Wisconsin card sorting test; WMS-R, Wechsler's memory scale-revised; Unk, unknown.
Cognitive performance: ↓, Cocaine users performed more poorly than controls; ↔ Cocaine users and controls performed equally, ↑ Cocaine users outperformed controls.

is strongly correlated with cognitive performance as assessed by current measures, the findings obtained by Fernandez-Serrano et al. [75] should be interpreted with considerable caution.

As may be seen in Table 1, multiple tests are used to tap a specific domain [76]. If the findings converge, then we are more likely to say the test has validity, however, only five out of twenty-two studies [9,14,76–76–78] in Table 1 administered more than one measure per domain. Five out of twenty-two studies [7,13,15,22,79] did not match groups based on age, and seven did not match groups on years of education [9,13,14,20,76,80,129]. Additionally, eleven out of those twenty-two studies [3,9,14,22,77,81–83,122,123,129] did not control for the extensive use of other psychoactive drugs, and thirteen (13/22) did not interpret their findings within the normative context. Thus, the functional significance, or clinical relevance is unclear.

In sum, when it comes to neuropsychological studies investigating the long-term effects of cocaine on cognitive functioning, Table 1 clearly shows that most of them have not controlled for important demographic variables and for drug use, and similarly have overlooked assessing their cognitive data within the context of a normative database. Thus, the clinical importance of such findings cannot be determined. While published norms are available for tests such as the Stroop, Wisconsin Card Sorting Task, Rey Complex Figure Task, and Rey Auditory Verbal Learning Test, the findings gleaned by neuropsychological studies administering these measures must be interpreted relative to those norms and not be based solely upon differences between the experimental group and the control group. Taking that step would go a long way toward resolving the perplexing issue of the nature of impairment, an issue that pervades the literature investigating the effects of long-term cocaine use on cognitive functioning.

4.2. MRI studies investigating brain structure sizes of abstinent cocaine abusers without cognitive testing

As seen in Table 2, a growing number of investigators have used MRI techniques to investigate the long-term effects of cocaine use on brain structure. Some studies assess behavior by administering both MRI and cognitive measures [84–86], while other studies make conclusions regarding behavior based solely on MRI [87–89].

In one study conducted by Franklin et al. [89] researchers compared the gray and white matter concentrations in the brains of cocaine abusers with non-drug-using controls by using MRI voxel-based morphometry, a technique that can examine local tissue volume differences. The goal was to investigate whether there were structural brain differences between groups' in areas of decision-making and autonomic arousal. The researchers found that, compared to the control group, the cocaine group exhibited varying gray matter concentration in the prefrontal regions (5%–11%): the ventralmedial orbitofrontal, anterior cingulate, anteroventral insular, and superior temporal cortices. No differences were found between the two groups in white matter concentration, a finding consistent with that of a study that used MRI to look at abstinent cocaine abusers [90]. This is at odds, however, with another study that found varying white matter volume in cocaine users and no evidence of age-related changes [91]. The findings of Franklin et al. [89] led investigators to speculate that the brains of cocaine abusers are structurally dissimilar to those of non-drug-using controls and, further, that differences detected in the brain areas involved in decision-making, inhibition, and emotional valence to environmental stimuli may better explain behavioral deficits in individuals with cocaine use disorder.

Franklin et al. [89] were the first to report discrete gray matter differences in chronic cocaine users. The cocaine abusers were older than the controls (42 vs. 32), and the researchers acknowledged the importance of controlling for this important demographic variable since brain structure changes with age. Indeed, they included age in their design matrix as a covariant. Additionally, the researcher's sample was only male participants. Studying only males limits the generalizability of findings to the broader cocaine-abusing population. Other caveats include the small number of participants studied, and the inclusion of individuals with ADHD and antisocial personality disorder in the cocaine group, but not in the control group. Thus, although Franklin et al. found that certain areas of cocaine abusers' brains had varying gray matter concentration, it is not possible to conclude from the MRI images that cocaine use, specifically, *causes* [*emphasis ours*] reduced gray matter concentration.

The literature concerning gray matter differences has yielded inconsistent results, with other researchers observing no differences in gray matter volume between individuals with cocaine dependence and non-drug-using controls. The latter study used MRI to compare the structural changes in the brains of cocaine abusers and non-drug-using controls, and the researchers did not see any differences in gray matter. While many studies attempt to control for drug use and other psychiatric disorders, others assume that some psychiatric symptoms and forms of drug use, e.g., impulsivity, nicotine use, and depressive symptoms are inherent in drug dependence [88]. Yet other research suggests that these variables individually correlate with volume reductions in the frontal brain structures and with depression [92], impulsivity [93], and the smoking of nicotine [94,95]. Crunelle et al. [88] used MRI voxel-based morphology to investigate the combined impact of these comorbidities on the brain morphology of cocaine abusers and non-drug-using controls. They found varying gray matter volumes in the cocaine-abusing group only in the left middle frontal gyrus when they compared that group to the controls and observed no differences in white matter volume. Within the cocaine-abusing group trait impulsivity was associated with varying gray matter volume in the right orbitofrontal cortex, the left prefrontal gyrus, and the right superior frontal gyrus. However, the right inferior parietal gyrus gray matter volume and non-planning impulsivity relationship was not significant after controlling for smoking severity and depressive symptoms. Smoking severity, depressive symptoms, and duration of cocaine use all had no observed effect on regional gray matter volumes. Those findings led the investigators to suggest that, whatever the associations between frontal gray matter volume and trait impulsivity may be, they are minimally influenced by the severity of nicotine intake and of depressive symptoms. With increased severity and/or duration of dependence symptoms, however, those variables might become important.

Connolly et al. [87] and Crunelle et al. [88] aimed to examine and explain any underlying pathology found within the domains of cognitive functioning solely by measuring differences in brain structure without an objective assessment of behavior. Because Crunelle et al. [88] did not find a correlation between the three BIS subscale scores, they suggested that their measures of impulsiveness may be revealing a neurobiological disconnect in cocaine users. Keeping that suggestion in mind, investigators should administer multiple behavioral tasks that measure the various facets of impulsivity. Even given the present study's limitations (see Table 2), at the very least it shines some light upon the ongoing need to better assess substance-abusing populations that have comorbid disorders. By contrast, interpretations based solely upon brain imaging data tell us little about actual, day-to-day impulsive behavior.

Table 2 summarizes three out of six MRI studies [87–89] where investigators made conclusions about behavior even though cognitive testing was not included. This raises concern because it illustrates the propensity to interpret any brain differences as pathology, even though cognitive measures assessing behavior were not administered. Moreover, two out of those six MRI studies [86,87] did not control for level of education, and five [84–88] did not control for the use of other psychoactive drugs.

4.3. MRI studies investigating brain structure sizes of abstinent cocaine abusers with cognitive testing included

As may be seen in Table 2, a growing number of investigators are

Table 2
Imaging studies. MRI, fMRI, PET, EEG.

Investigators	Domains tested	Participants	Period of abstinence	Cognitive and brain findings	Caveats
Connolly et al. [87]	*Cognitive testing not included*	Abstinent cocaine users (initially met DSM-IV criteria for dependence = 43	Minimum 1 week	Cognitive: Not included	Gray matter concentration not compared against normative data set, which makes it difficult to make assumptions about decreased GM and its correlation to cocaine users
		Controls = 43		Brain: ↓ Grey matter (GM) in ACC, inferior frontal gyrus and insular cortex (associated with years of use)	Controls had higher level of education
				↑ GM anterior and posterior cingulate, insular, right ventral and left dorsal prefrontal cortex (associated with abstinence duration)	The influence of drug use other than cocaine not controlled
				↑ GM in users with longer abstinence	No behavioral data obtained
Crunelle et al. [88] (MRI)	*Impulsivity* (VBM)	Cocaine users met DSM-IV criteria for dependence: N = 30	Unk	Cognitive: Not included	Gray matter concentration not compared against normative data set, which makes it difficult to make assumptions about decreased GM and it's correlation to cocaine users
	Cognitive testing not included	Controls = 33		Brain: ↓ GM volumes left middle frontal gyrus and right superior frontal gyrus	More nicotine smokers in cocaine group than controls
					No behavioral data obtained
Ersche et al. [84] (MRI)	*Response Inhibition* (Stop-Signal task)	Cocaine users met DSM-IV criteria for cocaine dependence: N = 60	Unk	Cognitive: ↑ ⟵Response inhibition; i.e. slow reaction time and missed significantly more targets compared to controls	Gray matter concentration not compared against normative data set, which makes it difficult to make assumptions about decreased
	Sustained Attention (RVIP)	Controls: N = 60		↑ Sustained attention; i.e. fewer commission errors paired with longer responses compared to controls	Cocaine users high levels of self-reported impulsivity did not reflect their behavioral performance that prolonged responses
				Brain:↓ grey matter volume in the basal in orbitofrontal, cingulate and insular cortex, temporoparietal and cerebellar cortex	Questionnaire measures unrelated to brain structure
				↑ Grey matter volume in basal ganglia	The influence of drug use other than cocaine not controlled
Franklin et al. [89] (MRI)	*Cognitive testing not included*	Cocaine users met DSM-IV criteria for dependence: N = 13	Unk	Cognitive: Not included	Gray matter concentration not compared against normative data set, which makes it difficult to make assumptions about decreased GM and its correlation to cocaine users
		Controls = 16		Brain:↓ GM volumes in vmOFC, ACC, AVI and STC	The influence of other psychiatric disorders such as ADHD and ASP not controlled
					Small number of participants studied
					Only male participants studied

(*continued on next page*)

Table 2 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive and brain findings	Caveats
Hanlon et al. [85] (MRI)	*Psychomotor performance, recognition memory, working memory, attentional set-shifting and planning* (CANTAB battery)	Cocaine users met DSM-IV criteria for dependence: N = 24	Abstainers: M = 1.9 days	Cognitive: current users had ↓ reaction time and accuracy on pattern recognition memory, delayed match to sample and planning	IQs were lower for current users and abstainers than controls
		Current cocaine abstainers: N = 24 Non drug-using controls: N = 25	Current users: M = 243.8	Current users and abstainers↓ IDED set-shifting compared to controls ↔ Current users and abstainers	No sig correlations between WM and task performance Cocaine users all tested positive at image acquisition. No sobriety test was conducted to rule out acute effects of cocaine
				Brain: ↑ GM volume in abstainers compared to current users Current users had ↓ cortical gray matter density in right medial, left middle, and bilateral inferior frontal gyri compared to controls. Current users had ↓ subcortical GM density in the right caudate and the bilateral cerebellum. Abstainers had ↓ GM density in right caudate/putamen and bilateral cerebellum compared to controls. ↔ WM volume in abstainers compared to controls Current users had ↓ GM and WM compared to abstainers Within the current users and abstainers GM density was correlated with performance on multiple measures	Unable to disentangle effects of cocaine abstinence form alcohol abstinence
Sim et al. [86] (MRI)	*Psychomotor speed* (Trails A)	Cocaine users met DSM-IV criteria for dependence: N = 40 Controls = 41	Unk	Cognitive: ↓ Psychomotor speed	Controls had higher level of education
	Executive function (Trails B, Stroop)			↓ Executive function	The influence of other psychiatric disorders such as ADHD and ASP not controlled
	Motor performance (GPT)			↑ Motor performance	Did not control for the use of drugs other than cocaine
	(VBM)			Brain:↓ GM volumes rOFC ↓ GM volumes in bilateral PMC ↓ GM volumes in bilateral TC ↓ GM volumes in left thalamus ↓ GM volumes in bilateral cerebellum ↓ WM volumes in lower cerebellum	
Barros-Loscertales et al. [127]	*Inhibitory control* (“Counting Stroop task”)	Cocaine users met DSM-IV criteria for dependence: N = 16	Minimum 2-4 days	Cognitive: ↔ inhibitory control	No differences found in behavioral data. Thus behavioral data did not support imaging data
		Controls: N = 16		Brain: ↓ right inferior frontal cortex, right inferior parietal and superior temporal cortex	Only one cognitive measure included The influence of drug use other than cocaine not controlled Small number of participants studied Only male participants studied

(*continued on next page*)

Table 2 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive and brain findings	Caveats
Bell et al. [97] (fMRI) (EEG)	*Response inhibition* (Go/No-Go)	Abstinent cocaine dependent: N = 27 Controls: N = 45	Avg 32.3 weeks, minimum duration of abstinence was found in only one of the participants (min = 0.87 weeks, max = 100), 14 patients with the shortest duration had avg of 13.4 weeks of cessation	Cognitive: ↔ response inhibition Duration of abstinence, years of cocaine use and age were not sig predictors of correct stops. Brain: fMRI and EEG↔ within any of the 7 ROI.	Only one cognitive measure included The influence of drug use other than cocaine not controlled
Bustamante et al. [8] (fMRI)	*Attention Working Memory* (n-back task)	Cocaine users met DSM-IV criteria for dependence: N = 15 Controls: 15	Minimum 4-5 days	Cognitive:↔ Attention and working memory Brain: ↓ right inferior parietal cortex	No differences found in behavioral data. Thus, behavioral data did not support imaging data The influence of drug use other than cocaine not controlled Small number of participants studied Only male participants studied
Castelluccio et al. [96] (fMRI)	*Response Inhibition (*Go/No-Go) *Impulsivity* (BIS/BAS, BIS-11, SPSRQ, SS Form V, Padua Inventory, BART, EDT)	Cocaine users met DSM-IV criteria for dependence: N = 30 Former cocaine users: N = 29 Healthy controls: N = 35	Mean 51.2w	Cognitive:↔ Response inhibition Brain: Current users: ⟵↑ in pregenual cingulate gyrus and left angular/ supramarginal gyri Former users: ⟵↑ in right middle frontal/preentral gryi, right inferior parietal lobule, and left angular/ supramarginal gyri	No behavioral results reported (Go/No-Go) The influence of other drugs other than cocaine not controlled
Goldstein et al. [109] (fMRI)	*Set-shifting/Executive function* (Stroop) *Response Inhibition*	Cocaine users met DSM-IV criteria for cocaine dependence: N = 14 (cocaine abuse = 1) No control group	Ranged from 1-96 days Median = 12 days	Cognitive:↔ in accuracy or speed between the drug and neutral conditions Brain↑ drug-related activation in cdACC, ↑ negative valence attributed to drug words, but not neutral words ↑ cdACC, in frontal regions, parietal, occipital lobes and the in the caudate, thalams, and cerebellum ↓ activation bilaterally in the rACC/ mOFC, insula parahippocampus gyrus, and in the cuneus and lingual gyrus	Did not obtain significant behavioral differences between the drug and neutral conditions on Stroop task No control group Only one cognitive measure included Small number of participants
Hester and Garavan [99] (fMRI)	*Response Inhibition* (Go/No-Go) with *Working Memory* (WM-IT)	Cocaine users = 15 Controls = 15	Minimum 72h, Mean 42h	Cognitive: ↓ Response inhibition Brain: ↓ ACC ↓ Prefrontal regions: the right superior frontal gyrus, and right pre-SMA	Controls had higher level of education Controls were several years younger Only one cognitive measure included and it was not compared against normative data set, which makes it difficult to determine the clinical importance of findings Small number of participants studied

(*continued on next page*)

Table 2 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive and brain findings	Caveats
Kaufman et al. [5] (fMRI)	*Response Inhibition* (Go/No-Go)	Cocaine users (diagnostic information not provided): N = 14 Controls: N = 13	Minimum 72h/18-72h	Cognitive:↓ inhibitory control Brain:↓ ACC and insula during STOPS in Go/No-Go task ↔ Right inferior parietal lobule and rDLPC for STOPS ↓ ACC, rMFG, left insula and left inferior frontal gyrus during ERRORS in Go/No-Go task	Only one cognitive measure included Participants educational information not reported Diagnostic information for psychiatric disorders not included Unable to determine the influence of comorbid psychiatric disorders Cognitive data not compared to normative dataset. Thus, the clinical importance of findings could not be determined Small number of participants studied
Kübler et al. [103] (fMRI)	*Verbal working memory* *Visuospatial working memory* *Attention switching*	Cocaine users (diagnostic information not provided): N = 13 Controls: N = 14	Minimum 72	Cognitive: ↔ verbal working memory ↓ Visuospatial working memory Brain: ↓left cingulate gyrus ↓ Medial frontal gyrus ↓ Right middle frontal gyrus ↓ Right precuneus ↓ Cingulate gyrus ↔ DLPFC ↔ Anterior frontal cortex	Controls were several years younger Verbal task performance demonstrated that cocaine users were not uniformly impaired in all aspects of attention switching The influence of drug use other than cocaine not controlled Small number of participants studied
Li et al. [100] (fMRI)	*Response Inhibition* (Stop Signal task)	Cocaine users met DSM-IV criteria for dependence: N = 15 Controls: N = 15	Minimum 14 days	Cognitive: ↔ Response Inhibition Brain: ↓ rACC	Only one cognitive measure included Small number of participants studied Only male participants studied
Mayer et al. [102] (fMRI)	*Set-Shifting/Executive functioning* *(Stroop-visual & auditory)*	Chronic cocaine abusers (CCA): N = 14 Controls: N = 16	Minimum 3 days, M = 7 days	Cognitive: ↔ selective attention response time for low and high frequency trials Brain: ⟵ ↑ activation in prefrontal cortex, striatum, and thalamus	Cocaine group had sig lower IQ scores compared to controls The influence of drug use other than cocaine not controlled Small number of participants studied
Morein-Zamir et al. [101] (fMRI)	*Response Inhibition* (Stop signal task)	Recreational cocaine users = 24 Controls = 32	Provided negative urine sample on day of test	Cognitive: ↔ response inhibition Brain: ↑ ⟵ dmPFC and ACC ↔ Right inferior frontal cortex	Did not provide objective measure for cocaine use Only one cognitive measure included
Preller et al. [13] (fMRI)	*Social cognition* (Social gaze task, eye tracking)	Study I: Cocaine users met DSM-IV criteria for dependence: N = 80 Controls: N = 60 Study II: Cocaine users met DSM-IV criteria for dependence: N = 16 Controls: N = 16	Minimum 3 days	Study I: Eye tracking: ↓ Emotional engagement in social interaction (eye-tracking) Study II: Brain:↓ ROI mOFC	Reliable objective measure of urine toxicology not reported (only self-report) The influence of alcohol dependence not controlled Behavioral data not compared normative dataset. Thus, the clinical importance of findings could not be determined The influence of drug use other than cocaine not controlled (including drug use in control group) Small number of participants studied in Study II

(*continued on next page*)

Table 2 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive and brain findings	Caveats
Tomasi et al. [10] (fMRI)	*Sustained attention* (Drug word task)	Cocaine users met DSM-IV-TR criteria for abuse and dependence: 20 Controls: 20	Seventeen cocaine abusers provided a positive urine for cocaine on the day of testing. Three cocaine abusers provided a negative urine for cocaine on the day of testing.	Cognitive: ↔ Sustained attention Brain: ↓ Activation in DLPC, cerebellum, thalamus and left caudate ↓ Positive connectivity in thalamus, cerebellum and rostral cingulate	The influence of nicotine not controlled Cognitive data not compared against normative data set. Thus, the clinical importance of findings could not be determined Only one cognitive measure included Small number of participants studied
Verdejo-Garcia et al. [104] (fMRI)	*Decision-making* (Moral dilemma task)	Cocaine users met DSM-IV-TR criteria for dependence: N = 10 Controls: N = 14	Minimum10 days	Cognitive: ↔ Responses to moral dilemmas Brain: ↓ ACC, left insula and brain stem ↓ Resting state functional connectivity between ACC, thalamus, insula and brain stem	There were no differences between groups on moral dilemma tasks. Thus, the relevance of brain findings and moral judgment in cocaine abusers is unclear Cognitive data not compared against normative data set. Thus, the clinical importance of findings could not be determined Small number of participants studied
Bolla et al. [107] (PET)	*Decision-making* (Iowa Gambling Task)	Cocaine abusers : N = 13 Controls: N = 13	25 days	Cognitive: ↔ Decision-making Brain: ↑⟵ in right OFC, ↓ right DLPFC and MPFC.	Cognitive data not compared against normative data set. Thus, the clinical importance of findings could not be determined Only one cognitive measure included Controls were several years younger No differences found in behavioral data. Thus, behavioral data did not support imaging data Small number of participants studied
Bolla et al. [108] (PEt)	*Set-shifting/Executive function* (Stroop)	Cocaine users met DSM-IV criteria for cocaine abuse: N = 13 Controls: N = 13	Minimum 23 days	Cognitive: ↔ Stroop Brain:↓ right LPC and left ACC ↑ rACC	Cocaine users housed for 23 days, compared to controls housed for 3 days Two outliers driving negative correlation Controls were several years younger No differences found in behavioral data. Thus, behavioral data did not support imaging data Small number of participants studied

(*continued on next page*)

Table 2 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive and brain findings	Caveats
Goldstein et al. [109] (PET)	*Set-shifting/Executive Function* (WCST, number of categories; WCST preservative errors; Stroop Color-Word Interference Score age corrected; Trail Making Test, part B seconds; Booklet Categories Test number of errors) *Immediate verbal memory* (CVLT, WMS logical memory immediate, WMS paired associates immediate) *Delayed verbal memory* (WMS logical memory delayed, CVLT delayed free-recall, CVLT recognition hits) *Visual memory* (WMS visual reproduction immediate; WMS visual reproduction delayed, BVRT number of errors; number of correct) *Attention* (Symbol digit modalities test written, Trail making A, WMS digit span subtest scaled score, Cancellation test) *Language* (Controlled Oral Word Association Test, Boston Naming Test, WAIS-R) Grouped into 4 scales: (Visual memory, verbal knowledge, verbal memory and attention/executive functioning)	Cocaine users met DSM-III or IV criteria for dependence : N = 42 Alcohol users met DSM-III or IV criteria for dependence: N = 40 Controls = 72	Minimum 14 days	Cognitive: Mild neurocognitive impairment (< 1 SD below control mean) ↓ Performance on NP dimensions (Visual memory, Verbal knowledge, Verbal memory and Attention/executive functioning) Users who reported current or past alcohol use had↓ in Attention/executive function compared to users who did not report alcohol use. Brain: ⟵↑ DLPFC predicted with Visual memory and Working memory ↑ ACC predicted Attention/executive functioning	Did not match groups on demographic variables (i.e. sex, handedness, age and education) Did not control for the time period between the NP and PET studies
Gooding et al. [110] (EEG)	*Attention* (Auditory oddball event-related task) (CPT)	Cocaine users met DSM-IV criteria for cocaine dependence (CDI): N = 18 Controls (CON): N = 16	Minimum 3 weeks	Cognitive: ↓ CPT discriminability and errors of commission ↔ Response criterion ↓ Auditory oddball event-related task Brain:↓ P300 amplitude reduction	Did not obtain significant behavioral differences on tasks Two groups did not differ significantly in terms of P300 latency Groups not matched for education Small number of participants

(*continued on next page*)

Table 2 (*continued*)

Investigators	Domains tested	Participants	Period of abstinence	Cognitive and brain findings	Caveats
Parvaz et al. [128] (EEG)	*Executive functioning; reward prediction error-feedback negativity* (Gambling Task)	Cocaine users met DSM-IV criteria for dependence (tested positive) (CUD+): N = 25	CUD+ participants used within past 72h	Cognitive: ↔ in effectiveness of task	Reward prediction error was not compared to normative performance, which makes it difficult to determine the clinical significance of impairment in the current findings
		Cocaine users met DSM-IV criteria for dependence (tested negative: (CUD−) N = 25 Controls : 25	CUD- participants reported having used cocaine majority of the past 90 days	Brain: CUD+ and CUD− ↔ NF modulation to loss CUD− ↔ NF modulation to win CUD+ ⟵↑ FN to unpredicted vs. predicted wins Controls ↑ ⟵ FN to unpredicted compared with unpredicted wins (intact + RPE) ↓ FN to unpredicted compared to predicted loses (intact - RPE)	Only one cognitive measure included

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; ACC, Anterior Cingulate Cortex; ASP, Antisocial Personality Disorder; AVI, anterovenral insular; BART, Balloon Analog Risk Task; BIS/BAS, Behavioral Inhibition Activation System; BIS II, Barratt Impulsivity Scale; CANTAB, Cambridge Neuropsychological Test Automated Battery; cdACC, caudal-dorsal Anterior Cingulate Cortex; COC-, Cocaine negative; COC+, Cocaine positive; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; dmPRC, dorsomedial prefrontal cortex; DLPFC, Dorsal lateral prefrontal cortex; ; DSM-III, Diagnostic and Statistical Manual of Mental Disorders 3rd Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4rd Edition; DSM-IV; EDT, Experimental Discounting Task; FN, Feedback Negativity; GM, Grey Matter; GPT, Grooved Pegboard Test h, hours; IDED, intradimensional/extradimensional; IQ, intelligence quotient; LRC, Lateral Prefrontal Cortex; M, Mean; mOFC, medial Orbital Frontal Cortex; MPFC, medial prefrontal cortex; NF, Negative Feedback; OFC, Orbitofrontal Cortex; PMC, Premotor Cortex; pre-SMA, presupplementary motor area; rACC, right Anterior Cingulate Cortex; rDLPC, right Dorsolateral Prefrontal Cortex; rMFG, right Medial Frontal Gyrus; rOFC; right Orbitofrontal cortex; ROI, Region of Interest; RPE, Reward Prediction Error; RVIP, Rapid Visual Information Processing Task; SD, Standard Deviation; SPSRQ, Sensitivity to Punishment and Severity to Reward Questionnaire; SS form V; Sensation Seeking Scale form V; STC, Superior Temporal Cortex; TC, Temporal Cortex; Unk; Unknown; VBM, Voxel-based morphometry; WAIS-R, Wechsler's adult intelligent scale-revised; WCST, Wisconsin card sorting test; WM, White Matter; WM-IT, Working Memory load inhibitory task; WMS, Wechsler Memory Scale.
Cognitive: ↓, decreased performance in cocaine users;↑, increased performance in cocaine users; ↔, no difference in performance between cocaine users and controls.
Brain activity: ↓, decreased activity in cocaine users; ↑, increased activity in cocaine users; ↔, no difference in activity between cocaine users and controls.

using MRI procedures combined with neuropsychological testing, in an effort to understand the impact of long-term cocaine use on cognitive functioning. Ersche et al. [84] examined self-report impulsivity, and performance on tasks assessing response inhibition and sustained-attention in cocaine abusers and non-drug-using controls. They also used MRI to compare structural brain changes occurring in the frontal striatal brain systems during test performance. These researchers found that the cocaine abusers reported more trait impulsivity and appetitive motivation than did the controls; however, when task performance was assessed, the cocaine group demonstrated an overall slowing of responses on the stop signal and sustained attention tasks. These findings are inconsistent with impulsive responding. In addition, researchers found that greater duration of cocaine abuse was associated with changes in gray matter volume in the basal ganglia and orbitofrontal, cingulate, insular, temporoparietal, and cerebellar cortices. These findings led investigators to speculate that cocaine use disorder is accompanied by a deficit in attentional processing caused by cocaine-induced structural changes in the frontostraital networks.

The findings of Ersche et al. [84] should be interpreted with the confines of several limitations. First, since brain images were collected at just one time-point for both groups, it is impossible to determine whether, as the authors claim "cocaine induced structural changes in cortical organization *cause* [*emphasis ours*] abnormalities of sustained attention and attentional control in cocaine-dependent individuals [84]." Since preexisting differences were not measured, it is unclear whether there were existing abnormalities prior to the onset of cocaine use. Second, the researchers did not control for the use of drugs other than cocaine. Several individuals in the cocaine group met the DSM-IV criteria for nicotine, alcohol, cannabis, and heroin dependences; some of which exert detrimental effects on cognitive performance. This makes it difficult to disentangle the impact of one specific form of drug use on cognitive performance. Additionally, the researchers omitted information on variables such as education and for other psychiatric disorders such as attention deficit hyperactivity disorder (ADHD) and anxiety disorder. Thus, it is disconcerting that these study results were interpreted as revealing pathology, when the differences found should have been assessed within the framework of a normative database.

4.4. Functional MRI studies investigating neuronal activity in abstinent cocaine abusers with cognitive testing included

Functional MRI (fMRI) has also been used to investigate long-term cocaine abusers. This imaging technique uses the blood's oxygen level in the brain as an indirect measure of neural activity, known as the blood oxygen level dependent signal. One advantage of fMRI over MRI is that it provides information about brain functioning and, more specifically, about how networks of brain structures collaborate to effect complex activities such as behavioral or cognitive tasks.

Kaufman et al. [5] employed event-related fMRI to capture brain activity in cocaine abusers and non-drug-using controls while both groups completed a Go/No-Go task. These researchers found that, during task performance, the cocaine abusers made significantly more errors of commission and omission and had less activity in the cingulate cortex as well as other cortical regions. Even though the cocaine abusers were older than the controls (mean age 37 vs. 30 years) and researchers administered only one measure assessing response inhibition, the researchers concluded that cocaine use disorder is accompanied by disruptions in cognitive control of behavior and by dysfunction in certain cortical structures. By contrast, some studies have reported no differences in behavior but have highlighted differences in fMRI results. For example, Castelluccio et al. [96] also employed fMRI and administered the Go/No-Go task to cocaine abusers and controls, and they found no differences between the groups. These researchers did, however, note that the cocaine abusers exhibited significantly greater activation in the cingulate and other cortical regions during their commission of false alarms. Such conflicted results make it difficult to draw conclusions about the impact of cocaine on inhibitory control, especially when methodologies and confounding limitations differ from one study to the next.

Table 2 summarizes fourteen fMRI studies investigating neural activity in abstinent cocaine users and individuals with cocaine use disorders. Nine studies administered only one cognitive measure to assess a domain [5,8,10,97–101,127], and eight studies did not control for the use of other psychoactive drugs [8,10,80,96,97,102,103,127]. Moreover, the vast majority (eleven out of fourteen) [8,10,96–98,100–104,127] of studies did not find significant differences between groups on cognitive measures, so based their conclusions solely on their fMRI findings.

Overall, the MRI literature is replete with misleading language with respect to brain pathology (e.g., "cocaine *causes abnormalities* [*emphasis ours*] in areas of the brain"), conflicting structural differences, methodological limitations, and a general tendency to suggest impairment in the absence of corroborating behavioral findings. All such drawbacks make it very difficult to contextualize the functional significance of the findings. Most of the fMRI method's conclusions are not made within the context of a normative range, which not only is problematic, but also often constitutes a sheer misinterpretation of what is or is not normal.

4.5. PET studies investigating brain metabolism in abstinent cocaine abusers with cognitive testing included

Because evidence of cocaine neurotoxicity in animals has been found in areas of the brain involved in cognitive functioning [105], some have speculated that long-term cocaine use by humans produces similar metabolic abnormalities [106].

Bolla et al. [107] employed PET and the Iowa gambling task to measure decision-making in 25-day abstinent cocaine abusers. In this highly cited study, researchers found no statistically significant differences between cocaine abusers and controls on task performance. However, PET data revealed that cocaine abusers showed greater activation during performance on the Iowa gambling task in the right OFC and less activation in the right DLPC and left MPFC compared to controls. The researchers concluded that cocaine abusers show persistent functional abnormalities in prefrontal neural networks involved in decision-making and that the effects are related to cocaine abuse. Their conclusion, however, is misleading. First, behavioral results did not support the imaging findings and second, brain metabolism was not assessed prior to cocaine abuse, thus the relationship to decision-making and cocaine abuse is unclear. One year later Bolla and colleagues employed PET and a modified-Stroop task to measure response inhibition and attention. Although cocaine abusers were significantly older than the control participants (36 vs. 30), they performed equally well on the modified-Stroop test. PET data extrapolated from the test performance revealed that, as compared to the controls, the cocaine users had less activity in the left anterior cingulate cortex and the right lateral prefrontal cortex and greater activity in the right anterior cingulate cortex, pointing to a conflict-related effect. It also must be noted that, in addition to the small sample size, for the duration of the study cocaine users were housed in an inpatient hospital for significantly longer than were the controls (23 vs. 3 days) The researchers concluded that, when it comes to assessing cognitive impairments, behavioral assays are less sensitive than is neuroimaging. One concern associated with these studies is that the investigators included *only one measure* to determine the degree of functioning within the domain of interest. Performance on multiple tasks, all of them assessing the same domains, should be evaluated before making any function-related claims because individual tasks may tap into slightly different components of the domain of interest. In other words, the measures must be functionally validated in advance; otherwise there may be a lack of construct validity, a possibility particularly of consequence in studies that utilize but a single task to measure a cognitive domain. It is vital that each

group be treated similarly in order to control for such possible confounds such as at-home sleep patterns and stress, and conversely, the stress of being confined to a hospital environment and its routines; for these can adversely affect test performance. In Bolla et al. [107,108] no differences were found between the two groups with respect to the cognitive tasks performance; the imaging differences were limited, and the cause and meaning of these differences were unclear. Thus, this case illustrates the propensity among researchers to construe brain differences as being pathological, even though in this study no differences in the cognitive measure were found between the groups. Although the cocaine users performed just as well as the controls, the researchers have assumed that all the participants performed within the normal age and education-matched range on the modified-Stroop task. However, it must be made clear that this was not the case. Furthermore, in order to determine the clinical implications of group performance, it is necessary to be able to make informed predictions about the performance of a particular group if participants' prior scores did not fall within the demographically matched normal range. Only then is it possible to draw meaningful conclusions about performance differences. Numerous studies that have observed differences between groups have provided no such comparative information, thereby making it difficult to determine the clinical importance of their findings.

Unlike Bolla et al. [108], Goldstein et al. [109] administered neuropsychological measures that generated age-adjusted scores (since level of performance varies across demographic variables such as age, not adjusting for these variables results in diminished predictive validity). These researchers sought to determine the severity of neuropsychological impairment in individuals with cocaine dependence and in non-drug-using controls. They did so by administering a neuropsychological battery assessing verbal knowledge, visual memory, verbal memory, attention, and executive functioning. They found that the cocaine-dependent individuals demonstrated mild cognitive impairment and that, as compared to the controls, they performed less well in the neuropsychological dimensions of the task. The researchers also compared the neurocognitive performance of the cocaine-dependent group with that of a group with alcohol dependence and found that the alcohol group was more impaired than was the cocaine group, based on neuropsychological measures. Using PET, they also looked at whether performance on the neuropsychological battery was associated with resting glucose metabolism in the brain. After statistically controlling for age and education, in both groups metabolism in the dorsolateral prefrontal cortex predicted visual and working memory factors and the anterior cingulate gyrus predicted attention and executive functioning. Relative to other psychopathological disorders such as schizophrenia, the severity of neuropsychological impairment in cocaine addiction was modest, but nevertheless, the authors warned against seeing a complete absence of neurocognitive deficits within the sphere of cocaine addiction.

Out of the three PET studies summarized in Table 2, two studies not match groups on age [108,109] and two did not find significant differences between groups on cognitive measures [107,108]. The clinical importance of both Bolla et al. [108] and Goldstein et al. [109] remains ambiguous. Both studies found that cocaine abusers exhibited a degree of cognitive impairment. While Bolla et al. [108] based their conclusions on PET findings, those of Goldstein et al. [109] were derived from a neuropsychological test battery. The studies also differed in sample size, number of tasks administered, and use or non-use of demographically adjusted scores. It is unclear what PET imaging tells us about the neurocognitive functioning of individuals with cocaine use disorder, given that findings are open to debate and that doubts persist as to whether metabolic changes in the brain are linked to a specific drug of abuse.

5. Discussion

Researchers investigating the effects of cocaine use on human cognitive functioning have employed various methodologies. While basic animal research has presented researchers with some valuable models, useful when they are investigating the effects of cocaine when it is administered under controlled conditions, limitations associated with these studies make it difficult to extrapolate to similar effects in humans. Nonetheless, studies combining neuroimaging and neuropsychological methods have considerably broadened the human laboratory data. As for the MRI and fMRI studies, imaging results invariably tend to take precedence over the behavioral data and to scant the latter when it does not corroborate the imaging findings. We have seen that some studies have been unable to replicate results, perhaps owing to several methodological limitations such as not controlling for age, education, and other drug use. The findings of PET studies remain unclear, as a result of conflicting behavioral data that show either no differences or only mild impairment in cocaine abusers compared to controls.

While there is, of course, no perfect study and all research requires follow-up for corroboration, similar difficulties of interpretation affect the literature comprised strictly of neuropsychological studies. As long as researchers continue to select only statistically significant comparisons, we can expect their estimates to be overstated. Poor performance on tests, however, should not immediately be construed as revealing deficits or impairments. There may be alternative explanations for poor performance (test anxiety, depression, lack of motivation), and all such factors underscore the need to control for confounding variables.

While researchers may not have the ability to control for some extraneous variables, it is critical that they attempt to match, or control groups on the three chief dependent variables (i.e., age, education, sex) and for drug use. For example, in several studies [5,99,100,110], the performance of older individuals with cocaine use disorder (~40 years) was compared with that of younger non-drug-using controls (~30 years), and this could have influenced the outcome. In the case of the Stroop test, for example, several researchers have found age-related decrements in their samples [111–114]. Rosselli et al. [111] studied 938 participants, aged 20–89 years, who completed an abbreviated Stroop color-naming task while a subset of 281 participants also completed card sorting, simple reaction time, and choice reaction time tasks. The researchers observed age-related increases in incongruent color-naming latency and in card-sorting perseverative errors. Their findings suggested that age differences in Stroop interference were attributable partially to a general slowing but also to age-related changes in such task-specific processes as inhibitory control. Some attribute age-related decline to processing speed and thus do not construe it along with evidence of specific decline when working such constructs as cognitive flexibility and control [115]. Klein et al. [94] reported that test duration differentially affects the performance of young and old participants. Many cognitive measures can be exhausting and onerous to participants, and that fact underscores the importance of employing test batteries with normative scores such as the NIH toolbox, for they are brief and convenient. These constitute a "common currency" among researchers, allowing for comparisons across a wide range of studies and populations [116].

Years of education have also been shown to be a variable that impacts cognitive performance. Sim et al. [86] assessed the performance of individuals with cocaine dependence and non-drug-using controls on measures of psychomotor speed, executive function and motor performance. They found that individuals with cocaine dependence demonstrated poorer performance on these measures compared to controls. However, it's important to note that the controls had higher levels of education, and the researchers did not control for the use of drugs other than cocaine (see Table 2), which may have influenced the outcome. In a study that investigated the validity of demographic adjustments on neuropsychological test performance, Vanderploeg et al. [117] found that younger or more educated subjects consistently performed better than did older or less educated subjects. Additionally, the researchers found that the use of demographically-adjusted neuropsychological

scores results in higher diagnostic classification accuracy than the use of non-adjusted scores [117]. Lastly, differences in neuropsychological test performance have been shown to be associated with sex [118]. For example, Rahman and Clarke [119] found that male recreational cocaine users performed better than female recreational cocaine users on visuospatial perception and category fluency, while females outperformed men on all verbal learning measures except immediate recall. Thus, demonstrating evidence for sex-related neurocognitive variations and the importance of sex-matched groups in addition to sex-adjusted normative scores.

Most neuropsychologists are unable to determine the premorbid level of cognitive functioning of cocaine abusers, the level reached before the drug was being abused, and thus they frame their comparisons around one time-point of drug abuse and another one year later. Instead, we suggest that test performance and cognitive functioning should be assessed within the context of participants' expected performance as predicted by their demographic characteristics. For some neuropsychologists the criterion for determining impairment is 1, 1.5, or 2 standard deviations below the mean of the normative sample. While a test score 1 standard deviation below the mean may not be statistically significant, it may nonetheless indicate impairment to some neuropsychologists, while others may choose to locate impairment within the range of 1.5 or 2 standard deviations [120]. Some researchers determine normality by generating T scores based upon a participant's demographic characteristics. Heaton et al. [118], for example, generated T scores based upon age and education level by using scores from the Halstead-Reitan battery, a set of neuropsychological tests used to assess the condition and functioning of the brain, and other tests as well. Using this method, any T score below 40 (greater than 1 standard deviation below the mean) represents impaired performance [118]. Establishing these important criteria of impairment will allow us to (a) speak more confidently about the clinical relevance of study findings and (b) more accurately characterize the cognitive functioning of individuals with cocaine use disorder.

Several meta-analyses investigating the effects of cocaine on cognitive functioning have come to be seen as virtually constituting a compendium of studies assessing the performance of cocaine users and non-drug-using controls on a battery of cognitive tasks. Nonetheless, while studies show per domain differences and no differences, and in some cases effect sizes of differences, they too rarely include any discussion of whether test scores fell within the normal range [21,34]. Rather, the literature is pervaded by sweeping conclusions such as this one: "the long-term effects of cocaine show a wide array of deteriorated cognitive functions, indicating that long-term cocaine use is characterized by a general impairment across functions, rather than by specific deficits" [21]. The data accrued by the studies highlighted in this review lend no support to that claim. Although executive function and working/verbal memory are the domains within which differences between cocaine abusers and non-drug-using controls have most consistently been detected, showing that a single critical value crosses the significance threshold is not sufficient to determine the impact of cocaine use on functioning. Quite simply, the mere existence of differences does not prove impairment. We must continually remind ourselves of the need to rigorously assess the practical and clinical significance of each new study's findings.

5.1. Implications

Over interpretations caused by a lack of methodological rigor can lead to beliefs about cocaine and its users that are not supported by the evidence. For example, some of those who approach this issue from a treatment perspective have suggested that individuals with cocaine use disorder are unable to benefit from cognitive behavioral therapy [121]. Such an assertion is unwarranted given the data from the studies reviewed here. This is especially so since numerous studies have shown that many cocaine abusers use drugs other than cocaine or have other psychiatric disorders in addition to cocaine use disorder. Such confounding factors make it difficult to elucidate the unique effect of cocaine use on individuals treated with cognitive behavioral therapy. Thus, it is imperative that, henceforth, cocaine users be more accurately characterized, thereby allowing us to develop wiser and scientifically better-attuned drug treatment programs and public policies.

Declaration of interest

The authors report no financial interests or any conflict of interests.

Acknowledgements

We thank Kaytee Turetsky and Christopher Medina-Kirchner for reading the manuscript and providing constructive comments.

References

[1] A. Hughes, M.R. Williams, R.N. Lipari, S. Van Horn, State estimates of past year cocaine use among young adults: 2014 and 2015, CBHSQ Rep. Substance Abuse and Mental Health Services Administration (US), Rockville (MD), 2013 Accessed 28 February, 2018 http://www.ncbi.nlm.nih.gov/books/NBK424783/.
[2] M.S. Shiels, N.D. Freedman, D. Thomas, A. Berrington de Gonzalez, Trends in U.S. drug overdose deaths in Non-Hispanic Black, Hispanic, and Non-Hispanic White Persons, 2000–2015, Ann. Intern. Med. 168 (2018) 453–455, http://dx.doi.org/10.7326/M17-1812.
[3] M.T. Fillmore, C.R. Rush, Impaired inhibitory control of behavior in chronic cocaine users, Drug Alcohol Depend. 66 (2002) 265–273, http://dx.doi.org/10.1016/S0376-8716(01)00206-X.
[4] R. Hester, Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity, J. Neurosci. 24 (2004) 11017–11022, http://dx.doi.org/10.1523/JNEUROSCI.3321-04.2004.
[5] J.N. Kaufman, T.J. Ross, E.A. Stein, H. Garavan, Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging, J. Neurosci. 23 (2003) 7839–7843.
[6] J.P. Caulkins, B. Kilmer, P.H. Reuter, G. Midgette, Cocaine's fall and marijuana's rise: questions and insights based on new estimates of consumption and expenditures in US drug markets, Addiction (Abingdon, Engl.) 110 (2015) 728–736, http://dx.doi.org/10.1111/add.12628.
[7] N. Albein-Urios, J.M. Martinez-González, Ó. Lozano, L. Clark, A. Verdejo-García, Comparison of impulsivity and working memory in cocaine addiction and pathological gambling: implications for cocaine-induced neurotoxicity, Drug Alcohol Depend. 126 (2012) 1–6, http://dx.doi.org/10.1016/j.drugalcdep.2012.03.008.
[8] J.-C. Bustamante, A. Barrós-Loscertales, N. Ventura-Campos, A. Sanjuán, J.-J. Llopis, M.-A. Parcet, C. Ávila, Right parietal hypoactivation in a cocaine-dependent group during a verbal working memory task, Brain Res. 1375 (2011) 111–119, http://dx.doi.org/10.1016/j.brainres.2010.12.042.
[9] M.J. Fernández-Serrano, J.C. Perales, L. Moreno-López, M. Pérez-García, A. Verdejo-García, Neuropsychological profiling of impulsivity and compulsivity in cocaine dependent individuals, Psychopharmacology (Berl.) 219 (2012) 673–683, http://dx.doi.org/10.1007/s00213-011-2485-z.
[10] D. Tomasi, N.D. Volkow, R. Wang, J.H. Carrillo, T. Maloney, N. Alia-Klein, P.A. Woicik, F. Telang, R.Z. Goldstein, Disrupted functional connectivity with dopaminergic midbrain in cocaine abusers, PLoS One 5 (2010) e10815, http://dx.doi.org/10.1371/journal.pone.0010815.
[11] K.I. Bolla, R. Rothman, J.L. Cadet, Dose-related neurobehavioral effects of chronic cocaine use, J. Neuropsychiatry Clin. Neurosci. 11 (1999) 361–369.
[12] S.L. Simon, C.P. Domier, T. Sim, K. Richardson, R.A. Rawson, W. Ling, Cognitive performance of current methamphetamine and cocaine abusers, J. Addict. Dis. 21 (2001) 61–74, http://dx.doi.org/10.1300/J069v21n01_06.
[13] K.H. Preller, L.M. Hulka, M. Vonmoos, D. Jenni, M.R. Baumgartner, E. Seifritz, I. Dziobek, B.B. Quednow, Impaired emotional empathy and related social network deficits in cocaine users: empathy and mentalizing in cocaine users, Addict. Biol. 19 (2014) 452–466, http://dx.doi.org/10.1111/adb.12070.
[14] L.M. Hulka, C. Eisenegger, K.H. Preller, M. Vonmoos, D. Jenni, K. Bendrick, M.R. Baumgartner, E. Seifritz, B.B. Quednow, Altered social and non-social decision-making in recreational and dependent cocaine users, Psychol. Med. 44 (2014) 1015–1028, http://dx.doi.org/10.1017/S0033291713001839.
[15] P.A. Woicik, C. Urban, N. Alia-Klein, A. Henry, T. Maloney, F. Telang, G.-J. Wang, N.D. Volkow, R.Z. Goldstein, A pattern of perseveration in cocaine addiction may reveal neurocognitive processes implicit in the Wisconsin Card Sorting Test, Neuropsychologia 49 (2011) 1660–1669, http://dx.doi.org/10.1016/j.neuropsychologia.2011.02.037.
[16] A. Bechara, Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective, Nat. Neurosci. 8 (2005) 1458–1463, http://dx.doi.org/10.1038/nn1584.
[17] S.L. Dolan, R.A. Martin, D.J. Rohsenow, Self-efficacy for cocaine abstinence: pretreatment correlates and relationship to outcomes, Addict. Behav. 33 (2008) 675–688, http://dx.doi.org/10.1016/j.addbeh.2007.12.001.
[18] E.A.A. van der Plas, E.A. Crone, W.P.M. van den Wildenberg, D. Tranel,

A. Bechara, Executive control deficits in substance-dependent individuals: a comparison of alcohol, cocaine, and methamphetamine and of men and women, J. Clin. Exp. Neuropsychol. 31 (2009) 706–719, http://dx.doi.org/10.1080/13803390802484797.
[19] E. Aharonovich, D.S. Hasin, A.C. Brooks, X. Liu, A. Bisaga, E.V. Nunes, Cognitive deficits predict low treatment retention in cocaine dependent patients, Drug Alcohol Depend. 81 (2006) 313–322, http://dx.doi.org/10.1016/j.drugalcdep.2005.08.003.
[20] N.P. Vadhan, C.L. Hart, M. Haney, W.G. van Gorp, R.W. Foltin, Decision-making in long-term cocaine users: effects of a cash monetary contingency on Gambling task performance, Drug Alcohol Depend. 102 (2009) 95–101, http://dx.doi.org/10.1016/j.drugalcdep.2009.02.003.
[21] D.B. Spronk, J.H.P. van Wel, J.G. Ramaekers, R.J. Verkes, Characterizing the cognitive effects of cocaine: a comprehensive review, Neurosci. Biobehav. Rev. 37 (2013) 1838–1859, http://dx.doi.org/10.1016/j.neubiorev.2013.07.003.
[22] S. Liu, S.D. Lane, J.M. Schmitz, A.J. Waters, K.A. Cunningham, F.G. Moeller, Relationship between attentional bias to cocaine-related stimuli and impulsivity in cocaine-dependent subjects, Am. J. Drug Alcohol Abuse 37 (2011) 117–122, http://dx.doi.org/10.3109/00952990.2010.543204.
[23] G. Schoenbaum, B. Setlow, Cocaine makes actions insensitive to outcomes but not extinction: implications for altered orbitofrontal–amygdalar function, Cereb. Cortex 15 (2005) 1162–1169, http://dx.doi.org/10.1093/cercor/bhh216.
[24] J.W. Dalley, K. Lääne, Y. Pena, D.E.H. Theobald, B.J. Everitt, T.W. Robbins, Attentional and motivational deficits in rats withdrawn from intravenous self-administration of cocaine or heroin, Psychopharmacology (Berl.) 182 (2005) 579–587, http://dx.doi.org/10.1007/s00213-005-0107-3.
[25] K.M. Kantak, T. Udo, F. Ugalde, C. Luzzo, N.D. Pietro, H.B. Eichenbaum, Influence of cocaine self-administration on learning related to prefrontal cortex or hippocampus functioning in rats, Psychopharmacology (Berl.) 181 (2005) 227–236, http://dx.doi.org/10.1007/s00213-005-2243-1.
[26] T.A. Stalnaker, M.R. Roesch, D.J. Calu, K.A. Burke, T. Singh, G. Schoenbaum, Neural correlates of inflexible behavior in the orbitofrontal-amygdalar circuit after cocaine exposure, Ann. N. Y. Acad. Sci. 1121 (2007) 598–609, http://dx.doi.org/10.1196/annals.1401.014.
[27] K.A. Burke, T.M. Franz, N. Gugsa, G. Schoenbaum, Prior cocaine exposure disrupts extinction of fear conditioning, Learn. Mem. 13 (2006) 416–421, http://dx.doi.org/10.1101/lm.216206.
[28] I.A. Mendez, K.S. Montgomery, C.L. LaSarge, N.W. Simon, J.L. Bizon, B. Setlow, Long-term effects of prior cocaine exposure on Morris water maze performance, Neurobiol. Learn. Mem. 89 (2008) 185–191, http://dx.doi.org/10.1016/j.nlm.2007.08.005.
[29] J.A. Crespo, J. Manzanares, J.M. Oliva, J. Corchero, T. Palomo, E. Ambrosio, Extinction of cocaine self-administration produces a differential time-related regulation of proenkephalin gene expression in rat brain, Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 25 (2001) 185–194, http://dx.doi.org/10.1016/S0893-133X(01)00221-4.
[30] E.A. Kiyatkin, P.L. Brown, Fluctuations in neural activity during cocaine self-administration: clues provided by brain thermorecording, Neuroscience 116 (2003) 525–538, http://dx.doi.org/10.1016/S0306-4522(02)00711-X.
[31] L. Lu, J.W. Grimm, Y. Shaham, B.T. Hope, Molecular neuroadaptations in the accumbens and ventral tegmental area during the first 90 days of forced abstinence from cocaine self-administration in rats, J. Neurochem. 85 (2003) 1604–1613, http://dx.doi.org/10.1046/j.1471-4159.2003.01824.x.
[32] P.W. Kalivas, X.-T. Hu, Exciting inhibition in psychostimulant addiction, Trends Neurosci. 29 (2006) 610–616, http://dx.doi.org/10.1016/j.tins.2006.08.008.
[33] D. Jovanovski, S. Erb, K.K. Zakzanis, Neurocognitive deficits in cocaine users: a quantitative review of the evidence, J. Clin. Exp. Neuropsychol. 27 (2005) 189–204, http://dx.doi.org/10.1080/13803390490515694.
[34] S. Potvin, K. Stavro, É. Rizkallah, J. Pelletier, Cocaine and cognition: a systematic quantitative review, J. Addict. Med. 8 (2014) 368–376, http://dx.doi.org/10.1097/ADM.0000000000000066.
[35] M.D. Wunderli, M. Vonmoos, S.M. Niedecker, L.M. Hulka, K.H. Preller, M.R. Baumgartner, T. Kraemer, E. Seifritz, M.P. Schaub, D. Eich-Höchli, B.B. Quednow, Cognitive and emotional impairments in adults with attention-deficit/hyperactivity disorder and cocaine use, Drug Alcohol Depend. 163 (2016) 92–99, http://dx.doi.org/10.1016/j.drugalcdep.2016.03.026.
[36] H.C. Breiter, R.L. Gollub, R.M. Weisskoff, D.N. Kennedy, N. Makris, J.D. Berke, J.M. Goodman, H.L. Kantor, D.R. Gastfriend, J.P. Riorden, R.T. Mathew, B.R. Rosen, S.E. Hyman, Acute effects of cocaine on human brain activity and emotion, Neuron 19 (1997) 591–611, http://dx.doi.org/10.1016/S0896-6273(00)80374-8.
[37] G.F. Koob, Drugs of abuse: anatomy, pharmacology and function of reward pathways, Trends Pharmacol. Sci. 13 (1992) 177–184, http://dx.doi.org/10.1016/0165-6147(92)90060-J.
[38] P.W. Kalivas, N.D. Volkow, The neural basis of addiction: a pathology of motivation and choice, Am. J. Psychiatry 162 (2005) 1403–1413, http://dx.doi.org/10.1176/appi.ajp.162.8.1403.
[39] G.F. Koob, M.L. Moal, Drug abuse: hedonic homeostatic dysregulation, Science 278 (1997) 52–58, http://dx.doi.org/10.1126/science.278.5335.52.
[40] N.D. Volkow, G.F. Koob, A.T. McLellan, Neurobiologic advances from the brain disease model of addiction, N. Engl. J. Med. 374 (2016) 363–371, http://dx.doi.org/10.1056/NEJMra1511480.
[41] J.-H. Baik, Dopamine signaling in reward-related behaviors, Front. Neural Circuits 7 (2013), http://dx.doi.org/10.3389/fncir.2013.00152.
[42] J.-M. Beaulieu, R.R. Gainetdinov, The physiology, signaling, and pharmacology of dopamine receptors, Pharmacol. Rev. 63 (2011) 182–217, http://dx.doi.org/10.1124/pr.110.002642.
[43] A.C. Dolphin, G protein modulation of voltage-gated calcium channels, Pharmacol. Rev. 55 (2003) 607–627, http://dx.doi.org/10.1124/pr.55.4.3.
[44] C. Gao, M.E. Wolf, Dopamine receptors regulate NMDA receptor surface expression in prefrontal cortex neurons, J. Neurochem. 106 (2008) 2489–2501, http://dx.doi.org/10.1111/j.1471-4159.2008.05597.x.
[45] A.E. Kisilevsky, S.J. Mulligan, C. Altier, M.C. Iftinca, D. Varela, C. Tai, L. Chen, S. Hameed, J. Hamid, B.A. MacVicar, G.W. Zamponi, D1 receptors physically interact with N-type calcium channels to regulate channel distribution and dendritic calcium Entry, Neuron 58 (2008) 557–570, http://dx.doi.org/10.1016/j.neuron.2008.03.002.
[46] X. Sun, Y. Zhao, M.E. Wolf, Dopamine receptor stimulation modulates AMPA receptor synaptic insertion in prefrontal cortex neurons, J. Neurosci. 25 (2005) 7342–7351, http://dx.doi.org/10.1523/JNEUROSCI.4603-04.2005.
[47] B.J. Venton, A.T. Seipel, P.E.M. Phillips, W.C. Wetsel, D. Gitler, P. Greengard, G.J. Augustine, R.M. Wightman, Cocaine increases dopamine release by mobilization of a synapsin-dependent reserve Pool, J. Neurosci. 26 (2006) 3206–3209, http://dx.doi.org/10.1523/JNEUROSCI.4901-04.2006.
[48] A.M. Barr, W.J. Panenka, G.W. MacEwan, A.E. Thornton, D.J. Lang, W.G. Honer, T. Lecomte, The need for speed: an update on methamphetamine addiction, J. Psychiatry Neurosci. Jpn. 31 (2006) 301–313.
[49] M.S. Kleven, W.L. Woolverton, L.S. Seiden, Lack of long-term monoamine depletions following repeated or continuous exposure to cocaine, Brain Res. Bull. 21 (1988) 233–237, http://dx.doi.org/10.1016/0361-9230(88)90236-5.
[50] S.Y. Yeh, E.B. De Souza, Lack of neurochemical evidence for neurotoxic effects of repeated cocaine administration in rats on brain monoamine neurons, Drug Alcohol Depend. 27 (1991) 51–61, http://dx.doi.org/10.1016/0376-8716(91)90086-E.
[51] S. Benmansour, S.M. Tejani-Butt, M. Hauptmann, D.J. Brunswick, Lack of effect of high-dose cocaine on monoamine uptake sites in rat brain measured by quantitative autoradiography, Psychopharmacology (Berl.) 106 (1992) 459–462, http://dx.doi.org/10.1007/BF02244815.
[52] J.H. Goodman, R.S. Sloviter, Cocaine neurotoxicity and altered neuropeptide Y immunoreactivity in the rat hippocampus; a silver degeneration and immunocytochemical study, Brain Res. 616 (1993) 263–272, http://dx.doi.org/10.1016/0006-8993(93)90217-B.
[53] L.J. Ryan, M.E. Martone, J.C. Linder, P.M. Groves, Cocaine, in contrast to D-amphetamine, does not cause axonal terminal degeneration in neostriatum and agranular frontal cortex of long-evans rats, Life Sci. 43 (1988) 1403–1409, http://dx.doi.org/10.1016/0024-3205(88)90307-4.
[54] G.D. Cappon, L.L. Morford, C.V. Vorhees, Enhancement of cocaine-induced hyperthermia fails to elicit neurotoxicity, Neurotoxicol. Teratol. 20 (1998) 531–535, http://dx.doi.org/10.1016/S0892-0362(98)00004-X.
[55] S. Stephans, B. Yamamoto, Methamphetamine pretreatment and the vulnerability of the striatum to methamphetamine neurotoxicity, Neuroscience 72 (1996) 593–600, http://dx.doi.org/10.1016/0306-4522(95)00587-0.
[56] A.M. Belcher, E.M. Feinstein, S.J. O'Dell, J.F. Marshall, Methamphetamine influences on recognition memory: comparison of escalating and single-day dosing regimens, Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 33 (2008) 1453–1463, http://dx.doi.org/10.1038/sj.npp.1301510.
[57] M.L. O'Neil, R. Kuczenski, D.S. Segal, A.K. Cho, G. Lacan, W.P. Melega, Escalating dose pretreatment induces pharmacodynamic and not pharmacokinetic tolerance to a subsequent high-dose methamphetamine binge, Synapse 60 (2006) 465–473, http://dx.doi.org/10.1002/syn.20320.
[58] D.S. Segal, R. Kuczenski, M.L. O'Neil, W.P. Melega, A.K. Cho, Escalating dose methamphetamine pretreatment alters the behavioral and neurochemical profiles associated with exposure to a high-dose methamphetamine binge, Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 28 (2003) 1730–1740, http://dx.doi.org/10.1038/sj.npp.1300247.
[59] L.A. Briand, S.B. Flagel, M.J. Garcia-Fuster, S.J. Watson, H. Akil, M. Sarter, T.E. Robinson, Persistent alterations in cognitive function and prefrontal dopamine D2 receptors following extended, but not limited, access to self-administered cocaine, Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 33 (2008) 2969–2980, http://dx.doi.org/10.1038/npp.2008.18.
[60] B.T. Chen, H.-J. Yau, C. Hatch, I. Kusumoto-Yoshida, S.L. Cho, F.W. Hopf, A. Bonci, Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking, Nature 496 (2013) 359–362, http://dx.doi.org/10.1038/nature12024.
[61] X.-B. Gao, G. Hermes, Neural plasticity in hypocretin neurons: the basis of hypocretinergic regulation of physiological and behavioral functions in animals, Front. Syst. Neurosci. 9 (2015), http://dx.doi.org/10.3389/fnsys.2015.00142.
[62] M. Li, P. Xu, Y. Xu, H. Teng, W. Tian, Q. Du, M. Zhao, Dynamic expression changes in the transcriptome of the prefrontal cortex after repeated exposure to cocaine in mice, Front. Pharmacol. 8 (2017), http://dx.doi.org/10.3389/fphar.2017.00142.
[63] L.B. Areal, A.L. Herlinger, F.S. Pelição, C. Martins-Silva, R.G.W. Pires, Crack cocaine inhalation induces schizophrenia-like symptoms and molecular alterations in mice prefrontal cortex, J. Psychiatr. Res. 91 (2017) 57–63, http://dx.doi.org/10.1016/j.jpsychires.2017.03.005.
[64] K. Rasakham, H.D. Schmidt, K. Kay, M.N. Huizenga, N. Calcagno, R.C. Pierce, T.L. Spires-Jones, G. Sadri-Vakili, Synapse density and dendritic complexity are reduced in the prefrontal cortex following seven days of forced abstinence from cocaine self-administration, PLoS One 9 (2014) e102524, , http://dx.doi.org/10.1371/journal.pone.0102524.
[65] O. George, C.D. Mandyam, S. Wee, G.F. Koob, Extended access to cocaine self-administration produces long-lasting prefrontal cortex-dependent working memory impairments, Neuropsychopharmacol. Off. Publ. Am. Coll.

Neuropsychopharmacol. 33 (2008) 2474–2482, http://dx.doi.org/10.1038/sj.npp.1301626.
[66] M. Muriach, R. López-Pedrajas, J.M. Barcia, M.V. Sanchez-Villarejo, I. Almansa, F.J. Romero, Cocaine causes memory and learning impairments in rats: involvement of nuclear factor kappa B and oxidative stress, and prevention by topiramate, J. Neurochem. 114 (2010) 675–684, http://dx.doi.org/10.1111/j.1471-4159.2010.06794.x.
[67] T.A. Stalnaker, Y. Takahashi, M.R. Roesch, G. Schoenbaum, Neural substrates of cognitive inflexibility after chronic cocaine exposure, Neuropharmacology 56 (2009) 63–72, http://dx.doi.org/10.1016/j.neuropharm.2008.07.019.
[68] T.A. Stalnaker, M.R. Roesch, T.M. Franz, K.A. Burke, G. Schoenbaum, Abnormal associative encoding in orbitofrontal neurons in cocaine-experienced rats during decision-making, Eur. J. Neurosci. 24 (2006) 2643–2653, http://dx.doi.org/10.1111/j.1460-9568.2006.05128.x.
[69] M. Gossop, P. Griffiths, B. Powis, J. Strang, Cocaine: patterns of use, route of administration, and severity of dependence, Br. J. Psychiatry 164 (1994) 660–664, http://dx.doi.org/10.1192/bjp.164.5.660.
[70] S.I. Dworkin, S. Mirkis, J.E. Smith, Response-dependent versus response-independent presentation of cocaine: differences in the lethal effects of the drug, Psychopharmacology (Berl.) 117 (1995) 262–266.
[71] S.E. Hemby, C. Co, T.R. Koves, J.E. Smith, S.I. Dworkin, Differences in extracellular dopamine concentrations in the nucleus accumbens during response-dependent and response-independent cocaine administration in the rat, Psychopharmacology (Berl.) 133 (1997) 7–16.
[72] J.N. Porter, A.S. Olsen, K. Gurnsey, B.P. Dugan, H.P. Jedema, C.W. Bradberry, Chronic cocaine self-administration in rhesus monkeys: impact on associative learning, cognitive control, and working memory, J. Neurosci. 31 (2011) 4926–4934, http://dx.doi.org/10.1523/JNEUROSCI.5426-10.2011.
[73] J.N. Porter, K. Gurnsey, H.P. Jedema, C.W. Bradberry, Latent vulnerability in cognitive performance following chronic cocaine self-administration in rhesus monkeys, Psychopharmacology (Berl.) 226 (2013) 139–146, http://dx.doi.org/10.1007/s00213-012-2903-x.
[74] J.N. Porter, D. Minhas, B.J. Lopresti, J.C. Price, C.W. Bradberry, Altered cerebellar and prefrontal cortex function in rhesus monkeys that previously self-administered cocaine, Psychopharmacology (Berl.) 231 (2014) 4211–4218, http://dx.doi.org/10.1007/s00213-014-3560-z.
[75] M.J. Fernández-Serrano, M. Pérez-García, A. Verdejo-García, What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? Neurosci. Biobehav. Rev. 35 (2011) 377–406, http://dx.doi.org/10.1016/j.neubiorev.2010.04.008.
[76] L.S. Colzato, W.P.M. van den Wildenberg, N.C. van Wouwe, M.M. Pannebakker, B. Hommel, Dopamine and inhibitory action control: evidence from spontaneous eye blink rates, Exp. Brain Res. 196 (2009) 467–474, http://dx.doi.org/10.1007/s00221-009-1862-x.
[77] S.J. Moeller, T. Maloney, M.A. Parvaz, N. Alia-Klein, P.A. Woicik, F. Telang, G.-J. Wang, N.D. Volkow, R.Z. Goldstein, Impaired insight in cocaine addiction: laboratory evidence and effects on cocaine-seeking behaviour, Brain 133 (2010) 1484–1493, http://dx.doi.org/10.1093/brain/awq066.
[78] L.G. De Oliveira, L.P. Barroso, C.M. Silveira, Z.V.D.M. Sanchez, J. De Carvalho Ponce, L.J. Vaz, S.A. Nappo, Neuropsychological assessment of current and past crack cocaine users, Subst. Use Misuse 44 (2009) 1941–1957, http://dx.doi.org/10.3109/10826080902848897.
[79] K.H. Preller, N. Ingold, L.M. Hulka, M. Vonmoos, D. Jenni, M.R. Baumgartner, F.X. Vollenweider, B.B. Quednow, Increased sensorimotor gating in recreational and dependent cocaine users is modulated by craving and attention-deficit/hyperactivity disorder symptoms, Biol. Psychiatry 73 (2013) 225–234, http://dx.doi.org/10.1016/j.biopsych.2012.08.003.
[80] K.H. Preller, M. Herdener, L. Schilbach, P. Stampfli, L.M. Hulka, M. Vonmoos, N. Ingold, K. Vogeley, P.N. Tobler, E. Seifritz, B.B. Quednow, Functional changes of the reward system underlie blunted response to social gaze in cocaine users, Proc. Natl. Acad. Sci. 111 (2014) 2842–2847, http://dx.doi.org/10.1073/pnas.1317090111.
[81] L.S. Colzato, W.P.M. van den Wildenberg, B. Hommel, Impaired inhibitory control in recreational cocaine users, PLoS One 2 (2007) e1143, http://dx.doi.org/10.1371/journal.pone.0001143.
[82] H.C. Fox, E.D. Jackson, R. Sinha, Elevated cortisol and learning and memory deficits in cocaine dependent individuals: relationship to relapse outcomes, Psychoneuroendocrinology 34 (2009) 1198–1207, http://dx.doi.org/10.1016/j.psyneuen.2009.03.007.
[83] C.C. Streeter, D.B. Terhune, T.H. Whitfield, S. Gruber, O. Sarid-Segal, M.M. Silveri, G. Tzilos, M. Afshar, E.D. Rouse, H. Tian, et al., Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals, Neuropsychopharmacology 33 (2008) 827–836.
[84] K.D. Ersche, A. Barnes, P.S. Jones, S. Morein-Zamir, T.W. Robbins, E.T. Bullmore, Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence, Brain 134 (2011) 2013–2024, http://dx.doi.org/10.1093/brain/awr138.
[85] C.A. Hanlon, D.L. Dufault, M.J. Wesley, L.J. Porrino, Elevated gray and white matter densities in cocaine abstainers compared to current users, Psychopharmacology (Berl.) 218 (2011) 681–692, http://dx.doi.org/10.1007/s00213-011-2360-y.
[86] M.E. Sim, I.K. Lyoo, C.C. Streeter, J. Covell, O. Sarid-Segal, D.A. Ciraulo, M.J. Kim, M.J. Kaufman, D.A. Yurgelun-Todd, P.F. Renshaw, Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects, Neuropsychopharmacology 32 (2007) 2229–2237.
[87] C.G. Connolly, R.P. Bell, J.J. Foxe, H. Garavan, Dissociated grey matter changes with prolonged addiction and extended abstinence in cocaine users, PLoS One 8 (2013) e59645, , http://dx.doi.org/10.1371/journal.pone.0059645.
[88] C.L. Crunelle, A.M. Kaag, G. van Wingen, H.E. van den Munkhof, J.R. Homberg, L. Reneman, W. van den Brink, Reduced frontal brain volume in non-treatment-seeking cocaine-dependent individuals: exploring the role of impulsivity, depression, and smoking, Front. Hum. Neurosci. 8 (2014), http://dx.doi.org/10.3389/fnhum.2014.00007.
[89] T.R. Franklin, P.D. Acton, J.A. Maldjian, J.D. Gray, J.R. Croft, C.A. Dackis, C.P. O'Brien, A.R. Childress, Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients, Biol. Psychiatry 51 (2002) 134–142.
[90] J.A. Matochik, E.D. London, D.A. Eldreth, J.-L. Cadet, K.I. Bolla, Frontal cortical tissue composition in abstinent cocaine abusers: a magnetic resonance imaging study, NeuroImage 19 (2003) 1095–1102, http://dx.doi.org/10.1016/S1053-8119(03)00244-1.
[91] G. Bartzokis, M. Beckson, P.H. Lu, N. Edwards, P. Bridge, J. Mintz, Brain maturation may be arrested in chronic cocaine addicts, Biol. Psychiatry 51 (2002) 605–611.
[92] E. Bora, A. Fornito, C. Pantelis, M. Yücel, Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies, J. Affect. Disord. 138 (2012) 9–18, http://dx.doi.org/10.1016/j.jad.2011.03.049.
[93] S.S. Cho, G. Pellecchia, K. Aminian, N. Ray, B. Segura, I. Obeso, A.P. Strafella, Morphometric correlation of impulsivity in medial prefrontal cortex, Brain Topogr. 26 (2013) 479–487, http://dx.doi.org/10.1007/s10548-012-0270-x.
[94] N. Alia-Klein, M.A. Parvaz, P.A. Woicik, A.B. Konova, T. Maloney, E. Shumay, R. Wang, F. Telang, A. Biegon, G.-J. Wang, J.S. Fowler, D. Tomasi, N.D. Volkow, R.Z. Goldstein, Gene × disease interaction on orbitofrontal gray matter in cocaine addiction, Arch. Gen. Psychiatry 68 (2011) 283–294, http://dx.doi.org/10.1001/archgenpsychiatry.2011.10.
[95] X. Zhang, B.J. Salmeron, T.J. Ross, X. Geng, Y. Yang, E.A. Stein, Factors underlying prefrontal and insula structural alterations in smokers, NeuroImage 54 (2011) 42–48, http://dx.doi.org/10.1016/j.neuroimage.2010.08.008.
[96] B.C. Castelluccio, S.A. Meda, C.E. Muska, M.C. Stevens, G.D. Pearlson, Error processing in current and former cocaine users, Brain Imaging Behav. 8 (2014) 87–96, http://dx.doi.org/10.1007/s11682-013-9247-y.
[97] R.P. Bell, J.J. Foxe, L.A. Ross, H. Garavan, Intact inhibitory control processes in abstinent drug abusers (I): a functional neuroimaging study in former cocaine addicts, Neuropharmacology 82 (2014) 143–150, http://dx.doi.org/10.1016/j.neuropharm.2013.02.018.
[98] R.Z. Goldstein, D. Tomasi, S. Rajaram, L.A. Cottone, L. Zhang, T. Maloney, F. Telang, N. Alia-Klein, N.D. Volkow, Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction, Neuroscience 144 (2007) 1153–1159, http://dx.doi.org/10.1016/j.neuroscience.2006.11.024.
[99] R. Hester, H. Garavan, Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity, J. Neurosci. 24 (2004) 11017–11022, http://dx.doi.org/10.1523/JNEUROSCI.3321-04.2004.
[100] C.R. Li, C. Huang, P. Yan, Z. Bhagwagar, V. Milivojevic, R. Sinha, Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men, Neuropsychopharmacology 33 (2008) 1798–1806.
[101] S. Morein-Zamir, P. Simon Jones, E.T. Bullmore, T.W. Robbins, K.D. Ersche, Take it or leave it: prefrontal control in recreational cocaine users, Transl. Psychiatry 5 (2015) e582, http://dx.doi.org/10.1038/tp.2015.80.
[102] A.R. Mayer, C.E. Wilcox, T.M. Teshiba, J.M. Ling, Z. Yang, Hyperactivation of the cognitive control network in cocaine use disorders during a multisensory Stroop task, Drug Alcohol Depend. 133 (2013) 235–241, http://dx.doi.org/10.1016/j.drugalcdep.2013.04.029.
[103] A. Kübler, K. Murphy, H. Garavan, Cocaine dependence and attention switching within and between verbal and visuospatial working memory, Eur. J. Neurosci. 21 (2005) 1984–1992, http://dx.doi.org/10.1111/j.1460-9568.2005.04027.x.
[104] A. Verdejo-Garcia, O. Contreras-Rodríguez, F. Fonseca, A. Cuenca, C. Soriano-Mas, J. Rodriguez, R. Pardo-Lozano, L. Blanco-Hinojo, S. de Sola Llopis, M. Farré, M. Torrens, J. Pujol, R. de la Torre, Functional alteration in frontolimbic systems relevant to moral judgment in cocaine-dependent subjects, Addict. Biol. 19 (2014) 272–281, http://dx.doi.org/10.1111/j.1369-1600.2012.00472.x.
[105] J.F. Marshall, A.M. Belcher, E.M. Feinstein, S.J. O'Dell, Methamphetamine-induced neural and cognitive changes in rodents, Addict. Abingdon Engl. 102 (Suppl. 1) (2007) 61–69, http://dx.doi.org/10.1111/j.1360-0443.2006.01780.x.
[106] P. Seeman, B. Madras, Imaging of the Human Brain in Health and Disease, Elsevier, 2013.
[107] K. Bolla, D. Eldreth, E. London, K. Kiehl, M. Mouratidis, C. Contoreggi, J. Matochik, V. Kurian, J. Cadet, A. Kimes, F. Funderburk, M. Ernst, Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task, NeuroImage 19 (2003) 1085–1094, http://dx.doi.org/10.1016/S1053-8119(03)00113-7.
[108] K. Bolla, M. Ernst, K. Kiehl, M. Mouratidis, D. Eldreth, C. Contoreggi, J. Matochik, V. Kurian, J. Cadet, A. Kimes, F. Funderburk, E. London, Prefrontal cortical dysfunction in abstinent cocaine abusers, J. Neuropsychiatry Clin. Neurosci. 16 (2004) 456–464, http://dx.doi.org/10.1176/jnp.16.4.456.
[109] R.Z. Goldstein, A.C. Leskovjan, A.L. Hoff, R. Hitzemann, F. Bashan, S.S. Khalsa, G.-J. Wang, J.S. Fowler, N.D. Volkow, Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex, Neuropsychologia 42 (2004) 1447–1458, http://dx.doi.org/10.1016/j.neuropsychologia.2004.04.002.
[110] D.C. Gooding, S. Burroughs, N.N. Boutros, Attentional deficits in cocaine-dependent patients: converging behavioral and electrophysiological evidence, Psychiatry Res. 160 (2008) 145–154, http://dx.doi.org/10.1016/j.psychres.2007.

11.019.
[111] M. Rosselli, A. Ardila, M.N. Santisi, M.D.R. Arecco, J. Salvatierra, A. Conde, B. Lenis, Stroop effect in Spanish–English bilinguals, J. Int. Neuropsychol. Soc. 8 (2002) 819–827.
[112] E. Strauss, E.M.S. Sherman, O. Spreen, A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary, Oxford University Press, 2006.
[113] E.V. Sullivan, A. Pfefferbaum, E. Adalsteinsson, G.E. Swan, D. Carmelli, Differential rates of regional brain change in callosal and ventricular size: a 4-year longitudinal MRI study of elderly men, Cereb. Cortex 12 (2002) 438–445, http://dx.doi.org/10.1093/cercor/12.4.438.
[114] N.R. Swerdlow, J. Paulsen, D.L. Braff, N. Butters, M.A. Geyer, M.R. Swenson, Impaired prepulse inhibition of acoustic and tactile startle response in patients with Huntington's disease, J. Neurol. Neurosurg. Psychiatry 58 (1995) 192–200, http://dx.doi.org/10.1136/jnnp.58.2.192.
[115] B. Uttl, P. Graf, Color-Word Stroop test performance across the adult life span, J. Clin. Exp. Neuropsychol. 19 (1997) 405–420, http://dx.doi.org/10.1080/01688639708403869.
[116] S. Weintraub, S.S. Dikmen, R.K. Heaton, D.S. Tulsky, P.D. Zelazo, P.J. Bauer, N.E. Carlozzi, J. Slotkin, D. Blitz, K. Wallner-Allen, et al., Cognition assessment using the NIH Toolbox, Neurology 80 (2013) S54–S64.
[117] R.D. Vanderploeg, B.N. Axelrod, M. Sherer, J. Scott, R.L. Adams, The importance of demographic adjustments on neuropsychological test performance: a response to reitan and wolf son (1995), Clin. Neuropsychol. 11 (1997) 210–217, http://dx.doi.org/10.1080/13854049708407054.
[118] R.K. Heaton, I. Grant, C.G. Matthews, Differences in neuropsychological test performance associated with age, education, and sex, Neuropsychol. Assess. Neuropsychiatr. Disord. (1986) 100–120.
[119] Q. Rahman, C.D. Clarke, Sex differences in neurocognitive functioning among abstinent recreational cocaine users, Psychopharmacology (Berl.) 181 (2005) 374–380, http://dx.doi.org/10.1007/s00213-005-2257-8.
[120] M.D. Lezak, Neuropsychological Assessment, Oxford University Press, 2004.
[121] E. Aharonovich, Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment, Drug Alcohol Depend. 71 (2003) 207–211, http://dx.doi.org/10.1016/S0376-8716(03)00092-9.
[122] P.J. Cunha, A. Bechara, A.G. de Andrade, S. Nicastri, Decision-making deficits linked to real-life social dysfunction in crack cocaine-dependent individuals: decision making in cocaine-dependent individuals, Am. J. Addict. 20 (2011) 78–86, http://dx.doi.org/10.1111/j.1521-0391.2010.00097.x.
[123] R. Sellaro, B. Hommel, L.S. Colzato, Increased response conflict in recreational cocaine polydrug users, Exp. Brain Res. 232 (2014) 113–119, http://dx.doi.org/10.1007/s00221-013-3724-9.
[124] K. Soar, C. Mason, A. Potton, L. Dawkins, Neuropsychological effects associated with recreational cocaine use, Psychopharmacology (Berl.) 222 (2012) 633–643, http://dx.doi.org/10.1007/s00213-012-2666-4.
[125] M.T. Fillmore, C.R. Rush, Impaired inhibitory control of behavior in chronic cocaine users, Drug Alcohol Depend. 66 (2002) 265–273.
[126] M. Reske, C.A. Eidt, D.C. Delis, M.P. Paulus, Nondependent stimulant users of cocaine and prescription amphetamines show verbal learning and memory deficits, Biol. Psychiatry 68 (2010) 762–769, http://dx.doi.org/10.1016/j.biopsych.2010.04.021.
[127] A. Barrós-Loscertales, J.-C. Bustamante, N. Ventura-Campos, J.-J. Llopis, M.-A. Parcet, C. Ávila, Lower activation in the right frontoparietal network during a counting Stroop task in a cocaine-dependent group, Psychiatry Res. Neuroimaging 194 (2011) 111–118, http://dx.doi.org/10.1016/j.pscychresns.2011.05.001.
[128] M.A. Parvaz, A.B. Konova, G.H. Proudfit, J.P. Dunning, P. Malaker, S.J. Moeller, T. Maloney, N. Alia-Klein, R.Z. Goldstein, Impaired neural response to negative prediction errors in cocaine addiction, J. Neurosci. 35 (2015) 1872–1879, http://dx.doi.org/10.1523/JNEUROSCI.2777-14.2015.
[129] M. Vonmoos, L.M. Hulka, K.H. Preller, D. Jenni, M.R. Baumgartner, R. Stohler, K.I. Bolla, B.B. Quednow, Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset, Br. J. Psychiatry 203 (2013) 35–43, http://dx.doi.org/10.1192/bjp.bp.112.118091.