Impulsivity in cocaine-dependent individuals with and without attention-deficit/ hyperactivity disorder

Abstract

Background: Cocaine-dependent individuals (CDI) display increased impulsivity. Despite its multi-factorial nature however, most studies in CDI have treated impulsivity monolithically. Moreover, the impact of attention-deficit/hyperactivity disorder (ADHD) has often not been taken into account. This study investigates whether CDI+ADHD differ from CDI without an ADHD diagnosis and healthy controls (HC) on several impulsivity measures. **Methods**: 34 CDI, 25 CDI+ADHD and 28 HC participated in this study. Trait impulsivity was assessed with the motor, attentional and non-planning subscales of the Barratt Impulsiveness Scale (BIS-11). Neurocognitive dimensions of impulsivity were examined with the stop signal task (SST), delay discounting task (DDT) and information sampling task (IST). **Results**: Relative to HC, both CDI and CDI+ADHD scored higher on all BIS-11 subscales, required more time to inhibit their responses (SST) and sampled less information before making a decision (IST). Greater discounting of delayed rewards (DDT) was only found among CDI+ADHD. Compared to CDI without ADHD, CDI+ADHD scored higher on the BIS-11 non-planning and total scale and showed higher discounting rates. **Conclusion**: CDI score higher on several indices of impulsivity relative to HC, regardless of whether they have concomitant ADHD. CDI+ADHD are specifically characterized by a lack of future orientation compared to CDI without ADHD.

1. Introduction

Impulsivity is among the most common diagnostic criteria in the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) [1]. Although the construct has been predominantly approached from a personality perspective (i.e., trait impulsivity) [2,3], growing scientific interest has been noted for impulsivity in neurocognitive research [4]. At a neurocognitive level, a distinction is often made between two types of impulsivity; impulsive action and impulsive choice [5]. *Impulsive action* refers to failures to withhold/suppress inappropriate/prepotent actions, thus reflecting poor response inhibition [5,6]. *Impulsive choice* on the other hand, refers to impulsive decisions, often resulting from a distorted evaluation of delayed consequences. Delay discounting for instance, occurs when the subjective value of an outcome decreases because its delivery is delayed and is typically indexed by an individual's preference for smaller immediate rewards relative to larger delayed rewards. Another often-overlooked aspect of impulsive choice, reflection impulsivity, refers to the tendency not to collect and evaluate enough information before making complex decisions [7]. Importantly, the distinction between impulsive action and impulsive choice has been justified by neurobiological evidence supporting distinct cortico-striatal substrates underlying both dimensions of impulsivity [8].

Impulsivity is a hallmark characteristic of substance use disorders (SUDs) in general, and of cocaine dependence in particular [9]. Over the years, several studies have shown that cocaine-dependent individuals (CDI) demonstrate notable deficits on tasks indexing aspects of impulsive action and impulsive choice. On laboratory paradigms of motor inhibition for instance, chronic cocaine users typically display a lower probability of inhibiting their responses and require more time to inhibit their responses to stop signals compared to healthy controls (HC) [10]. In addition, CDI have been found to discount delayed monetary rewards more steeply than do non-drug-using controls, suggesting higher levels of impulsive choice in this group [11,12,13]. Notably, recent studies have established the clinical relevance of impulsivity in substance-dependent individuals. In particular, elevated levels of impulsive action and choice at treatment onset have been found to predict poor addiction treatment outcomes [14,15]. For example, higher levels of impulsive choice in CDI were recently identified as a significant predictor of premature drop-out from treatment in a therapeutic community [16]. These and other findings suggest that treatment outcomes for CDI may be improved by targeting impulsivity.

Whereas the relationship between cocaine dependence and impulsivity is rarely disputed, impulsivity research in substance-dependent individuals in general and CDI specifically has historically been slowed due to the absence of a uniformly agreed-upon definition of the construct impulsivity. As noted previously, there is substantial empirical evidence indicating that impulsivity is a multi-factorial construct comprised of several related components [17,18,19,20]. In addition, these different components of impulsivity appear to recruit different brain circuitries and may be susceptible to diverse pharmacological influences [21]. Although these findings suggest that elucidating which impulsivity aspects are more relevant to cocaine dependence than others may have important treatment implications, relatively little research has evaluated various aspects of impulsivity in CDI simultaneously. Rather, most studies have been conducted in separate groups, each performing impulsivity paradigms targeting impulsive action or impulsive choice independently. Whereas these studies demonstrate that cocaine dependence is associated with both impulsive action [11] and

impulsive choice [11,12], direct comparisons should be interpreted with caution because of major differences in the sample characteristics of these studies (e.g., age, clinical vs. general population, duration of cocaine use, cocaine use severity, etc). In addition, most previous studies in cocaine users have not taken into account the effects of other disorders that are known to adversely affect impulsivity in a fashion similar to cocaine addiction. Indeed, trait impulsivity and impairments in impulsive action and impulsive choice are not specific to cocaine dependence but have been considered as risk factors common to all externalizing disorders, including bipolar, antisocial and borderline personality disorders [22,23]. High impulsivity is also considered a core feature of attention deficit/hyperactivity disorder (ADHD) [5,24,25,26,27,28,29], a developmental disorder that frequently co-occurs with cocaine dependence [30]. Indeed, estimates of co-morbidity between cocaine dependence and ADHD in addiction treatment settings typically range from 10% to 35% [31,32,33,34]. Given the high prevalence of ADHD in chronic cocaine users, ADHD might be a significant confounding factor when examining neurocognition in general and impulsivity in particular among CDI. It might be questioned for instance whether higher levels of impulsive action and impulsive choice in CDI are specifically associated with the presence of a comorbid ADHD diagnosis. Alternatively, ADHD may have an additive effect on impulsivity in CDI. In support of the latter hypothesis, a study in gamblers found that the comorbidity of ADHD and problem gambling was associated with higher trait impulsivity relative to problem gambling without ADHD [35]. As both impulsivity as well as the presence of ADHD among CDI have been found to predict worse addiction treatment outcomes [15,16,36,37,38], elucidating the specific impulsivity profile of CDI with ADHD may be of significant clinical relevance.

With the present study, we sought to investigate multiple indices of impulsivity among a sample of CDI and explore the effects of ADHD on impulsivity in this group. In accordance with the multi-factorial nature of impulsivity, three neurocognitive tasks indexing dissociable dimensions of impulsivity and a personality questionnaire measuring three different components of trait impulsivity were administered to a group of CDI, CDI+ADHD and HC. Both clinical groups were expected to show enhanced impulsivity relative to non-drug-using controls. Since impulsivity is one of the hallmarks of ADHD, our second hypothesis was that CDI with an ADHD diagnosis would present more pronounced deficits on several indices of impulsivity when compared to CDI without ADHD.

2. Methods

2.1. Setting and Participants

A total of 87 individuals participated in this study. Fifty-nine of these were CDI, who were all recruited from inpatient detoxification programs. All centers required complete abstinence from drugs and alcohol, with the exception of caffeine and nicotine. Aside from scheduled activities (e.g., group activities such as physical exercise, physician visits), residents were not permitted to leave the center grounds during treatment. Regular drug testing was further provided and any substance use was grounds for dismissal from the detoxification center. Based on a screening questionnaire and diagnostic interview (see 2.2. Assessments), thirty-four were classified as CDI without ADHD, and 25 were classified as CDI with an ADHD diagnosis. None of the participants in the latter group were being treated with psycho-stimulants at the time of assessment. Residents were approached for participation

by the staff members within the first 4 days of their arrival at the detoxification center. In order to participate in the current study, individuals had to meet the DSM-IV criteria for cocaine dependence at the time of admission to the treatment program and report cocaine as their primary substance of abuse. Individuals were excluded if they had (1) past or current major DSM diagnosis of psychotic disorders; (2) a history of neurological condition, such as strokes, intracranial hemorrhages and/or head injuries with loss of consciousness for longer than 30 min; (3) an intellectual quotient (IQ) lower than 70 and; (4) insufficient comprehension of the Dutch language to understand test instructions. Eligible participants were interviewed and tested within the first week from starting treatment (range 3–8 days). All CDI had a minimum of three days of abstinence (range = 3-60 days, mean = 12.62 days, SD = 12.01) at the time of assessment. Trait impulsivity scores and neurocognitive performance of the CDI were compared to a control group of 28 healthy individuals, who were volunteers, recruited by word of mouth from the community. The exclusion criteria for the control group were: (1) meeting DSM-IV criteria for any psychoactive substance dependence other than nicotine; (2) having a positive ADHD interview and (3) the above-mentioned exclusion criteria for the CDI. Ethical approval for the study was granted by the Ethical Review Board of the Faculty of Psychology and Educational Sciences at Ghent University.

2.2. Assessments

2.2.1. Background and drug use characteristics

A demographic form was used to collect basic demographic information (e.g., age, gender, education). Information regarding drug use, including the presence of poly-drug use (i.e., concomitant or consecutive use of various licit or illicit drugs, with the exclusion of pharmacological agents), was assessed using a Dutch translation of the European version of the *Addiction Severity Index* (ASI), a semi-structured clinical assessment interview [39,40]. The psychometric properties of the ASI are well established with strong retest reliability and concurrent, predictive, and discriminate validities [41]. Additional information about the frequency and duration of drug use was collected using the *Interview for Research on Addictive Behavior* [42]. To make a timesaving but accurate estimation of the current intellectual abilities, IQ was estimated using two subtests of the *Wechsler Adult Intelligence Scale*, third edition [43]: matrix reasoning and information. This dyadic short form has been found to be appropriate for obtaining a good estimate of full scale IQ in a psychiatric sample: the estimated IQ derived from the administration of this short form has a correlation of .92 with the full scale IQ [44].

2.2.2. ADHD assessment

For the screening of ADHD in the CDI, the *ADHD Rating Scale* (ARS) [45] was used. The ARS is a self-report rating scale, which includes all the 18 DSM-IV items on inattention, hyperactivity, and impulsivity. The questionnaire screens for the presence of symptoms in both childhood and adulthood. In the Dutch version of the ARS, five DSM-IV items containing double statements were reformulated in two statements, so that the total number of items was 2 x 23. In the analyses, the 23 item scores were recalculated to the original 18 DSM-IV items. Each of the 46 items is scored on a 4-point likert scale ranging from 0 (rarely or never) to 3 (very often). A symptom was considered as present if the answer

given to the item was ‘often’ or ‘very often’ (score of 2 or 3). Whereas a less stringent cut-off score of 4 DSM-IV criteria has been recommended for adults [45,46], we used the more stringent cut-off score of 6 symptoms for both childhood and adulthood symptoms. This cut-off score was applied to avoid over-diagnosing ADHD, as symptoms associated with intoxication or withdrawal may mimic ADHD symptoms. The ADHD Rating Scale has been used in epidemiological and clinical research in adults [45]. Internal consistency of the ARS scales in our sample was high (Cronbach’s alpha = .84-.94) (see Table 2), and the consistency of the Inattention scale was higher than that of the Hyperactivity/Impulsivity scale. Positive screening results, i.e., 6 or more symptoms of either inattention or impulsivity/hyperactivity during both childhood and adulthood, were followed by a diagnostic interview using the separate ADHD-module of the *Mini-International Neuropsychiatric Interview* (M.I.N.I.Plus) [47]. A M.I.N.I.Plus–derived ADHD diagnosis is established if, prior to the age of 7, a subject meets 6 of 10 criteria for ADHD and, during adult years, a subject meets 9 of 14 criteria. Similar to the DSM-criteria, the M.I.N.I.Plus requires impairment from the symptoms to be present in two or more settings. The instrument does not differentiate between inattentive and hyperactive subtypes.

Definition of CDI and CDI+ADHD

Only subjects who had a positive ARS screener (i.e., those who reported 6 or more symptoms of either inattention or impulsivity/hyperactivity during both childhood and adulthood) and fulfilled confirmation of adult ADHD diagnosis using the ADHD-module of the M.I.N.I.Plus were assigned to the CDI+ADHD group. Of the 59 CDI who were screened, 27 subjects screened positive using the ARS. Of these, 25 met the criteria for ADHD using the ADHD-module of the M.I.N.I. Accordingly, 25 subjects were assigned to the CDI+ADHD group. All the remaining subjects (n=34), who were either screen negative (n=32) or interview negative (n=2), were included in the CDI without ADHD group. In HC, the presence of ADHD was excluded using the ADHD-module of the M.I.N.I.Plus.

2.2.3. Impulsivity

2.2.3.1. Self-report questionnaire

The *Barratt Impulsiveness Scale*, version 11 (BIS-11) [48] is a self-report questionnaire consisting of 30 items, with responses on a four-point Likert-type scale ranging from “rarely/never” to “almost always/always”. The questionnaire measures three distinct trait dimensions of impulsivity: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness. These three domains yield three subscores, which can be summed to yield a total score. Cumulative scores range from 30 (low in trait impulsivity) to 120 (high in trait impulsivity). The questionnaire has been shown to be reliable in both clinical and population-based samples, with Cronbach’s alpha coefficients ranging from .79 to .83 [48]. Cronbach’s alpha of the total BIS score in the present study was .79. Cronbach alpha’s for non-planning, motor and attentional impulsivity were .67, 62 and .39, respectively.

2.2.3.2. Neurocognitive tasks

Impulsive action: Inhibition of a pre-potent response was measured by a *stop signal task* (SST), operated using E-Prime experiment generation software [49]. A total of 240 trials were presented with a go/stop ratio of 80/20, of which the first 60 trials served as practice trials to obtain stable performance (not included in the analyses). Go-trials require the subjects to react as quickly as possible to a series of left- or rightward pointing airplanes appearing on the screen by pressing a corresponding key ("left" or "right"). This speeded reaction time task establishes a prepotency to respond. On a subset of trials, the go-stimulus is followed, after a variable delay, by a visual stop-signal (i.e., a cross) presented on top of the airplane, to which participants are instructed to inhibit their response. Stop-signals were presented using a tracking algorithm [49], a procedure which dynamically adjusts the delay at which the stop-signal appears after the onset of the go-signal (i.e., the presentation of the airplane) to control inhibition probability. This algorithm ensures a 50% rate of successful inhibition for each subject and compensates for differences in choice reaction time between participants. The main dependent variable reflecting inhibitory control, the stop signal reaction time (SSRT), reflects the time needed to inhibit the pre-potent response once the stop-signal occurs. Longer SSRTs therefore reflect worse inhibitory control. Secondary measures included mean reaction time (MRT) to go-stimuli and intra-individual variability in reaction times to go-stimuli, as indexed by the coefficient of variation (CV) (= SDMRT/MRT).

Impulsive choice: The *delay discounting task* (DDT) was administered in order to measure the preference for small immediate rewards over large delayed rewards [50]. Subjects had to make preference judgments between a future and an immediate hypothetical monetary reward. The task consisted of six blocks with eight preference judgments per block. The future reward was the same for all trials of a given block, with a block-specific delay in days (i.e., 5, 30, 180, 365, 1095, 3650). The immediate reward varied in magnitude from trial to trial, depending on the responses made by the subjects [50]. The indifference points, indicating which immediately delivered amount of money would be preferred equally to the delayed reward, obtained for each delay were plotted and hyperbolic discount functions were derived through curve-fitting analysis. The k-value, which indexes the degree of delay reward discounting, was used as the dependent variable; as k increases, the person discounts the future reward more steeply and thus higher k-values correspond to higher levels of impulsive choice.

The *information sampling task* (IST) [7] was used to index reflection impulsivity. This dimension of impulsive choice refers to the tendency to gather and evaluate information before making a decision. The IST presents a series of trials with an array of 25 grey boxes, with two larger colored panels (e.g., red and blue) below at the foot of the screen. Upon being selected, boxes open to reveal one of these two colors. On each trial, subjects had to decide which of the two underlying colors were in the majority. Two conditions were presented: in the fixed win (FW) condition, subjects could win 100

points for correct choices or lose 100 points for incorrect choices, regardless of the number of boxes opened. Subjects did not lose points by opening boxes. In the decreasing win (DW) condition, the possible number of points for a correct answer started at 250, and the number of available points decreased by 10 with every box opened. Thus, subjects could win more points for earlier decisions. The penalty for a wrong choice remained the same at 100 points. The primary outcome measures were the average number of boxes opened and the probability (P) of the subject being correct at the point of decision in each condition [7]. This P(correct) is highly correlated with the number of boxes opened but provides a more sensitive measure of the information available at the time of decision (i.e., it is more directly related to the levels of certainty tolerated during decision-making). A higher number of boxes opened and higher P(correct)-values indicate less impulsivity.

2.3. Data analysis

Initial data analysis involved assessing differences between the three groups on demographic (e.g., gender, age, education) and clinical variables (i.e., IQ), using parametric or non-parametric statistics as appropriate. For drug-related variables, independent t-tests were used to compare the two cocaine groups on continuous variables, and chi-square tests for dichotomous variables (e.g., poly-drug use). Healthy controls were not included in these analyses, because their drug use values were always 0. In order to assess group differences related to impulsivity, univariate (e.g., BIS-11 total scores), multivariate (e.g., BIS-11 subscales) or repeated measures ANOVA's (e.g., IST) were performed followed by post-hoc Bonferroni testing when the ANOVA revealed a significant group effect. Variables that significantly differed between the HC and groups of cocaine users (i.e., IQ and years of education) or between the two cocaine groups (i.e., poly-drug-use) were entered as covariates in all analyses. To assess the degree to which indices of impulsivity discriminated between CDI with and without ADHD, a logistic regression analysis was conducted on the impulsivity variables that demonstrated significant between-group differences, with ADHD status as the dependent variable. Predictive accuracy was summarized using standard descriptors, including sensitivity and specificity. Correlations between impulsivity measures and cocaine use variables in the cocaine groups were assessed using Pearson product-moment correlations. All statistical analyses were conducted using the Statistical Package for the Social Science (SPSS) software version 22.

3. Results

3.1. Background information

Socio-demographic and some clinical characteristics of the three groups are summarized in Table 1. Chi-square analysis revealed a trend for differences in the distribution of male and female participants. The three groups did not differ significantly on age. However, HC had a significantly higher number of years of education and higher IQ-scores as compared to CDI and CDI+ADHD. The two clinical groups did not differ significantly from one another on these variables.

Independent t-tests revealed that both cocaine groups did not significantly differ from one another in terms of their age of cocaine onset, past month cocaine use and duration of cocaine use (years) (see Table 1). They also showed a similar pattern of past month use for other substances, such as alcohol,

marihuana, opiates and amphetamines. The two groups did not differ in terms of their mean days of abstinence (i.e., reported length of time since the last use of cocaine at the time of the testing). However, poly-drug use was significantly more prevalent in the comorbid group, with 92% of these comorbid subjects reporting using multiple substances simultaneously (as compared to 62% in the non-comorbid group).

Table 1: Group characteristics of HC, CDI and CDI with ADHD

	Variables	HC (n=28)	CDI (n=34)	CDI+ADHD (n =25)	Test statistic
Demographics	Gender (M:F)	19/9	29/5	23/2	[$X^2_{(2)} = 5.63$, $p = .06$]
	Age	30.39 ± 9.77	30.79 ± 5.90	28.04 ± 7.53	[$F_{(2,49)} = 1.16$, $p = .32$]
	Education (years)	14.36 ± 2.11	12.53 ± 2.27	11.32 ± 2.25	[$F_{(2,84)} = 12.74$, $p < .001$]
Clinical	IQ	108.54 ± 12.23	88.71 ± 9.43	86.40 ± 7.57	[$F_{(2,84)} = 41.76$, $p < .001$]
Cocaine use	Age of first cocaine use	NA	20.12 ± 4.98	18.48 ± 3.92	[$t_{(57)} = 1.36$, $p = .18$]
	Cocaine use past month (days)	NA	16 ± 11.50	13.12 ± 10.93	[$t_{(57)} = .97$, $p = .34$]
	Duration of cocaine use (years)	NA	8.18 ± 7.53	7.44 ± 6.49	[$t_{(57)} = .393$, $p = .70$]
Alcohol and other substances (past month)	Alcohol (days)	-	13.21 ± 12.55	14.88 ± 11.19	[$t_{(57)} = -.53$, $p = .60$]
	Marihuana (days)	/	5.18 ± 10.56	10.88 ± 13.85	[$t_{(43)} = -1.72$, $p = .09$]
	Opiates (days)	/	/	.92 ± 4.02	[$t_{(57)} = -1.34$, $p = .19$]
	Amphetamines (days)	/	1.47 ± 5.48	1.64 ± 6.03	[$t_{(57)} = -.112$, $p = .91$]
	Poly-drug use (%)	NA	62%	92%	[$X^2_{(1)} = 6.95$, $p = .01$]
	Abstinence (days)	NA	12.15 ± 9.87	13.24 ± 14.56	[$t_{(57)} = -.339$, $p = .74$]

Data are presented as means ± SD, unless otherwise indicated. M: male, F: female.
NA: Not applicable
- Information not available

In order to fully characterize differences between the CDI and CDI+ADHD group, Table 2 displays the number of ADHD symptoms on the ARS for both groups, with the two domains of inattention and hyperactivity-impulsivity scored separately. As expected, differences between both groups in terms of their mean number of ADHD symptoms during childhood and adulthood were highly significant and showed large effect sizes (*r*), ranging from .49 to .75.

Table 2: Cronbach alpha's (α) and number of ADHD symptoms in CDI and CDI+ADHD, for both inattention (IA) (0-9) and hyperactivity/Impulsivity (HI) (0-9) on the ADHD Rating Scale (ARS).

ARS Scales	Cronbach α	CDI	CDI+ADHD	Test Statistic
Childhood_IA	.94	3.12 ± 2.94	7.56 ± 1.26	[$t_{(47.48)}$ = -7.88 p < .001]
Childhood_HI	.92	2.71 ± 2.14	6.12 ± 2.55	[$t_{(57)}$ = -5.58 p < .001]
Childhood_Total	.96	5.83 ± 4.61	13.68 ± 3.13	[$t_{(57)}$ = -7.36 p < .001]
Adult_IA	.87	2.44 ± 1.89	6.2 ± 2.12	[$t_{(57)}$ = -7.15 p < .001]
Adult_HI	.84	2.85 ± 2.11	5.32 ± 2.38	[$t_{(57)}$ = -4.21 p < .001]
Adult_Total	.91	5.29 ± 3.61	11.52 ± 3.03	[$t_{(57)}$ = -6.99 p < .001]

Data are presented as means ± SD.

3.2. Impulsivity

3.2.1. Impulsivity across groups

3.2.1.1. Self-report questionnaire

The results of the BIS-11 self-report questionnaire data are presented in Table 3. One-way ANOVA of BIS-11 total scores revealed a significant main effect of group, due to increased scores in the two clinical groups relative to the HC (both p < .001). This effect remained significant while controlling for differences in IQ (see Table 3) or years of education (p < .001). Post-hoc comparison further revealed significantly higher BIS-11 total scores in the comorbid relative to the non-comorbid group of CDI, which remained significant when taking into account the effects of poly-drug use ($F_{(1,56)}$ = 13.64, p < .001, ES = .44). Multivariate ANOVA of the subscale ratings showed a significant overall group effect while taking into account differences in IQ (Wilks' Lambda = 10.68, p < .001) or years of education (Wilks' Lambda = 8.96, p < .001), with significant univariate effects on the motor, attentional, and non-planning subscales (see Table 3). The two clinical groups scored higher on all three subscales relative to HC (all p < .001). In addition, post-hoc comparison revealed significant differences between the CDI and CDI+ADHD on the non-planning subscale, on which the comorbid group scored significantly higher than the CDI-only group. Differences between the two clinical groups on the non-planning subscale remained significant when controlling for the effects of poly-drug use ($F_{(1,56)}$ = 18.25, p < .001, ES = .50).

Table 3: Scores of HC, CDI and CDI+ADHD on the total and subscales of the BIS-11

	HC	CDI	CDI+ADHD	Test statistic while controlling for IQ	Post-hoc effects of group
BIS_Total	54.29 ± 8.79	68.56 ± 9.42	78.60 ± 8.08	[$F_{(2,83)}$ = 34.41, p < .001]	HC<CDI<CDI+ADHD
BIS_Motor	19.04 ± 3.50	24.44 ± 4.84	27.16 ± 4.19	[$F_{(2,83)}$ = 19.52, p < .001]	HC<[CDI=CDI+ADHD]
BIS_Attention	12.89 ± 2.41	17.73 ± 3.88	19.28 ± 3.18	[$F_{(2,83)}$ = 15.43, p <. 001]	HC<[CDI=CDI+ADHD]
BIS_Non-planning	22.36 ± 4.01	26.68 ± 4.32	31.76 ± 4.02	[$F_{(2,83)}$ = 25.91, p < .001]	HC<CDI<CDI+ADHD

Data are presented as means ± SD.

3.2.1.2. Neurocognitive tasks

Impulsive action

Stop Signal Task: The mean probability of successful inhibition on stop trials was 50% and no participants were identified whose inhibition accuracy deviated 10% or more from the targeted 50%, indicating that the dynamic tracking algorithm worked well for all subjects. Significant group differences were found in SSRTs, which remained significant while controlling for the effects of IQ (see Table 4) or years of education ($p < .001$). Post-hoc analyses showed that SSRTs were significantly longer in the two clinical groups compared to the HC (see Fig.1). However, slowed processing of the stop-stimulus is in itself not informative with regard to the primacy of disinhibition, since it could equally well reflect an impairment of attention to the stop-signal. As such, the slowed processing of the stop-stimulus was studied in relation to the processing speed of the go-stimuli (i.e., mean go-signal reaction times, MRT). Although we found a trend towards a group effect on MRTs, a post-hoc ANCOVA revealed that group effects on SSRTs remained significant after controlling for these differences ($F_{(2,83)} = 10.14$, $p < .001$). The effect of mean go-signal RTs as a covariate on SSRTs was far from significant ($p = .91$). Accordingly, a specific lack of inhibitory control rather than a deficit in attention underlies the difference between CDI and HC. The two clinical groups did not significantly differ from one another in terms of SSRTs ($p = .81$). Finally, a significant main effect of group was found for the intra-individual coefficient of variance (CV) (see Table 4). Post-hoc analyses revealed significantly greater reaction time variability in CDI+ADHD relative to HC ($p = .019$). A non-significant trend towards greater reaction time variability in the comorbid relative to the CDI-only group was further found ($p = .07$).

Insert Figure 1

Fig. 1. Mean go-stimuli RTs (response latency) and mean SSRT (stopping latency) for HC, CDI and CDI+ADHD.

Impulsive choice

Delay Discounting Task: Delay discounting rates (*k-values*) were estimated by nonlinear regression using Mazur's hyperbolic model. Figure 2 represents the fitted hyperbolic discounting curves on the mean indifference points per group. The discounting equation (hyperbolic model) provided a good fit to the data, accounting for 95%, 88%, and 83% of the variance for HC, CDI, and the CDI+ADHD, respectively. Because of positively skewed distributions of discounting coefficients, natural logarithm-transformed *k* values were estimated = ln(k+0.001) and employed in the analyses of discounting. All *k*-based analyses presented hereafter are based on the log-transformed values. Analysis of variance comparing transformed *k*-values for all three groups revealed a significant main group effect, which remained significant while controlling for IQ (see Table 4). Similar results were obtained when years of education was entered as a covariate ($p < .001$). Bonferroni post-hoc tests were used to compare each group to every other. No significant difference in ln(k)-values between HC and CDI without ADHD was found ($p = .28$). However, we did find significantly higher ln(k)-values in the CDI+ADHD group as compared to the HC ($p < .001$). The comorbid group also had significantly higher discounting

scores relative to the CDI without ADHD ($p < .001$). Because the comorbid group was more likely to use multiple substances, a supplementary analysis of covariance was performed to assess the effects of poly-drug use. However, group differences in delay discounting remained significant while controlling for the effects of poly-drug use ($F_{(1,56)} = 17.40$, $p < .001$, ES = .49).

Insert Figure 2

Fig. 2. Points represent the median indifference points at the 6 different delay intervals (i.e., 5, 30, 180, 365, 1095, and 3650 days) for HC, CDI and CDI+ADHD. Lines show the best-fitting discounting functions generated by the hyperbolic model. The graphic demonstrates that CDI+ADHD show steeper discounting curves compared to the two other groups.

Information Sampling Task: Figure 3 shows the average number of boxes opened per condition as a function of group. As expected, the number of boxes opened per condition was significantly related to the probability of making a correct choice at the point of decision ($r = .98$, $p < .001$). Therefore, we focus our main analyses on the P(correct) variable.

P(correct): P(correct)-data were analyzed using a repeated measures ANOVA with condition (FW, DW) as within-subject variable and group as the between-subject variable. There was a significant main effect of condition ($F_{(1,82)} = 98.03$, $p < .001$), due to subjects sampling less information in the DW condition compared to the FW condition. As such, participants tolerated more uncertainty (lower P(correct)) in the DW than in the FW condition and thus, demonstrated sensitivity to the task contingencies. Paired *t*-tests revealed that these significant differences in the degree of information sampling between the FW and DW conditions were present in all three groups (all $p < .001$), meaning that all groups were broadly sensitive to the altered reward characteristics of the two conditions and were motivated to win points. There was also a main effect of group ($F_{(2,82)} = 15.76$, $p < .001$). Post-hoc analysis (collapsed across condition) showed that, compared to controls, both CDI and CDI+ADHD tolerated significantly more uncertainty in their decisions (all $p < .001$). However, this group effect became non-significant while controlling for differences in IQ ($F_{(2,81)} = 2.81$, $p = .07$). Finally, we found a significant condition*group interaction ($F_{(2,82)} = 4.48$, $p = .01$), which remained significant after controlling for IQ ($F_{(2,81)} = 3.97$, $p = .02$) or years of education ($F_{(2,81)} = 4.27$, $p = .02$). The nature of the significant group*condition interaction term was elucidated by calculating a difference score for the number of boxes opened in the FW and DW conditions. Figure 4 displays box adjustment in the three groups, representing the degree to which subjects adjust their behavior to the reward contingencies. We found a significant group effect on box adjustment, due to greater box adjustment in HC than in the CDI ($p < .001$) and CDI+ADHD ($p = .04$). Although the main effect of group on box adjustment remained significant while controlling for IQ (see Table 4) or years of education ($p < .001$), the difference between HC and CDI+ADHD became non-significant ($p = .07$). Contrary to our expectations, we also found a trend towards greater box adjustment in the CDI+ADHD compared to the CDI ($p = .06$). When the two clinical groups were directly compared to one another in terms of their box adjustment, taking into account differences in poly-drug use, we found significantly higher levels of box adjustment in the CDI+ADHD relative to the CDI without ADHD ($F_{(1,56)} = 6.06$, $p = .02$).

Insert Figure 3

Fig. 3. Number of boxes opened in the fixed reward (FW) and in the decreasing win (DW) conditions of the IST for HC, CDI and CDI+ADHD.

Insert Figure 4

Fig. 4. Mean adjustment scores on the IST for HC, CDI and CDI+ADHD.

Table 4: Scores of HC, CDI and CDI+ADHD on neurocognitive tasks of impulsivity

	HC	CDI	CDI+ ADHD	Test statistic while controlling for IQ	Post-hoc effects of group
SST					
SSRT	224.06 ± 33	277.61 ± 51.16	280.87 ± 69.32	[$F_{(2,83)}$ = 5.78, p = .004]	HC<[CDI=CDI+ADHD]
MRT Go-stimuli	516.03 ± 123.75	483.30 ± 84.02	505.37 ± 81.66	[$F_{(2,83)}$ = 2.87, p = .06]	-
CV	.21 ± .04	.22 ± .06	.25 ± .04	[$F_{(2,83)}$ = 4.37, p = .016]	CDI+ADHD>HC CDI+ADHD=CDI
DDT					
Ln(k)	-6.50 ± .47	-6.35 ± .58	-5.36 ± 1.36	[$F_{(2,83)}$ = 15.22, p < .001]	CDI+ADHD>[HC=CDI]
IST					
BoxesOpened (/25)	14.95 ± 3.93	10.43 ± 4.54	9.72 ± 3.45	[$F_{(2,81)}$ = 2.18, p = .12]	(NS after controlling for IQ)
P(correct)	.85 ± .08	.75 ± .09	.74 ± .07	[$F_{(2,81)}$ = 2.81, p = .07]	(NS after controlling for IQ)
Box Adjustment	7.42 ± 5.19	2.88 ± 2.54	4.98 ± 4.89	[$F_{(2,83)}$ = 6.39, p = .003]	CDI<[HC=CDI+ADHD]

Data are presented as means ± SD.
Abbreviations: CV: coefficient of variance, DDT: delay discounting Task, IST: information sampling task, Ln(k): natural log transformed k-values, MRT: mean reaction time, NS: non-significant: SSRT: stop signal reaction time, SST: stop signal task.

3.2.1.3. Logistic regression analysis

A logistic regression analyses was conducted, with the impulsivity variables that demonstrated significant differences between the CDI and CDI+ADHD (i.e., BIS-11 non-planning scores and ln(k)-values) as the predictor variables. A test of a model combining these impulsivity variables as predictors against a constant only model was statistically significant, indicating that non-planning impulsivity and delay discounting reliably distinguished between CDI with and without ADHD ($\chi^2(2) = 29.83$, $p < .001$), with 53% of the (pseudo)variance in ADHD status explained (Nagelkerke R square = .533). The model yielded an overall correct classification of 81.4 %, with a sensitivity and specificity of 76% and 85.3%, respectively.

3.2.2. Correlations among impulsivity measures

Pearson product-moment correlations were calculated between impulsivity measures and cocaine use variables in the cocaine sample (n=59) and are presented in Table 5. We applied a Bonferroni correction to control for multiple comparisons, resulting in corrected alpha level of 0.005 (i.e., 0.05/10). All three BIS-11 subscales significantly correlated ($p < .005$) with the BIS-11 total scale. We found no significant correlations between trait and neurocognitive measures of impulsivity, with the exception of a trend towards a positive correlation between scores on the BIS-11 non-planning subscale and DDT *k*-values ($p = .049$). No correlations were found between scores on the SST, DDT and IST, which is consistent with the idea that response inhibition, delay discounting and reflection impulsivity reflect separate dimensions of impulsivity. Scores on the motor, non-planning and total BIS-11 scales negatively correlated with the age of onset of cocaine use.

Table 5: Correlations between impulsivity and drug use variables

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
(1) BIS_Motor	1									
(2) BIS_Attentional	,257	1								
(3) BIS_Non-planning	,511*	,382*	1							
(4) BIS_Total	,814*	,618*	,820*	1						
(5) DDT_ln(k)	-,040	,007	,257	,101	1					
(6) SSRT	-,051	-,082	-,018	-,050	-,031	1				
(7) IST_P(correct)	,052	-,087	-,066	-,047	,035	,029	1			
(8) Past month cocaine use	,074	,121	,043	,125	-,281	-,061	-,183	1		
(9) Duration cocaine use	,352	,120	,302	,356	-,224	,029	,030	,116	1	
(10) Age of cocaine use onset	-,371*	-,293	-,419*	-,485*	-,009	,109	-,013	,002	-,300	1

* Correlation is significant at the $p < .005$ level (2-tailed)

Abbreviations: DDT_ln(k): natural log transformation of the discount rate, SSRT: stop signal reaction time, IST_P(correct): probability of being correct at the time of decision on the IST.

4. Discussion

The present study evaluated the relationship between different facets of impulsivity and cocaine dependence and explored the effect of ADHD on this relationship. Both CDI with and without ADHD reported higher scores on the total and three subscales of the BIS-11 questionnaire (i.e., trait impulsivity) and required more time to inhibit motor responses on the SST (i.e., motor disinhibition) compared to healthy controls. While the increased impulsivity on these indices in CDI replicates previous findings [9,10], our study was the first to demonstrate that CDI (with and without ADHD) also sample less information on the IST prior to making a decision (i.e., reflection impulsivity) when compared to HC. With the exception of differences in reflection impulsivity, the increased impulsivity in the cocaine groups remained significant while controlling for differences in IQ. Overall, these findings indicate that CDI display and report higher levels of impulsivity than HC on a variety of impulsivity measures, regardless of whether or not they have a comorbid ADHD diagnosis. There was however one exception to this finding. Specifically, we found that only CDI+ADHD and not those without an ADHD diagnosis showed a more pronounced intolerance to delay-of-gratification on the DDT compared to HC. This finding in other words indicates that higher levels of delay discounting in CDI are specifically associated with the presence of ADHD or, at minimum, that steeper discounting of delayed rewards is a hallmark characteristic of the comorbidity between cocaine dependence and ADHD. Partially supporting this latter notion, a recent study found that, relative to HC, only ADHD patients with and not those without cocaine dependence were characterized by elevated levels of delay discounting [51]. These findings may suggest that chronic cocaine use interacts with the pathophysiology underlying ADHD to produce more pronounced and clinically significant discounting scores. Consequently, future studies examining delay discounting in CDI but also in subjects with an ADHD diagnosis should take into account the effects that either ADHD or cocaine dependence may have on delay reward discounting in these groups

The current study was also the first to directly compare scores on trait and neurocognitive measures of impulsivity between CDI with and without ADHD. We found that two specific indices of impulsivity, BIS-11 non-planning impulsivity and delay discounting respectively, were able to differentiate CDI from CDI with an ADHD diagnosis, with an overall classification accuracy of 81.4%. Our results more specifically suggest that ADHD may exert synergistic detrimental effects on the ability to plan ahead or orient towards future, rather than to immediate rewards in CDI. The higher scores on non-planning and choice impulsivity in the CDI+ADHD relative to the non-comorbid group of CDI remained significant while controlling for the effects of poly-drug use, which was higher in the comorbid group. Because other drug use characteristics did not differ between the two clinical groups, our findings suggest that drug use itself may not have accounted for the observed differences in impulsivity. These data are generally consistent with previous reports suggesting that trait impulsivity reflects a disposition that is present prior to the initiation of drug use [52] and with findings indicating that delay discounting is unaffected by drug use and/or abstinence [12,53,54,55]. As such, higher non-planning impulsivity and delay discounting in the comorbid group may have predated drug use, proportionally increasing the risk of developing a SUD. Alternatively, individuals with ADHD may be

more vulnerable for cocaine-induced catecholaminergic disruptions as a result of the pathophysiology underlying ADHD, even if amount and duration of cocaine use are similar to non-comorbid CDI [56]. Clearly, more research (longitudinally) is needed to evaluate the temporal relationship between non-planning impulsivity, delay discounting, ADHD and cocaine dependence.

In contrast with the disparities in delay discounting, indices of impulsivity on the SST (i.e., SSRT) and IST (i.e., P_correct) did not reveal any differences between the two cocaine subgroups. In light of the generally held view that poor response inhibition represents a core deficit in ADHD [57,58,59,60,61,62,63], the absence of differences in SSRTs between both groups was perhaps most surprising. Several potential explanations may account for this rather unexpected finding. Because individuals with low or moderate levels of dopamine transmission have previously been found to show benefits from stimulant drugs, cocaine use may have potentially enhanced the ability of subjects with ADHD to inhibit behavioral responses [64,65,66]. However, the fact that all subjects in our sample were abstinent for at least three days makes this interpretation less likely. Indeed, abstinence from drugs has been associated with decreased dopaminergic transmission in the prefrontal cortex and anterior cingulate, thereby impairing rather than enhancing response inhibition [64,67]. Some authors have also proposed the existence of two subtypes of ADHD, which lead to the generation of ADHD symptoms via two distinct pathways: the altered “motivational style” pathway, which generates a strong aversion to delays, and the disordered “thought and action” pathway, which leads to a more fundamental dysregulation of inhibitory control [68]. The former subtype has been suggested to arise through alterations in brain areas involved in reward processing, including the ventral striatum, and innervated by the mesolimbic branch of the dopamine system [68]. Hypothetically, subjects with this subtype may be more likely to engage in substance use behavior, explaining why our comorbid group was specifically characterized by greater delay discounting rather than poor inhibition. This notion would cohere with the growing recognition of excessive delay discounting as a trans-disease process [69]. It also remains possible that previous studies have overestimated the centrality of poor inhibitory control in subjects with ADHD, and that deficits related to motor inhibition are more specific to cocaine dependence than to ADHD [51]. Impairments in other aspects of response control on the other hand, including increased intra-subject variability in response times, might be more central to ADHD [70,71,72]. Finally, because both samples consisted of cocaine-dependent patients, i.e. a population that is by definition characterized by impaired inhibitory control, it remains possible that the absence of significant differences in SSRTs between the two clinical groups reflect a ceiling effect.

Clinical implications

Despite the overall descriptive nature of the current study, the findings presented here highlight several interesting directions for future (research) efforts aimed at improving the assessment and treatment of ADHD in CDI. The overall good discriminatory ability of the BIS-11 non-planning scale and DDT, combined with their brevity and ease of administration, suggests that these indices could be explored as clinical tools for brief screening in clinical settings. If well constructed and widely available, these screeners could serve to guide professionals in their referrals for assessment and treatment of ADHD in CDI. In contrast to a purely categorical perspective on ADHD, incorporating a dimensional

classification based on impulsivity scores may be of greater clinical utility in terms of predicting treatment outcomes, treatment planning and selection. Future studies aimed at developing norms and establishing clinically-relevant cut-off points may substantially help the clinical field moving forward in this respect.

During the past decades, several studies have found the presence of ADHD among CDI to be associated with worse addiction treatment outcomes, including higher rates of premature treatment drop-out and a greater propensity to relapse [31,36,37,73]. To date however, the mechanisms mediating the negative effects of ADHD on addiction treatment outcomes remain unexplored. A worthwhile prospect for future studies may therefore be to explore whether elevated impulsivity among CDI with ADHD accounts for their increased risk for treatment failure. Such a finding would be consistent with growing evidence indicating that non-planning impulsivity and delay discounting place drug users at higher risk for relapse or premature treatment drop-out [74,75] and would contribute to the isolation of possible mechanisms for intervention approaches.

Limitations

Several limitations of this study should be highlighted. First, healthy controls were not matched to the clinical groups in terms of IQ or years of education. Still, most of our findings remained significant when controlling for these variables. Second, our samples were relatively small. As such, subtle differences in performance between the two clinical groups may not have been detected. At the same time, this implies that the observed differences in impulsivity between CDI with and without an ADHD diagnosis represent relatively large effects, with effect sizes of .50 and .49 for non-planning and delay discounting respectively. Third, Cronbach's alpha of the BIS-11 attentional impulsivity subscale was poor in the current sample (i.e., .39). Given the low internal consistency, the observed between-group differences on this scale should be interpreted with appropriate caution. Fourth, our research diagnoses of ADHD were based entirely on self-report from participants, as opposed to diagnoses obtained from a comprehensive diagnostic assessment procedure. Still, adults have shown the ability to accurately rate childhood ADHD symptomatology [76]. Moreover, we used the more stringent cut-off score of 6 symptoms and focused on whether the reported symptoms were associated with impairment and whether impairment occurred in at least two situations. Our sample was composed entirely of individuals who reported cocaine as their primary substance of abuse; results may therefore not be representative of individuals seeking treatment for non-stimulant drugs (e.g., opioids, cannabis). Similarly, the CDI in our sample were patients with a high problem severity, as exemplified by low IQ and a need for inpatient treatment, warranting careful consideration when considering other groups of CDI. Finally, although we used a test battery measuring different core dimensions of impulsivity, not all impulsivity aspects were covered. For instance, we did not measure cognitive inhibition, which refers to the ability to suppress competing, distracting information. As preliminary evidence suggests that drug consumption in individuals with ADHD is associated with poor attentional inhibition in particular [77], future studies may benefit from including a measure of interference control while comparing CDI with and without ADHD.

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