Drug and Alcohol Dependence xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

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

Impulsivity in adult ADHD patients with and without cocaine dependence

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ARTICLE INFO

Article history:
Received 24 June 2012
Received in revised form 5 September 2012
Accepted 5 September 2012
Available online xxx

Keywords:
ADHD
Impulsivity
Cocaine dependence
Substance use disorder
Neurocognitive functioning

ABSTRACT

Background: Attention deficit hyperactivity disorder (ADHD) is present in about a quarter of patients with a substance use disorder (SUD) and impulsivity is a key feature of both disorders. However, very little is known about differences in impulse control and other cognitive functions between ADHD patients with and without SUD.
Methods: In adult male medication-naïve ADHD patients with and without comorbid cocaine dependence and healthy controls (matched on gender, age and IQ), we measured motor impulsivity (stop signal task), cognitive impulsivity (delay discounting task), divided attention (trail making test), interference (Stroop task), working memory (*n*-back task), and time reproduction (time reproduction task). Additionally, self-reported ADHD symptoms (using the ADHD Symptom Rating Scale; ASRS) and self-reported impulsivity (Barratt Impulsivity Scale; BIS) were assessed.
Results: Significantly higher levels of motor and cognitive impulsivity were found in ADHD patients with comorbid cocaine dependence compared to ADHD patients without cocaine dependence and controls, and both measures of impulsivity were highly correlated. No significant group differences were found on other cognitive measures. With regard to the self-report measures, only BIS attention subscores differed significantly between ADHD patients with and without cocaine dependence. ASRS and BIS scores were not significantly correlated.
Conclusion: This is the first study showing that ADHD patients with cocaine dependence are a distinctly more impulsive subpopulation compared to ADHD patients without cocaine dependence on objective measures of impulsivity. These findings are relevant to optimize psycho-education and treatment of ADHD patients with comorbid SUD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a childhood developmental disorder characterized by symptoms of inattention, hyperactivity and impulsivity. In children with ADHD, a wide range of impairments in cognitive functions are found, particularly regarding executive functions (i.e., response inhibition, working memory, planning, selective and divided attention, set-shifting, and time processing; O'Brien et al., 2010; Pasini et al., 2007; Valko et al., 2010; Willcutt et al., 2005). While ADHD symptoms often wane in adulthood, these symptoms may persist in some patients. Studies in adult ADHD patients reported on deficits in working memory (Finke et al., 2011; Marx et al., 2011), reward and emotional processing (Wilbertz et al., 2012; Marx et al., 2011; Ibáñez et al., 2011), time processing (Valko et al., 2010), and inhibitory control (Bramham et al., 2012; Cummins et al., 2011; Wilbertz et al., 2012). However, in adult ADHD patients, measures of impulsivity and selective attention are reported to improve with age (Bramham et al., 2012).

Adult ADHD is diagnosed in about a quarter of the patients with substance use dependence (SUD; van Emmerik-van Oortmerssen et al., 2012). ADHD is, like SUD, characterized by increased levels of impulsivity. For example, chronic cocaine abusers show increased motor impulsivity (Fillmore and Rush, 2002) and increased cognitive impulsivity (i.e., impulsive decision making) compared to non-drug using controls (Coffey et al., 2003; Heil et al., 2006). Additionally, in SUD, deficits in reward processing, attention, and working memory have been observed (Hester and Garavan, 2004; van Holst and Schilt, 2011; Verdejo-Garcia et al., 2006), suggesting a large overlap between ADHD and SUD in cognitive impairments.

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http://dx.doi.org/10.1016/j.drugalcdep.2012.09.006

Increased impulsivity, impaired attention, and/or working memory deficits may represent common risk factors for the development of ADHD and SUD, and as a consequence ADHD patients with increased levels of impulsivity may be more prone to develop a SUD later in life. While one of the leading hypothesis in ADHD research states that ADHD symptoms arise from primary cognitive/executive impairments (the executive dysfunction hypothesis), the combination with reward/motivational impairments is believed to play a key role in the pathophysiology of ADHD (dual pathway hypothesis; Sonuga-Barke, 2003; Willcutt et al., 2005). Various studies have been performed on cognitive impairments in (adult) ADHD patients, but no data are currently available on cognitive and/or motivational impairments in ADHD patients with comorbid SUD. This is unfortunate because current ADHD treatments (e.g., methylphenidate) are less effective in ADHD patients with SUD compared to ADHD populations without SUD (Carpentier et al., 2005; Levin et al., 2007), and, subsequently, treatments in ADHD patients with SUD could be significantly improved by simultaneously targeting deficits that are specific for ADHD patients with comorbid SUD.

Here, we investigate a variety of measures of neurocognitive functioning representing both the executive circuit (response inhibition, set-shifting, working memory, and time reproduction) and the reward/motivational circuit (delayed discounting) in non-medicated adult ADHD patients with and without cocaine dependence, and in non-drug using controls. We thereby include distinct measures of impulsivity relating to distinct neurobiological circuitries, including motor impulsivity (response inhibition arising from possible dysfunctions in the executive circuitry) and cognitive impulsivity (delayed discounting related to the reward/motivational circuitry). Additionally, trait impulsivity and self-reported ADHD symptoms were assessed, representing distinct subjective measures of impulsive behavior (Broos et al., 2012). We hypothesize that ADHD patients with and without cocaine dependence differ from control participants on measures of impulsivity, attention, time reproduction, and working memory compared to control participants. Additionally, we hypothesize that ADHD patients with comorbid cocaine dependence have increased levels of (motor and cognitive) impulsivity compared to ADHD patients without cocaine dependence (ADHD) and matched non-drug using healthy controls (HC).

2. Methods

2.1. Subjects

Male adult ADHD patients without cocaine dependence (ADHD; $n = 17$) and male adult ADHD patients with cocaine dependence (ADHD + COC; $n = 11$) were screened by experienced professionals from various Dutch Addiction and ADHD treatment centers. Non-drug using male healthy controls (HC; $n = 17$) were recruited by local advertisement leaflets and were matched on gender, age (between 22 and 50 years old) and IQ.

In ADHD and ADHD + COC patients, DSM-IV ADHD was diagnosed using the Connors' Adult ADHD Diagnostic Interview (CAADID; Conners et al., 1999). The CAADID assesses the presence of both adult and childhood ADHD criteria, including the criterion of childhood impairment. If patients did not meet the childhood impairment criterion they were excluded from study participation. Thus, all patients that were included in the study had a DSM-IV diagnosis of adult ADHD diagnosis including the childhood impairment. Cocaine dependence was diagnosed in ADHD + COC patients and excluded in HC and ADHD patients using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Also using the MINI, other psychiatric disorders were excluded in HC patients. Finally, participants were excluded when having serious medical illness, or when currently using any drugs other than alcohol, cannabis or nicotine.

The study was approved by the Academic Medical Center Ethical Committee and written informed consent was given by all participants before testing.

2.2. Clinical assessments

The Dutch version of the National Adult Reading Test (DART; Schmand et al., 1991) was used to assess IQ. Nicotine dependency was assessed using the Fagerström test for Nicotine Dependence (FTND; Heatherton et al., 1991). The Beck Depression Inventory (BDI; Beck and Steer, 1987) was used to measure symptoms of depression.

2.3. Cognitive function tasks

Participants were tested individually during a 3 h session. Testing occurred in a quiet room, in a fixed order. Fixed breaks were provided between tests to avoid fatigue. The neuropsychological battery assessed domains of cognitive functioning that have been found to be impaired in youth and adults with ADHD (Pennington and Ozonoff, 1996; Seidman et al., 2004; Tannock et al., 2006; Willcutt et al., 2005).

2.3.1. Motor impulsivity/response inhibition. The stop signal task (Logan et al., 1984) was used to measure response inhibition. Participants were presented with an arrow pointed to the right or the left and were required to push a corresponding (left or right) button on a response box as quickly as possible (go trials). In 25% of the trials, an auditory stop stimulus was presented several milliseconds following the presentation of the arrow, and participants were instructed to try to inhibit their response (stop trials). Participants performed 3 blocks of 128 trials each. For each block, a tracking algorithm was used such that participants inhibited their responses successfully in approximately 50% of the stop trials. The primary outcome measure was the stop signal reaction time (SSRT; a measure for the speed of inhibition), a high SSRT reflecting low response inhibition, and indicating higher motor impulsivity. Additionally, mean reaction times (MRT; representing psychomotor response speed) and accuracy of go trials (ACC) were measured.

2.3.2. Cognitive impulsivity/delayed discounting. The delay discounting task was used to measure impulsive decision making (cognitive impulsivity), by providing participants with a choice between an immediate small reward or a larger reward in the future (Bickel and Marsch, 2001). Participants were asked to choose between two hypothetical monetary rewards over a variety of delays in the future: 5 days, 1 and 3 months, and 1, 3 and 10 years. The task consisted of 6 blocks (one per delay), consisting of 6–8 trials each, and included an algorithm that assessed the participant's indifference points (Vx; the discounted value of a delayed reward) per delay using the hyperbolic equation by Mazur (1987). Lower indifference points represent increased cognitive impulsivity. The primary outcome measure was the discounting rate k, calculated from the participant's individual indifference points per delay (Bickel and Marsch, 2001; Mazur, 1987), where higher k values represent higher cognitive impulsivity. In addition, we calculated R^2 measures as an indicator of the fit of the curve to the hyperbolic function.

2.3.3. Interference control. The Stroop color-word task presents congruent stimuli (i.e., 'red' printed in red ink) and incongruent stimuli (i.e., 'yellowî in red ink) and measures interference between cognitive processes by requiring the participant to name the color ('red') regardless of the word ('red' or 'green'; Stroop, 1935). Our task presented stimuli in 4 different colors (red, green, blue and yellow) and included 5 blocks per condition, with 9 trials per block. The primary outcome measure was the reaction time during incongruent stimuli (RT_I) compared to the reaction times during congruent stimuli (RT_C), using the equation: $(RT_I - RT_C)/RT_C$, where higher ratios represent decreased interference control. To control for attentional differences, participants with mean accuracy under 75% were excluded from data analyses.

2.3.4. Time reproduction. A visual time reproduction paradigm (Rommelse et al., 2007) was used to assess time reproduction deficits, reflecting differences in time perception. Participants were required to reproduce a visual interval length by switching on and off a light bulb on a computer screen, including interval lengths of 1 s, 3 s, 6 s, 12 s and 20 s. The main outcome measures include the relative discrepancy score (a measure for the relative differences in lengths compared to the actual length interval, expressed as percentage deviation), where higher discrepancy scores indicate greater time reproduction deficits.

2.3.5. Attentional set-shifting. The trail making test was used to assess attentional set-shifting (Spreen and Strauss, 1991). The trail making test parts A and B were administered and the set-shifting score was calculated following Stuss et al. (2001) with the equation (log(Timing B – Timing A)/Timing A). High set-shifting scores are a measure for deficits in attentional set-shifting.

2.3.6. Working memory. The n-back task (Kirchner, 1958) is a continuous working memory task that requires subjects to indicate whether the current letter matches the one from n (usually 1–3) steps earlier. We used an in-house version of the task visualizing a worm and an apple with 4 holes from which the worm could occur. The task included 2 blocks of 20 trials per n-back condition (0-, 1-, and 2-back) and participants had to point out the location from where the worm appeared immediately, 1, or 2 steps earlier. The primary outcome measure was accuracy per condition, with more mistakes showing more important working memory deficits.

2.4. Self-report questionnaires

The Barratt Impulsivity Scale (BIS-11; Patton et al., 1995) is a self-report questionnaire and was used to assess (9 aspects of) subjective impulsivity. The ADHD

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Symptom Rating Scale (ASRS; Kooij et al., 2005) was used as a severity indicator of self-reported (current) ADHD symptoms in adulthood.

2.5. Statistics

All dependent variables (cognitive tasks and self-report questionnaires) were checked for normality of their distribution using Shapiro–Wilk normality tests. In normally distributed data, one-way ANOVAs were performed to assess group differences related to task performance and self-report questionnaire scores, followed by post hoc Bonferroni testing when the ANOVA revealed a significant group effect. When variables were not normally distributed, a logarithmic transformation was used for further analysis, or a non-parametric Kruskal–Wallis test was used to identify statistical differences between variables of independent samples that were not transformed (e.g., performance accuracy data). Correlations are described using Pearson's correlation coefficients. A significance level of 0.05 was used as statistically significant for all statistical tests and all data are presented as means ± standard deviation.

3. Results

3.1. Clinical characteristics

All clinical characteristics were normally distributed (Shapiro–Wilk tests $P > 0.05$) and means and standard deviations are presented in Table 1. Groups (HC, ADHD and ADHD + COC) did not differ significantly in age or IQ. Regarding ADHD subtypes, the ADHD group mainly consisted of combined and inattentive subtypes (100%), while the ADHD + COC group included mainly hyperactive and combined subtypes (91%).

ADHD + COC and HC groups contained more smokers (ADHD + COC 64%; HC 59%) than the ADHD group (41%) but this difference was not statistically significant. Also, the amount of cigarettes smoked did not differ between groups ($P = 0.052$), but ADHD + COC had statistically significantly higher FTND scores, indicating more severe nicotine dependence compared to both ADHD and HC groups ($P = 0.001$). Current use of substances other than cocaine (alcohol, cannabis, amphetamine, and heroin) did not differ between groups.

3.2. Cognitive function tasks

Table 2 shows the outcome measures for the neurocognitive tasks, including the ANOVA level of significance and the post hoc Bonferroni levels of significance.

3.2.1. Motor impulsivity. SSRT and MRT data were normally distributed in all groups (Shapiro–Wilk (SSRT): $P > 0.14$, MRT $P > 0.15$). However, ACC data were negatively skewed due to the generally high performance score and were analyzed using a non-parametric Kruskal–Wallis test.

Table 2 shows that SSRTs were significantly higher in the ADHD + COC group compared to the ADHD and HC groups ($P < 0.001$) and no significant differences between ADHD and HCs were found on SSRT ($P = 0.39$). In addition, no group differences were found on MRT measures and on ACC during go trials.

3.2.2. Cognitive impulsivity. Group discounting rates (k) were not normally distributed and therefore transformed using a logarithmic transformation, which resulted in normal distributions in all groups (Shapiro–Wilk $P_{HC} = 0.16$; $P_{ADHD} = 0.78$; $P_{ADHD+COC} = 0.07$).

Fig. 1 represents the fitted hyperbolic discounting curves on the mean indifference points per group. Table 2 shows that the discounting rate k significantly differed between groups with, post hoc, significantly higher k values for ADHD + COC compared to ADHD and compared to HC. No differences in k values were observed between ADHD and HC ($P = 1.000$). Additionally, R^2 measures are close to 1, indicating a very good fit to the hyperbolic discounting curve (see Fig. 1).

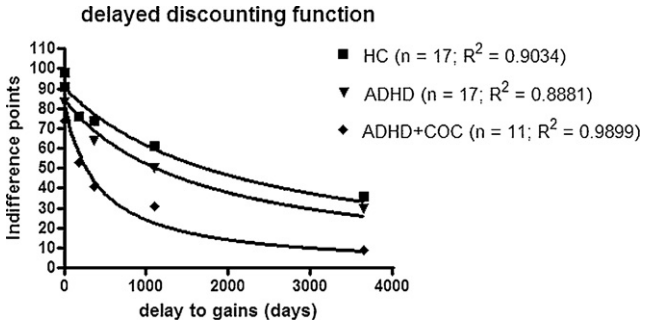

Fig. 1. The fitted hyperbolic discounting curves for the mean indifference points between large delayed and small immediate hypothetical monetary rewards, for control subjects (HC), and ADHD patients without cocaine dependence (ADHD) and ADHD patients with cocaine dependence (ADHD + COC). R^2 represents the fit of the curve to the hyperbolic function.

3.2.3. Interference control. Data from HCs are not presented due to inadequate sample size (data from 10 HC participants are missing). In addition, data from 2 ADHD and 1 ADHD + COC patients is missing due to computer failure. Therefore, we here present data on 15 ADHD and 10 ADHD + COC patients, and do not compare these to HC data. The main outcome measure, reaction time ratio, was distributed normally and no statistically significant group differences were found between ADHD and ADHD + COC on reaction time ratios and accuracy (see Table 2).

3.2.4. Time reproduction. For each separate time length interval, relative discrepancy scores were normally distributed and did not statistically differ between HC, ADHD, and ADHD + COC (see Table 2).

3.2.5. Attentional set-shifting. Data from 5 participants (4 HC and 1 ADHD) were missing due to test acquisition failures, and therefore data are presented for 13 HCs, 16 ADHD and 11 ADHD + COC patients. Data were normally distributed and no significant group differences in set shifting scores were found (see Table 2).

3.2.6. Working memory. Data were missing from 1 ADHD and 1 ADHD + COC participant due to computer failure. Accuracy data were not normally distributed and therefore analyzed using a non-parametric Kruskal–Wallis test over groups. No statistical significant differences were found in accuracy between groups, for the 1-back condition or for the 2-back condition (see Table 2).

3.3. Self-report questionnaires

All self-report questionnaire scores were normally distributed as indicated by Shapiro–Wilk P-values > 0.05.

3.3.1. Impulsivity. ADHD participants scored significantly higher than HCs on 7 out of 9 subscales of the BIS (Table 2), but there were no significant differences between HC and ADHD on the BIS subscales motor impulsivity ($P = 0.11$) and cognitive complexibility ($P = 0.52$). Compared to HCs, ADHD + COC patients scored significantly higher on all subscales of the BIS (see Table 2). ADHD and ADHD + COC patients only differed on the BIS subscale attention (Table 2).

3.3.2. ADHD symptoms. ADHD and ADHD + COC patients scored significantly higher on the ASRS than HCs, but there was no significant difference on the ASRS between the ADHD and ADHD + COC groups (see Table 2).

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Table 1
Clinical characteristics of control participants (HC), ADHD patients without cocaine dependence (ADHD) and ADHD patients with cocaine dependence (ADHD + COC). *Abbreviations*: DART, Dutch adult reading test. All data are represented as means ± standard deviation. A significance level of 0.05 (*) was used as statistically significant.

	HC $n = 17$	ADHD $n = 17$	ADHD + COC $n = 11$
Age (years)	31 ± 6	33 ± 7	36 ± 6
DART (IQ)	106 ± 4	105 ± 4	103 ± 6
ADHD subtype in adulthood			
Hyperactive N (%)	–	0/17 (0%)	2/11 (18%)
Inattentive N (%)	–	8/17 (47%)	1/11 (9%)
Combined N (%)	–	9/17 (53%)	8/11 (73%)
Nicotine use (amount of smokers N (%))	10/17 (59%)	7/17 (41%)	7/11 (64%)
Cigarettes per day for smokers	12 ± 6	8 ± 3	15 ± 6
FTND score for smokers*	3.9 ± 2.0	3.3 ± 1.0	6.9 ± 1.6*
Alcohol use (units per week)	3.2 ± 5.0	7.2 ± 5.3	3.7 ± 4.8
Cannabis use (grams per week)	0.3 ± 0.6	0.0 ± 0.1	0.6 ± 1.2
Amphetamine use (pills per month)	0	0	0
Heroin use (grams per week)	0	0	0
Cocaine use			
Years of cocaine use (mean, SD)	–	–	12.3 ± 6.0
Days since last cocaine use (mean, SD)	–	–	677 ± 569
Number of relapses (mean, SD)	–	–	1.5 ± 0.9

3.4. Correlation analyses

In none of the groups (ADHD, ADHD + COC, and HC), motor impulsivity (SSRT) and cognitive impulsivity (discounting rate k) were correlated significantly with any of the self-reported BIS subscales (all $r < 0.51$; all $P > 0.09$). Similarly, motor and cognitive impulsivity measures did not correlate with self-reported ADHD symptoms (ASRS scores) (all $r < 0.44$; all $P > 0.07$). However, in the total sample, significant correlations between impulsivity measures and BIS subscales and between impulsivity measures and ASRS scores were found (data not presented), but the correlations were mainly driven by some high scoring ADHD + COC patients and some low scoring HC participants, with little to no overlap in scores between groups. Therefore these correlations should be interpreted cautiously.

Measures of motor and cognitive impulsivity were highly correlated, and ADHD patients (with and without cocaine dependence) with more severe motor impulsivity also displayed more severe

Table 2
Primary outcome measures for neurocognitive tasks and self-reported questionnaires in control participants (HC), ADHD patients without cocaine dependence (ADHD) and ADHD patients with cocaine dependence (ADHD + COC). Statistical significance of the differences between groups is based on ANOVA, on ANOVA after logarithmic transformation (indicated by T) or on Kruskal–Wallis testing (indicated by KW). Even when logarithmic transformation was used for analysis, untransformed values are presented in this table for better correspondence with the current literature. We further indicate the Bonferroni levels of significance for the post hoc tests. *Abbreviations*: BIS: Barratt Impulsivity Scale; ASRS, ADHD Self-Report Scale; NS, not significant; * post hoc test difference between HC and ADHD groups; # post hoc test difference between HC and ADHD + COC groups; ˆpost hoc test difference between ADHD and ADHD + COC groups. Data are presented as mean ± standard deviation.

	HC	ADHD	ADHD + COC	ANOVA	Post hoc Bonferroni
Motor impulsivity (stop signal task)					
Stop signal reaction time (ms)	127.4 ± 20.6	146.2 ± 29.4	193.2 ± 57.3	$P < 0.001$	$^{\#}P < 0.001$; $^{\wedge}P = 0.04$
Mean reaction time (ms)	501.3 ± 134.2	522.7 ± 163.2	504.9 ± 74.5	NS ($P = 0.889$)	–
Accuracy on go trials (%)	98.9 ± 1.8	97.6 ± 2.7	98.2 ± 1.3	NS ($P = 0.103$) (KW)	–
Cognitive impulsivity (delay discounting task)					
Mean k value	0.0015 ± 0.0016	0.0013 ± 0.0014	0.0138 ± 0.0197	$P = 0.001$ (T)	$^{\#}P = 0.003$; $^{\wedge}P = 0.002$ (T)
Interference control					
Reaction time (ratio)	–	1.12 ± 0.12	1.17 ± 0.10	NS ($P = 0.442$)	–
Accuracy (%)	–	100 ± 1	98 ± 1	NS ($P = 0.424$) (KW)	–
Time reproduction (time reproduction task)					
Relative discrepancy score (1 s; %)	26.0 ± 9.3	22.1 ± 6.6	26.2 ± 7.8	NS ($P = 0.274$)	–
Relative discrepancy score (3 s; %)	14.0 ± 4.6	13.3 ± 4.8	12.0 ± 4.9	NS ($P = 0.557$)	–
Relative discrepancy score (6 s; %)	9.1 ± 4.5	8.3 ± 2.4	9.1 ± 3.6	NS ($P = 0.760$)	–
Relative discrepancy score (12 s; %)	7.1 ± 2.7	7.3 ± 3.6	9.1 ± 6.5	NS ($P = 0.426$)	–
Relative discrepancy score (20 s; %)	6.1 ± 3.0	6.1 ± 3.6	7.4 ± 6.2	NS ($P = 0.689$)	–
Attentional set-shifting (trail making test)					
Set shifting score	1.72 ± 0.63	1.77 ± 0.11	1.76 ± 0.10	NS ($P = 0.334$)	–
Working memory (n-back task)					
Accuracy 1-back (%)	98.8 ± 2.4	99.7 ± 1.1	98.6 ± 2.2	NS ($P = 0.212$) (KW)	–
Accuracy 2-back (%)	94.8 ± 6.8	93.9 ± 15.1	88.0 ± 23.1	NS ($P = 0.339$) (KW)	–
Self-reported impulsivity (BIS)					
Attention	8.9 ± 2.0	13.1 ± 2.4	15.5 ± 2.0	$P < 0.001$	$^{*}P < 0.001$; $^{\#}P < 0.001$; $^{\wedge}P = 0.019$
Motor impulsiveness	10.4 ± 1.8	12.4 ± 3.2	13.7 ± 3.0	$P = 0.007$	$^{\#}P = 0.007$
Self-control	13.0 ± 3.0	16.1 ± 2.5	18.5 ± 2.4	$P < 0.001$	$^{*}P = 0.005$; $^{\#}P < 0.001$
Cognitive complexibility	6.6 ± 1.5	7.6 ± 2.3	8.8 ± 2.1	$P = 0.025$	$^{\#}P = 0.021$
Perseverance	7.0 ± 1.5	10.6 ± 2.4	11.9 ± 1.7	$P < 0.001$	$^{*}P < 0.001$; $^{\#}P < 0.001$
Cognitive instability	3.4 ± 0.9	5.6 ± 1.5	5.3 ± 1.3	$P < 0.001$	$^{*}P = 0.001$; $^{\#}P < 0.001$
Attentional impulsiveness	11.9 ± 2.5	17.9 ± 3.2	19.1 ± 2.5	$P < 0.001$	$^{*}P < 0.001$; $^{\#}P < 0.001$
Motor impulsiveness	16.1 ± 2.9	21.4 ± 4.2	24.5 ± 3.9	$P < 0.001$	$^{*}P < 0.001$; $^{\#}P < 0.001$
Non-planning impulsiveness	19.6 ± 4.3	23.8 ± 3.9	27.3 ± 2.5	$P < 0.001$	$^{*}P = 0.01$; $^{\#}P < 0.001$
Self-reported ADHD symptoms (ASRS score)	2.4 ± 1.9	11.9 ± 3.7	13.4 ± 2.7	$P < 0.001$	$^{*}P < 0.001$; $^{\#}P < 0.001$

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impulsive decision making deficits (ADHD: $r = 0.70$, $P = 0.002$; ADHD + COC: $r = 0.93$, $P < 0.001$). However, this correlation was not observed in healthy controls ($r = 0.11$, $P = 0.70$).

Additionally, no correlations were found between ASRS scores and other performance indicators of other neurocognitive tasks, including interference control, time reproduction, set-shifting scores and working memory accuracy scores.

Finally, differences in smoking comorbidity may confound the relation between the presence of cocaine dependence and impulsivity (McClernon and Kollins, 2008). Therefore, we calculated the correlations between the FTND and the primary outcome measures (performance on the separate neurocognitive tasks). In our sample, FTND scores did not correlate with any of the primary outcome measures (all correlations lower than $r = 0.32$; $P \geq 0.13$).

4. Discussion

ADHD patients with cocaine dependence showed significantly higher levels of both motor and cognitive impulsivity than ADHD patients without cocaine dependence as well as healthy controls. However, no performance differences were found on other cognitive functions (interference control, attentional set-shifting, time reproduction and working memory) between ADHD patients with and without cocaine dependence, indicating that the observed differences in impulsivity cannot be attributed to a general deficit in executive functions in ADHD patients with cocaine dependence. Moreover, only one of the self-reported impulsivity subscales (BIS attention) was significantly higher in ADHD patients with cocaine dependence and no differences or correlations with ADHD symptom scores (ASRS scores) were observed compared to ADHD patients without cocaine dependence.

Previous research has shown differences between adult ADHD populations and healthy controls in a broad range of additional neurocognitive functions in both executive and motivational/reward circuitries (Bramham et al., 2012; Cummins et al., 2011; Finke et al., 2011; Ibáñez et al., 2011; Marx et al., 2011; Valko et al., 2010; Wilbertz et al., 2012), providing evidence for the dual-pathway model in ADHD (Sonuga-Barke, 2003). However, here, we observed no statistically significant differences on neurocognitive measures between healthy controls and ADHD patients (without cocaine dependence). This discrepancy with previous results might be due to the fact that we only included non-medicated adult ADHD patients that were diagnosed in adulthood, probably representing an ADHD population with fewer ADHD symptoms compared to adult ADHD patients diagnosed during childhood with persisting ADHD symptoms into adulthood and receiving medication to treat their ADHD symptoms. It should also be noted that our samples were relatively small and that subtle differences in performance could not be detected. The latter also implies that the observed differences in impulsivity between ADHD patients with and without cocaine dependence represent very robust and large effects, with effect sizes (Cohen's d) of 1.03 and 0.89 for motor and cognitive impulsivity, respectively.

These robust differences in two separate domains of impulsive behavior (response disinhibition as a marker for dysfunction in executive circuitry and delayed discounting as a marker for alterations in motivational/reward circuitry) between ADHD patients with and without cocaine dependence support the dual-pathway model of ADHD in ADHD patients with cocaine dependence. While both motor and cognitive impulse control depend on intact functioning of the frontal lobes (Watanabe et al., 2002; Winstanley et al., 2004), different parts of the frontal lobes are assumed to be related to the various subtypes of inhibition (Rubia et al., 2001). In a study by Malloy-Diniz et al. in ADHD patients, deficits were found on distinct components of impulsivity (motor, cognitive and attentional) but these measures were not significantly correlated (Malloy-Diniz et al., 2007), providing evidence for separate aspects of impulsive behaviors in ADHD. In contrast, in our study, we found a strong correlation between measures of motor and cognitive impulsivity in ADHD patients, here suggesting the presence of an overall impairment of frontal lobe function. This correlation between motor and cognitive impulsivity was even stronger in our sample of ADHD patients with cocaine dependence. Consistent with the literature (e.g., Broos et al., 2012), we did not observe this correlation in HCs, and one may speculate that, while HCs activate specific parts of frontal lobes necessary for adequate inhibition of motor or decision making, ADHD patients recruit additional perhaps overlapping frontal lobe (resulting from independent executive and motivational/reward) circuitries in an attempt to achieve adequate inhibition. Whether such overlapping inhibitory networks are involved in various impulse control processes in ADHD patients with and without SUD should be investigated in imaging studies during separate response inhibition and delay discounting tasks.

Our findings of increased motor and cognitive impulsivity in ADHD patients with cocaine dependence are in accordance with previous studies in chronic cocaine using individuals. For example, Fillmore and Rush (2002) found increased motor impulsivity (decreased response inhibition) in chronic cocaine users compared to matched healthy controls. However, measures of SSRT were much higher in controls and in chronic cocaine users in the Fillmore et al. study compared to our study, mean SSRT in control participants being twice as high as in our healthy controls. This discrepancy may reflect methodological aspects (task paradigm and/or study sample), but also demonstrates that comparing results from studies in cocaine users and cocaine dependent ADHD patients is not straightforward. Consequently, future studies should aim to compare impulsive behaviors between ADHD patients with and without cocaine dependence, non-ADHD cocaine dependent patients and HCs within a single design.

Our study has both strengths and limitations. A major strength of our study is that our sample was diagnosed using validated tests by trained professionals and that we included only non-medicated male patients and male controls that were matched for age and IQ. Also, patients were extensively screened to exclude the occurrence of other comorbid disorders to reduce possible confounding effects. However, ADHD patients with cocaine dependence were more heavy smokers (higher FTND scores), whereas the ADHD group without cocaine dependence included more ADHD patients with a predominantly inattentive subtype (47% compared to 27%). However, the observed differences in behavioral impulsivity in ADHD patients with and without cocaine dependence were very robust and FTND scores were not correlated with task performance, and therefore we consider it unlikely that these findings are driven by the differences in smoking behavior. Moreover, ASRS scores did not differ between ADHD patients with and without cocaine dependence. However, replication of our findings in larger samples is needed.

In conclusion, this is the first study showing that ADHD patients with comorbid cocaine dependence are more impulsive than age- and IQ-matched ADHD patients without cocaine dependence. With regard to the neuropsychological theories of ADHD, our results indicate the presence of increased impulsivity in ADHD patients with comorbid cocaine dependence related to dysfunctions in both the executive circuitry (response inhibition) and the reward/motivational circuitry (delayed discounting). These findings are important when considering treatment of ADHD patients

Please cite this article in press as: Crunelle, C.L., et al., Impulsivity in adult ADHD patients with and without cocaine dependence. Drug Alcohol Depend. (2012), http://dx.doi.org/10.1016/j.drugalcdep.2012.09.006

with comorbid SUD, and special attention should be paid to psychoeducation and the treatment of impulsive problems in these patients.

Role of funding source

This study was funded by the ZonMw Addiction Program (grant number #31160206), which had no role in the design of the study, collection and analysis of data and decision to publish.

This trial is registered at the Dutch Trial Register, www.trialregister.nl, under Trial ID number NTR3127.

Contributors

W. van den Brink, J. Booij, D.J. Veltman, C.L. Crunelle, and K. van Emmerik-van Oortmerssen were involved in the design of the study, the interpretation of the data, the writing of the report, and the decision to submit the paper for publication. Data collection was performed mainly by C.L. Crunelle.

Conflict of interest

No conflict declared

Acknowledgments

We thank Ms. A. van Els and Ms. K. Beekman for their help in obtaining these data, and thank Ms. M. Doeve, Dr. A.M.D.N. van Lammeren and Ms. F. Anjema for their help in the inclusions of participants in this study.

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