

Executive control deficits in substance-dependent individuals: A comparison of alcohol, cocaine, and methamphetamine and of men and women

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Substance dependence is associated with executive function deficits, but the nature of these executive defects and the effect that different drugs and sex have on these defects have not been fully clarified. Therefore, we compared the performance of alcohol- ($n = 33$; 18 women), cocaine- ($n = 27$; 14 women), and methamphetamine-dependent individuals ($n = 38$; 25 women) with sex-matched healthy comparisons ($n = 36$; 17 women) on complex decision making as measured with the Iowa Gambling Task, working memory, cognitive flexibility, and response inhibition. Cocaine- and methamphetamine-dependent individuals were impaired on complex decision making, working memory, and cognitive flexibility, but not on response inhibition. The deficits in working memory and cognitive flexibility were milder than the decision-making deficits and did not change as a function of memory load or task switching. Interestingly, decision making was significantly more impaired in women addicted to cocaine or methamphetamine than in men addicted to these drugs. Together, these findings suggest that drug of choice and sex have different effects on executive functioning, which, if replicated, may help tailor intervention.

Keywords: Decision making; Cognitive control; Alcohol dependence; Cocaine dependence; Methamphetamine dependence; Sex.

INTRODUCTION

Substance-dependent individuals (SDI) have been shown to have deficits in the domain of executive functioning (Verdejo-García & Pérez-García, 2007). Executive functioning involves the ability to plan, judge, and weigh several options, to make complex decisions, to have an accurate perception of one's own abilities, and to organize, implement, and control other cognitive functions such as memory (e.g., Oscar-Berman & Marinković, 2007;

Tranel, Anderson, & Benton, 1994). Neuropsychological and neuroimaging studies in humans, as well as lesion and electrophysiological studies in animals, suggest that executive functioning relies in large part on the prefrontal cortex (PFC) and its interactions with other brain regions (Stuss & Benson, 1986). This observation, together with studies reporting PFC neuronal loss in SDI (Adams et al., 1993; Krill, Halliday, Svoboda, & Cartwright, 1997), suggests that cognitive deficits observed in SDI may be associated with dysfunction

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of the PFC. The PFC is heterogeneous in its functions and may subserve diverse abilities related to cognitive control functions such as working memory, cognitive flexibility, and response inhibition. This raises the question whether the impairments in executive functioning reported in SDI can be explained by deficits in working memory and other cognitive domains that subserve executive functioning. The present study compared performance of alcohol-dependent individuals (SDI-alcohol), cocaine-dependent individuals (SDI-cocaine), and methamphetamine-dependent individuals (SDI-methamphetamine) on various measures of executive functioning including complex decision making, working memory, cognitive flexibility, and response inhibition. In addition, it is not well understood whether men and women are affected differently by chronic drug abuse, and this issue was addressed in the current study.

Executive functioning and substance dependence

Executive functioning is a complex construct, which involves different cognitive domains. Decision making is one domain of executive functioning that is impaired in heavy drug use. For example, SDI continue to use drugs despite negative health-related, psychological, social, and legal consequences (Verdejo-García et al., 2007a). The Iowa Gambling Task (IGT) is an experimental decision-making task that requires the integration of different aspects of executive functioning in order for successful completion (see Dunn, Dalgleish, & Lawrence, 2006). The key feature of the task is that participants have to forgo high short-term rewards (i.e., facsimile money) for long-term profit (e.g., Bechara, Damasio, & Damasio, 2000). Studies have consistently shown that SDI, including individuals addicted to alcohol, cocaine, and methamphetamine, pursue actions that bring immediate reward at the risk of incurring future negative consequences (Bechara & Damasio, 2002; Bechara & Martin, 2004; Scott et al., 2007; Verdejo-García et al., 2007a; Verdejo-García, Rivas-Pérez, Vilar-Lopez, & Pérez-García, 2007b), suggesting that these individuals have a “myopia for the future” (see also Rogers & Robbins, 2001). An important region involved in processing many types of reward and punishment and making rapid changes in response to environmental change is the orbitofrontal cortex (OFC), in particular the ventral and medial prefrontal cortex (VMPFC; e.g., Bechara et al., 2000). The OFC has been hypothesized to be dysfunctional in SDI (Adinoff

et al., 2006; Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Knutson, Westdorp, Kaiser, & Hommer, 2000; Tanabe et al., 2007). For example, using single photon emission computed tomography (SPECT), Adinoff and colleagues (2006) showed that individuals addicted to cocaine had reduced activity in the OFC relative to healthy comparisons when performing the IGT.

The functional integrity of the OFC, however, relies on neural systems that subserve memory, in particular working memory (Bechara, Tranel, & Damasio, 2002). Working memory is defined as the process of storing and online manipulation of information (Baddeley, 1994) and includes short-term storage, rehearsal, and the executive processes that operate on the contents of memory (Smith & Jonides, 1999). The dorsolateral prefrontal cortex (DLPFC) is thought to subserve working memory (Goldman-Rakic, 1992) and appears particularly important for the executive processor of mnemonic operations (Petrides, 2000). Studies with SDI have suggested that deficits in the working-memory domain are not purely due to a mnemonic impairment. Rather, impairments may be due to an executive control problem. Specifically, Bechara and Martin (2004) found that individuals addicted to alcohol, cocaine, or methamphetamine performed below normal levels on the working-memory task, but increasing the memory load did not influence performance. The task used in this study (i.e., the delayed nonmatch to sample; DNMS) includes a memory component and an executive component. Because performance of SDI was not influenced by increased memory load, the authors argued that the deficiency SDI displayed on this task must be related to the executive component of working memory as opposed to the storage component (Bechara & Martin, 2004). Thus, according to these authors, problems in SDI arise when a strategy should be efficiently implemented to memorize items (Bechara & Martin, 2004; Woods et al., 2005; see also Scott et al., 2007). However, to clarify the nature of the working-memory deficits in SDI, we need to evaluate performance on a task that specifically measures the mnemonic component of working memory. In this study we taxed the function of working memory with the Tic Tac Toe Test (Alting von Geusau, Stalenhoef, Huizinga, Snel, & Ridderinkhof, 2004), a modified version of the Corsi–Milner paradigm (Milner, 1971). Participants have to decide whether a pattern matches with a prespecified pattern; therefore the task taps specifically into the memory component of working memory. Furthermore, to directly elucidate the relationship between working memory and decision making, we determined the contribution of the mnemonic working-memory

domain to decision-making performance. Since the executive domain of working memory is thought to contribute to decision making (Bechara & Martin, 2004), we did not expect that the mnemonic domain would contribute to decision making. Working memory most likely consists of separate modules, but in this study we focused on visuospatial working memory (Baddeley, 1994).

Lastly, cognitive flexibility and response inhibition are important domains of executive functioning. There is evidence to suggest that alcohol abusers (Errico, King, Lovallo, & Parsons, 2002) and cocaine abusers (Klüber, Murphy, & Garavan, 2005) show poorer performance on measures of cognitive flexibility and response inhibition (see also Verdejo-García, Bechara, Recknor, & Pérez-García, 2006). To measure the performance of SDI on each of these specific cognitive domains, we included task-switching paradigms (Rogers & Monsell, 1995) and a response inhibition paradigm that are specifically designed to tap into these domains of executive functioning. In the switching task, participants rapidly switch between two or more reaction time (RT) tasks that are typically performed to the same set of stimuli (e.g., local and global figures; Miyake et al., 2002). Switching between tasks is associated with a sizable decrement in response speed and accuracy (Rogers & Monsell, 1995). We also included the Wisconsin Card Sorting Test (WCST) as a measure of cognitive flexibility, because it requires flexible adjustment of actions following performance feedback (Stuss & Levine, 2002). Response inhibition was assessed using the stop-signal task (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Logan & Cowan, 1984). The stop-signal paradigm has been developed to investigate the covert cognitive processes that constitute inhibitory control (Logan & Cowan, 1984). The task is unique because of its direct assessment of the ability to inhibit a prepotent action, especially at the cognitive or attentional level, as opposed to the motor response level.

Thus, the first aim of this study was to describe the pattern of executive-functioning deficits in SDI by evaluating their performance on complex decision making, working memory, cognitive flexibility, and response inhibition. The interpretation of executive deficits in substance dependence, however, is constrained by the possibility that different drugs may have different effects on brain functioning. Also, there is more and more evidence for sex-dependent brain-behavior relationships (Tranel, Damasio, Denburg, & Bechara, 2005). Therefore, in an attempt to fully understand patterns of executive functioning in SDI, it is important to examine the effects of different types of drugs and sex.

Drug type

There is mounting evidence to suggest that substance abuse affects an individual's executive functioning; however, the type of substance used may influence this particular relationship (Selby & Azrin, 1998). Gonzalez, Bechara, and Martin (2007) directly compared performance of alcoholics and methamphetamine-addicted individuals on the IGT and the delayed nonmatched to sample working-memory task. They found that the effects of alcohol on these measures were milder than the effects of methamphetamine (see also Bechara & Martin, 2004; Verdejo-García et al., 2007a). On the same note, chronic alcohol abuse seems to have less of an effect on executive functioning than does cocaine abuse (Easton & Bauer, 1997). In addition, nearly half of the 18 million alcoholics in the USA do not show any signs of cognitive, sensory, or motor impairments. When signs are present, deficits in tests of memory, fluency, cognitive flexibility, and perseverative responding are generally only mild (Oscar-Berman & Marinković, 2007). In contrast, chronic methamphetamine use, for example, has been associated with persistent cognitive impairments in various domains of executive functioning (Barr et al., 2006). Based on these findings, it seems reasonable to expect that different drug types may have differential effects on executive functioning. Specifically, we expected that chronic cocaine and methamphetamine abuse would be associated with more severe neurotoxic effects and hence more severe impairments on various measures of executive functioning relative to chronic alcohol abuse.

Sex

Another variable that may explain differences in performance on various measures of executive functioning may be sex. Interestingly, sex differences in healthy comparisons have been reported for the IGT. That is, men tend to perform slightly better than women (Bechara & Martin, 2004; Bolla, Eldreth, Matochick, & Cadet, 2004; Overman, 2004; Overman et al., 2006). For example, in a study reviewed by Overman (2004) men selected the advantageous decks 79% of the time by the third block, whereas women chose the advantageous decks 68% of the time at that time point. Sex-related differences in frontal-lobe metabolism rate during resting state as well as structural differences in the frontal lobes have been reported and may underlie the differences in performance between men and women on the IGT (Overman, 2004). Whether sex affects decision making in SDI

as well is not well understood, partly because women tend to be underrepresented in studies on drug abuse and decision making. Although findings on sex-related differences in SDI are still considered controversial (Oscar-Berman & Marinković, 2007), molecular (reviewed in Barr et al., 2006) as well as neuroimaging studies (e.g., Adinoff et al., 2006) have shown that methamphetamine and cocaine affect the central nervous system differently in men and women. This study aimed to contribute to the current knowledge on sex and drug abuse by exploring whether sex has an effect on executive functioning at a behavioral level.

Although sex may influence the relationship between executive functioning and substance abuse, it is important to keep in mind that not every experimental task is sensitive enough for potential differences between men and women. That is, except for mental rotation (e.g., Peters, Manning, & Reimers, 2007) and fine motor tasks (e.g., Nicholson & Kimura, 1996), differences between men and women in terms of cognitive control tend to be subtle. The IGT has been shown to be sensitive to sex differences in some studies (e.g., Overman, 2004); however, most studies with "simple" cognitive control tasks similar to those used in the current study do not tend to find sex differences at the behavioral level (see Bell, Willson, Wilman, Dave, & Silverstone, 2006; Heaton, 1981; Ray Li, Huang, Constable, & Sinha, 2006; Mulvihill, Skilling, & Vogel-Sprott, 1997; Overman, 2004; Yehene & Meiran, 2007). Therefore, we expected to find sex differences on the IGT only, with men outperforming women on this particular task (see Overman, 2004).

Summary

The goal of this study was to examine patterns of executive functioning deficits in SDI in different cognitive domains with a particular interest in exploring the effects of different types of substances used and the influence of sex. We expected decision making as measured with IGT to be deficient in SDI-cocaine and SDI-methamphetamine only (Gonzalez et al., 2007). In addition, it is hypothesized that working-memory deficiencies in SDI are due to the executive component of working memory (Bechara & Martin, 2004), suggesting that the mnemonic component is still intact. Based on this hypothesis, we expected that SDI would perform normally on our measure of working memory (see also Bechara & Martin, 2004). In terms of the other executive functioning tasks,

there is evidence to suggest that chronic substance abuse is associated with impaired performance on tasks that tap into cognitive flexibility and response inhibition (e.g., Klüber et al., 2005). We therefore hypothesized that SDI-cocaine and SDI-methamphetamine would show poorer performance on those measures of executive functioning as well.

The second goal was to further elucidate the relationship between decision making and other cognitive control functions. It has been suggested in the literature that the executive component of working memory (Bechara & Martin, 2004), cognitive flexibility, and response inhibition (Dunn et al., 2006) contribute to decision making. Based on these hypotheses, we predicted that performance on the shifting task, the WCST, and the response inhibition task would make significant contributions to the combined regression model of decision making. Because our working-memory task specifically taps into the mnemonic domain of working memory (Bechara & Martin, 2004) we did not expect working-memory performance to contribute to decision making.

METHOD

Participants

In total, 133 participants from the broader Iowa area participated in the study. Healthy, drug-free comparison participants ($n = 36$) were selected from a registry of such individuals maintained in the University of Iowa's Division of Behavioral Neurology and Cognitive Neuroscience. These participants were initially recruited through advertisement at the rehabilitation center. The selection criteria for the comparison participants included the absence of a history of mental retardation, learning disability, psychiatric disorder, substance abuse, neurological disorder, or systemic disease that may affect the central nervous system, based on clinical interviews conducted with these participants before their induction. The healthy comparisons in the current sample had not undergone neuropsychological assessment prior to this study. In contrast to the substance-dependent participants, no structured clinical interview was administered in the healthy group.

Substance-dependent individuals (SDI) consisted of inpatients who had been admitted to Mid-Eastern Center for Chemical Abuse (MECCA), an inpatient facility for detoxification and treatment. Of the 113 SDI who were included, 33 participants were primarily alcohol dependent,

38 participants were primarily cocaine dependent, and 27 participants were primarily methamphetamine dependent as indicated by the participants' reports. Drug of choice was defined as substance used >80% of the time prior to treatment, but some participants used other drugs occasionally in the 30 days prior to treatment, especially cannabis (see Table 1). Note that the nonacute effects on neuropsychological performance of cannabis tend to be mild (Gonzalez, 2007). All SDI had experienced serious substance abuse problems in the past that had required professional intervention, which was the reason for their treatment. The selection criteria for SDI were (a) meeting the DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition*; American Psychiatric Association, 1994) criteria for substance dependence; (b) absence of psychosis; and (c) no documented head injury or seizure disorder. Each SDI was tested at the end-stage of their treatment shortly before their discharge. The duration of abstinence from substance use was known in these participants based on their length of stay at MECCA. The time varied among individuals, but the minimum period of abstinence from any substance use was 15 days. Thus at the time of their testing, the SDI were no longer in acute withdrawal or taking any medications to control withdrawal (e.g., benzodiazepines). Urine toxicology screening for opiates, stimulants, and marijuana and breathalyzer tests were conducted on these SDI immediately before testing. SDI were also routinely checked at MECCA, including the day before they were brought for testing. Therefore, not only very recent substance use can be ruled out, but also it is

reasonable to rule out the use of substances during the entire period of abstinence. The Structured Clinical Interview for DSM-IV (SCID-IV) was used to assign Axis I diagnoses (including alcohol and other drug abuse and/or dependence). SDI whose preponderant use was alcohol or stimulant drugs were identified through verbal report. The results showing primary drug of choice are presented in Table 1. The areas of comorbid psychopathologies that we probed with the SCID were psychoses, major depressive disorder, and anxiety disorders. The sum of scores on each psychopathology was obtained, and participants who had a score greater than 3 were excluded from the study. SDI who met the criteria for psychoses or a current major depressive disorder were excluded.

All participants were adults and provided informed consent that was approved by the appropriate human subject committees at the University of Iowa. All participants were paid for their participation in gift certificates at an hourly rate. The demographic data of the groups are presented in Table 2. An analysis of variance (ANOVA) for mean age revealed a significant group difference, $F(3, 133) = 5.33, p < .01$. Post hoc comparisons showed that the SDI-alcohol were older than the four other groups. The SDI-methamphetamine, SDI-cocaine, and comparison group did not differ from each other in age.

A chi-square comparison revealed that there was no difference between groups in sex distribution. An ANOVA revealed that groups differed significantly in years of education, $F(3, 133) = 35.77, p < .001$, and post hoc comparisons revealed that the comparison group was significantly more

TABLE 1
Drug use histories of substance-dependent individuals who took part in the study

SDI	N	Occasional drug use in previous 30 days	
		Drug type	Number of participants
Alcohol	33	Amphetamine	2
		Cannabis	4
		Cocaine	1 (used in combination with cannabis)
Cocaine	27	Alcohol	7
		Amphetamine	1
		Cannabis	9
		Heroin	1 (used in combination with cannabis)
		Opiates/Analgesics	1
Methamphetamine	38	Sedatives/Hypnotics/Anti-Anxiety	1 (used in combination with cannabis)
		Alcohol	4 (used in combination with cannabis in 3 participants)
		Cannabis	12
		Cocaine	5 (used in combination with cannabis in 4 participants)
		Opiates/Analgesics	2 (used in combination with cannabis in 1 participant)
		Sedatives/Hypnotics/Anti-Anxiety	3 (used in combination with cannabis in 2 participants)

Note. SDI = substance-dependent individuals.

TABLE 2
Demographics of participants in the study

	<i>Healthy comparisons</i>	<i>SDI-alcohol</i>	<i>SDI-cocaine</i>	<i>SDI-methamphetamine</i>
Total <i>N</i>	36	33	27	38
Age (years: mean \pm <i>SD</i>)	28.9 \pm 9.8	37.9 \pm 9.9*	34.5 \pm 8.9	30.7 \pm 7.0
Gender (no. F/M)	17/19	18/15	14/13	25/13
Handedness	35 right-handed, 1 mixed	28 right-handed, 4 left-handed, 1 unknown	34 right-handed, 3 left-handed, 1 unknown	23 right-handed, 3 left-handed, 1 mixed
Education (years: mean \pm <i>SD</i>)	16.2 \pm 2.4	13.8 \pm 2.4*	11.4 \pm 2.2*	11.7 \pm 1.4*
Times used in past 30 days (mean \pm <i>SD</i>)	N.A.	2.7 \pm 3.5	2.9 \pm 4.5	3.8 \pm 5.0
Years of abuse (mean \pm <i>SD</i>)	N.A.	19.5 \pm 10.4	10.1 \pm 7.5	7.8 \pm 4.9

Note. Drug use refers to drug of choice (used >80% of the time). SDI = substance-dependent individuals. N.A. = not applicable.

*Significantly different from healthy comparison group at $p < .05$.

educated than all the SDI groups. The differences in age and years of education may be a concern when interpreting group difference in cognitive control, because both demographic variables have been found to influence performance on tasks that tap into executive functioning (Fals-Stewart & Bates, 2003). To take these demographic factors into account, we entered age and years of education as covariates in all our analyses.

Decision making. (Bechara, Damasio, Damasio, & Anderson, 1994). Decision making was tested with a computerized version of the Iowa Gambling Task (IGT). The task involves four decks of cards called A', B', C', and D'. In two decks (A' and B'), choosing a card is followed by a high gain of facsimile money, but at unpredictable points the selection of a card is followed by a high penalty, so that in the long run, these decks are disadvantageous. In the other two decks (C' and D'), the immediate gain is smaller but the future loss is also smaller, so that in the long run these decks are advantageous. The total number of trials was set at 100 card selections. Participants were told that the goal of the game is to win as much money as possible, but that some of the decks are worse than others, and that they should try to stay away from those decks in order to win the game.

To score the performance of the participant on the IGT, the number of cards picked from decks A' and B' are added in each block of 20 cards, and the number of cards picked from decks C' and D' are added separately in each block of 20 cards. A net score is then obtained by subtracting the total number of cards selected from disadvantageous minus disadvantageous decks: (C' + D') - (A' + B') for each block of 20 cards (Bechara & Martin, 2004).

Specific cognitive control tasks

Working memory. (Tic Tac Toe; Alting von Geusau et al., 2004). Participants sat in front of a computer screen on which a 3 \times 3 grid was continuously presented. The task consisted of two phases: a presentation phase and a recognition phase. During the presentation phase, a combination of Xs and Os was presented within the grid, containing a pattern of either 3 figures (low memory load) or 4 figures (high memory load). The recognition phase could be initiated by pressing the space bar. During the recognition phase Xs and Os were presented 600 ms each, one after another at different positions in the grid. The length of the series varied between 4 and 7 presentations for low load and between 4 and 9 presentations for high load. When the combination of presented Xs and Os matched the prespecified pattern indicated by the presentation phase, participants were required to press a left (z) or right (/) button at the keyboard (counterbalanced across participants). The task was presented in blocked order, starting with a practice block of 3 trials, followed by two blocks including 15 trials for load 3 and 15 trials for load 4 separately. The order of blocks was counterbalanced across participants to control for effects of time-on-task. The main dependent variables were the proportion correct responses and median RT in blocks of load 3 (low) versus load 4 (high).

Cognitive flexibility. (see also Rogers & Monsell, 1995). A cue was presented on the computer screen, consisting of a small or large figure, followed by a 400-ms delay, followed by a geometric figure. In this figure, lines of a global figure (square or rectangle) were composed of smaller local figures (squares or rectangles). Depending on the cue, participants were instructed to respond with a

left-hand response to squares and a right-hand response to rectangles (counterbalanced across participants). Thus, when the cue indicated a local figure, participants responded to the shape of the local figure by giving a left- or right-hand response. When the cue was a global figure, participants responded to the shape of the global figure by giving a left- or right-hand response. The cue changed in predictable order following four consecutive rules. The task consisted of two practice blocks for local and global figures separately and an experimental block of 160 trials. The main dependent variables were median RT and percentage errors on cue alternation and cue repetition trials.

The Wisconsin Card Sorting Test. (Stuss & Levine, 2002). The WCST is originally designed to measure rule-shifting and abstraction ability. Participants were presented with two decks of 64 cards each.

Participants were told that each time they sort a card the computer will tell them whether they were right or wrong, depending on the criterion at stake (i.e., sorting based on color, shape, or number). Subsequently, participants were told that once the rule was correctly applied for a (prespecified) number of trials, the matching principles changed unannounced, and participants were to adapt their strategy based on feedback from the computer. We included “perseverative error scores” and the “number of categories completed” as dependent variables.

Response inhibition. (Aron et al., 2003). Participants responded to a left or right pointing arrow on the screen by pressing the corresponding keys on the keyboard (“z” and “/”, respectively) with the left or right index finger. Arrows were presented in green against a black background screen, and the arrow direction varied randomly and with equal probability. On 25% of the trials, a stop-signal was presented consisting of a color change of the arrow—from green to red. The timing of the color change was dynamically adjusted and was targeted at 50% correct inhibits using a tracking algorithm. Upon successful stopping, the stop-signal delay on the next stop trial was increased by 50 ms. Failures to inhibit were followed by a 50-ms decrease in stop-signal delay. Participants were instructed to respond fast and as accurate to the go-signals and not to delay their go responses awaiting the possible occurrence of a stop-signal. The task consisted of a practice block of 50 trials and two experimental blocks of 100 trials each. The dependent variables were RTs to go-signals and stop-signal RT as an index of the speed of

response inhibition. Stop-signal RT was estimated using the horse-race model (for details, see Logan & Cowan, 1984).

RESULTS

The main goal of this study was to examine executive control functioning in SDI, taking into account drug type and sex. To this end, we performed analyses of covariance (ANCOVAs), which allow for estimating the variance explained by drug type and sex for performance on each individual cognitive task after controlling for confounding variables (i.e., age and education).

The second goal was to clarify the relationship between decision making and other cognitive domains, such as working memory. We addressed this question by performing a stepwise regression analysis. By using this type of regression we could determine whether individual variables contribute significantly to decision making. Variables are entered in the combined regression model based on whether they individually correlate with decision making (i.e., significant Pearson correlations).

ANCOVAs

Decision making

The number of advantageous choices on the IGT was submitted to a Sex (2) \times Group (healthy comparisons, SDI-alcohol, SDI-cocaine, and SDI-methamphetamine) \times Task Block (5) repeated measures ANOVA with age and years of education as covariates. This resulted in a main effect for group, $F(3, 112) = 3.10, p < .05$, sex, $F(1, 112) = 4.54, p < .05$, block, $F(4, 448) = 3.10, p < .05$, a significant Block \times Group interaction, $F(4, 448) = 2.13, p < .05$, and a marginally significant Block \times Group \times Sex interaction, $F(10, 448) = 1.8, p < .055$ (Greenhouse–Geisser). The Block \times Group interaction suggests that different groups learn at different rates, and this was examined by group-wise comparisons. For each group comparison, it was determined whether the groups differed in learning rate, which was statistically verified by Block \times Group interactions. As predicted, this resulted in significant interactions between healthy comparisons and SDI-cocaine, $F(3, 184) = 4.04, p < .01$, and between healthy comparisons and SDI-methamphetamine, $F(4, 220) = 7.82, p < .001$, but the interaction between healthy comparisons and SDI-alcohol was not significant ($p = .09$). Comparisons between SDI groups revealed that these groups did not differ significantly from each other.

Separate one-way ANCOVAs identified group differences for Blocks 2 through 5, with Tukey post hoc comparisons suggesting that the healthy comparisons choose more advantageously than SDI-cocaine and SDI-methamphetamine for Blocks 2 through 5 (all p s < .05). Healthy comparisons choose also more advantageously than SDI-alcohol in Block 4 and Block 5 (p s < .05).

Against expectations, no significant sex differences were found for the normal comparisons and SDI-alcohol, but interestingly, the Block \times Group \times Sex trend suggests that the women addicted to cocaine or methamphetamine perform worse on the IGT than do men addicted to the same drug phenotypes (see Figure 1).

Working memory

The repeated measures analysis for percentage correct with load (low vs. high) as within-subject factor and group (healthy comparisons, SDI-alcohol, SDI-cocaine, and SDI-methamphetamine) and sex (2) as between-subject factors resulted in a main effect for group, $F(1, 106) = 5.15$, $p < .001$. Age explained a significant proportion of the variance in working-memory performance, and the effect for load no longer reached significance after this variable had been entered as covariate (see also Bechara & Martin, 2004). Separate group comparisons identified significant group effects for healthy comparisons and SDI-cocaine, $F(1, 62) = 6.81$, $p < .05$, and for healthy comparisons and SDI-methamphetamine, $F(1, 52) = 13.05$, $p < .01$. Healthy comparisons made fewer errors than SDI groups, but the performance of the SDI did not worsen as a function of memory load (i.e., no significant Group \times Memory

Load interaction). Interestingly, the SDI-methamphetamine made more errors than the SDI-alcohol, $F(1, 42) = 4.26$, $p < .05$, and SDI-cocaine, $F(1, 48) = 6.50$, $p < .05$. Men and women in all groups performed comparably on this task as indicated by the nonsignificant effect for sex (see Figure 2).

Cognitive flexibility

Median RTs for correct responses were submitted to a Rule (local and focal) \times Switch (repetition, switch) \times Group (healthy comparisons, SDI-alcohol, SDI-cocaine, and SDI-methamphetamine) \times Sex (2) repeated measures analysis. Rule represents here the RTs for local and focal rules, whereas switch is representative for the RTs on repetition trials and switch trials. This analysis resulted in a main effect for group, $F(3, 112) = 2.73$, $p < .05$, and sex, $F(1, 112) = 8.20$, $p < .01$. Separate group comparisons revealed that the healthy comparisons were faster than the SDI-cocaine, $F(1, 66) = 5.24$, $p < .05$, and the SDI-methamphetamine, $F(1, 53) = 10.52$, $p < .01$. There was no differential decrement in response speed for the various drug groups as indicated by the nonsignificant Group \times Switch interaction (see Figure 3). Against predictions, regardless of group membership women were slower than men, as indicated by the main effect for sex.

Wisconsin Card Sorting Test

A group (healthy comparisons, SDI-alcohol, SDI-methamphetamine, and SDI-cocaine) and sex (2) ANOVA for perseverative errors with age and education as covariates resulted in a significant

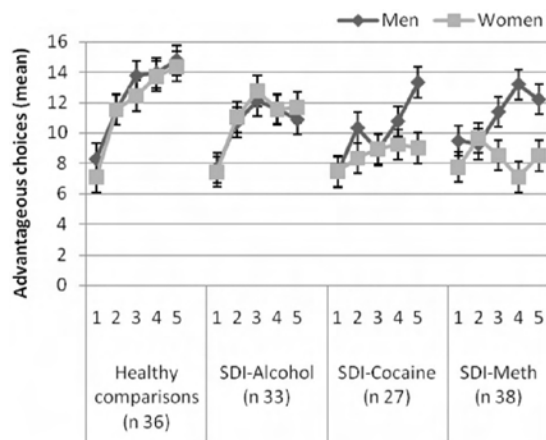


Figure 1. Iowa Gambling Task performance: Performance of comparison participants, alcohol-dependent individuals (SDI-alcohol), cocaine-dependent individuals (SDI-cocaine), and methamphetamine-dependent individuals (SDI-meth) on the Iowa Gambling Task (IGT).

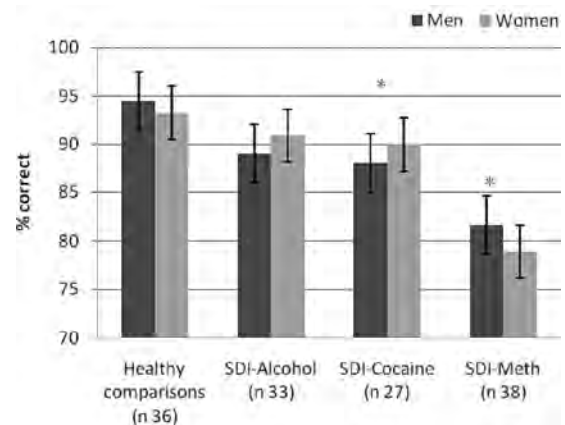


Figure 2. Working-memory performance: Performance of comparison participants, alcohol-dependent individuals (SDI-alcohol), cocaine-dependent individuals (SDI-cocaine), and methamphetamine-dependent individuals (SDI-meth) on the working-memory task. Men and women are plotted separately. Asterisks denote that SDI-cocaine and SDI-meth differ significantly from healthy comparisons.

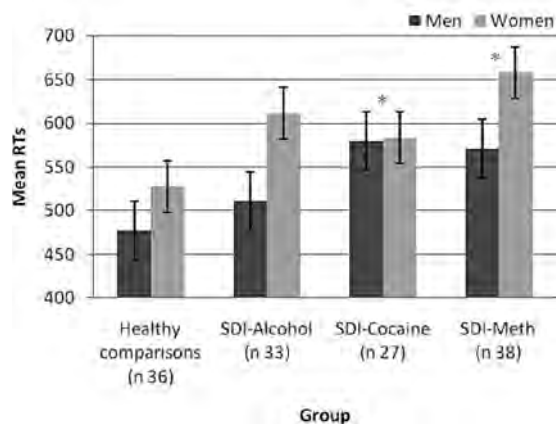


Figure 3. Switch task performance: Performance of comparison participants, alcohol-dependent individuals, cocaine-dependent individuals (SDI-cocaine), and methamphetamine-dependent individuals (SDI-meth) on the local-global task switch task, showing that SDI-cocaine and SDI-meth groups are slower than the healthy comparisons on this paradigm. Men and women are plotted separately. Asterisks denote that SDI-cocaine and SDI-meth differ significantly from healthy comparisons.

effect for age only, $F(1, 121) = 4.17$, $p < .05$, indicating that younger age is associated with fewer preservative errors. No main effects for group or sex were found (all $ps > .2$).

Response inhibition

Participants who failed to inhibit responses on more than 80% of the stop trials were excluded from the analysis ($n = 30$, 24% of our sample), because this would impair the estimation of the stop-signal reaction time. Mean RTs to go-signal trials (i.e., trials where no stop-signal was presented) and stop-signal RTs (SSRTs) were computed for each participant. First, it should be noted that all participants included in this analysis were able to inhibit their responses on about half of the trials on which a stop-signal instructed them to stop, so the tracking algorithm worked well for all groups (50%, 53%, 52%, and 51% for control, SDI-alcohol, SDI-methamphetamine, SDI-cocaine, respectively, $F < 1$).

Against expectations, the group (healthy comparisons, SDI-alcohol, SDI-methamphetamine, and SDI-cocaine) and sex (2) ANOVA for go-signal RTs with age and years of education as covariates did not result in a significant effect (all $ps > .10$). The same holds for SSRTs.

Stepwise regression analyses

We performed a stepwise regression analysis to clarify the relationship between decision-making performance (total advantageous – total disadvantageous), drug status, sex, and performance on

various executive-functioning tasks. With this method variables are entered in the model based on the semipartial correlation with the dependent variable—that is, based on the relationship between the individual variable and the dependent variable while controlling for the effect of the other variables on the dependent variable. For each new variable added, it is tested whether the variance explained (i.e., R^2) was significantly increased and whether both variables were needed. First we explored simple correlations between decision making and all other individual variables to determine which variables to include in the combined model. Decision making was significantly correlated with education ($r = .38$), drug status ($r = -.40$), sex ($r = -.23$), % correct on working memory ($r = .23$), total switching reaction time ($r = -.23$), and total correct on WCST ($r = -.24$), all $ps < .02$. Subsequently, these variables were used in the regression model. All the collinearity statistics were in the normal range, suggesting that the predictor variables were not highly correlated with each other. The first variable entered was drug status, which accounted for 17% of the variability in decision making, $F(1, 82) = 16.82$, $p < .001$; see Table 3). Sex was entered in the second step, which accounted for an additional 14% of the variability in decision making, $F_{change}(1, 81) = 16.54$, $p < .001$. Lastly, total correct on WCST contributed significantly to decision making and accounted for an additional 4.3% of the variability, $F_{change}(1, 80) = 5.34$, $p < .05$. Thus a total of 35% of the variability in decision making was explained by these three variables (see Table 3). The other variables, including percentage correct on working memory, total switch RT, and age did not meet the criteria to be included in the model. Even though collinearity cutoffs were not violated, significant intercorrelations between working memory and switching probably explained why

TABLE 3
Hierarchical regression analysis

Step		B	SE	β
1 ^a	Constant	24.66	4.61	
	Drug status	-10.98	2.68	-.41**
2 ^b	Constant	56.81	8.97	
	Drug status	-10.23	2.46	-.38**
	Sex	-22.11	5.44	-.38**
3 ^c	Constant	102.15	21.47	
	Drug status	-8.97	2.46	-.34**
	Sex	-23.08	5.31	-.39**
	Total correct WCST	-0.63	0.27	-.21*

Note. WCST = Wisconsin Card Sorting Test.

^a $R^2 = .17$. ^b $\Delta R^2 = .14$. ^c $\Delta R^2 = .04$ (all $ps < .05$).

* $p < .05$. ** $p < .001$.

these indices did not reach significance in the regression. We decided to drop switching to estimate the effect of working memory on decision making. Again, total percentage correct on the working-memory task did not contribute significantly to performance on the IGT ($p = .45$).

DISCUSSION

SDI with cocaine as their primary drug of choice and SDI with methamphetamine as their primary drug of choice performed below normal levels on all measures of decision making, working memory, and cognitive flexibility, as assessed with the IGT, the Tic Tac Toe working-memory test, and the task-switching paradigm, respectively. The deficits of cocaine- and methamphetamine-addicted individuals on working memory and cognitive flexibility were relatively mild, and the impairments did not increase as a function of delay (Bechara & Martin, 2004; Woods et al., 2005) or as a function of task switching. In addition, only drug status and sex, and to some extent also WCST performance, accounted for the variability in decision-making performance as modeled in the stepwise regression. Although performance on the working-memory task and switching task correlated individually with decision making, performance on neither of the tasks significantly contributed to decision making when modeled in combination with the other predictor variables.

Bechara and Martin (2004) speculated that impairment in working memory reported in SDI may lie in the executive component (including shifting and response inhibition). Furthermore, this type of working-memory dysfunction as opposed to the mnemonic component of working memory is thought to interfere with decision making. Our results are partly compatible with this notion, given that the memory component of working memory did indeed not contribute to decision making. The WCST as a measure of shifting contributed to decision making, indicating that shifting may play a role in IGT performance. However, our results also show that SDI-cocaine and SDI-methamphetamine performed below normal levels on our measure of working memory that explicitly tapped into mnemonic aspects of working memory, indicating that even this component of working memory may be mildly affected in SDI.

Contrary to our expectations, response inhibition as assessed with the stop-signal task, as well as performance on the WCST, was not affected in our sample of SDI. Some studies suggest that SDI are impaired on these tasks (e.g., Errico et al., 2002),

but deficits do not seem to be robust enough when covariates such as age and education are taken into account, especially with small sample sizes (see also Fals-Stewart & Bates, 2003). Convergent evidence has been reported for both the stop-signal task and the WCST in poly drug users, cocaine users, and methamphetamine abusers (Bartzokis et al., 2000; Grant, Contoreggi, & London, 2000; Hoffman et al., 2006; Verdejo-García et al., 2006; Verdejo-García & Pérez-García, 2007). In addition, duration of abstinence may be linked with performance improvements on these executive-functioning measurements. Longer duration of abstinence from alcohol for example, is associated with better performance on short-term memory task (Brandt, Butters, Ryan, & Bayog, 1983, as cited in Medina, Shear, Schafer, Armstrong, & Dyer, 2004). Similar results have been reported in abstinent cocaine abusers, in whom duration of abstinence was correlated with improved attention scores (O'Malley, Adamse, Heaton, & Gawin, 1992) and IGT performance (Bartzokis et al., 2000). Importantly, chronic cocaine abuse was still related to mild but definite neuropsychological deficiencies (O'Malley et al., 1992; Verdejo-García et al., 2006). In addition, although IGT performance was better in abstinent cocaine abusers ($n = 6$) than nonabstinent abusers ($n = 6$) in the study of Bartzokis et al. (2000), individual scores of the former group were still mostly in the impaired range. Thus, SDI-cocaine and SDI-methamphetamine do not seem to be impaired on some domains of executive functioning, which is probably related to duration of abstinence. In addition, Fals-Stewart and Bates (2003) have suggested that the brain may have the capacity to compensate for the effects of a single drug. Nevertheless, significant impairments in various domains of executive functioning (e.g., decision making) persist in people addicted to cocaine or methamphetamine. This suggests that the neurotoxicity of cocaine and methamphetamine may be associated with more severe and even permanent structural and functional damage to the frontal lobe.

On the other hand, individuals who identified alcohol as their drug of choice in our sample showed no evidence of deficits in decision making, working memory, cognitive flexibility, or response inhibition, indicating that the effects of alcohol in non-Korsakoff alcoholics on executive functioning are milder, if present at all (Gonzalez et al., 2007; Oscar-Berman & Marinković, 2007). Nevertheless, we need to interpret this finding with caution, since it is difficult to isolate "pure" users. We only included SDI who used their drug of choice over 80% of the time prior to their treatment, but drug

use is often not constant over their lifetime (Gonzalez et al., 2007), and especially the participants addicted to either cocaine or methamphetamine tended to use other drugs occasionally. Another complication is that substance dependence tends to be associated with mood disorders (see Bechara & Martin, 2004), and it is difficult to interpret the differential effects of drug phenotypes. However, from a treatment point of view, our findings may be helpful in tailoring intervention programs.

This study also made an attempt to address sex differences in SDI. Contrary to our expectations, no sex differences on the IGT were found in the healthy comparisons and the alcohol-dependent group. However, women addicted to either cocaine or methamphetamine showed more severe impairments in decision making than did men addicted to cocaine or methamphetamine. Interestingly, the possibility is raised that the OFC may be affected differently by cocaine or methamphetamine in men and women (Adinoff et al., 2003; Barr et al., 2006; Chang, Ernst, Strickland, & Mehringer, 1999; Levin et al., 1994; Scott et al., 2007). For example, Adinoff et al. (2006) showed that women addicted to cocaine showed deficient perfusion bilaterally in the medial OFC compared to healthy women, whereas men addicted to cocaine showed deficient perfusion on the both sides of the lateral OFC compared to healthy men. The significance of differences in activation patterns is not well understood, but might be associated with reward versus punishment processing (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). Also at a behavioral level there is evidence that substance abuse may impact men and women differently. Most notable is the notion of "telescoping" in women (i.e., faster progression to drug dependence after a relatively late onset), which is hypothesized to result from a sex-specific biological vulnerability to psychoactive substances (Becker & Hu, 2008; Zilberman, Tavares, & el-Guebaly, 2003). Taken together, there is emerging evidence for sex-specific effects of drugs on the central nervous system, and this issue needs further exploration.

Sex differences reported for IGT performance are not modulated by differences in the ability to reverse responses (Overman et al., 2006). Therefore, we believe that in spite of our finding that women in our sample were generally slower to switch, deficient switching is not the sole cause of sex differences in SDI. That women were slower to switch was unexpected and somewhat puzzling though. Although speculative, our results may be explained by the properties of the switching paradigm, which include fast and accurate left/

right distinction. Women are more likely to rate themselves as having a poorer ability to make left/right distinctions, and there is some evidence that such self-ratings influence actual performance (Jordan, Wüstenberg, Jaspers-Feyer, Fellbrich, & Peters, 2006). Also, young girls are somewhat more reluctant to shift their responding to a newly positive stimulus, which has been called "checking" behavior (Overman, Bachevalier, Schuhmann, & Ryan, 1996). However, self-ratings about left/right distinctions presumably do not influence simple switching (Jordan et al., 2006), and it is only in the early years of development that subtle sex differences in switching can be observed (Overman et al., 1994). Therefore, we need to evaluate this interpretation with cautiousness, and replication is warranted before firm conclusions about potential sex differences with regard to switching can be made.

A limitation of this study was the difference in age and education between healthy comparison participants and SDI. However, we took such differences into account by using ANCOVA. Age and education did explain a fair amount of the variance, but most group differences were still significant after age and education effects were partialled out. We are therefore confident that our group differences are not confounded by the differences in these attribute variables, and we would cautiously infer that the differences are, instead, due to drug abuse. The present study evaluated current executive functioning in SDI and did not address the question whether certain people have a biological predisposition (i.e., impulsivity) that may be a risk factor for the initiation of substance use. This scenario could be true; however, chronic substance use in addition to biological susceptibility may have an additive effect on preexisting vulnerabilities.

Another important issue to keep in mind is that in our version of the IGT, facsimile monetary rewards were used. Although it has been shown that IGT performance did not differ between groups that were either playing for facsimile money or real money, there was more variation in the facsimile group (Bowman & Turnbull, 2003). Larger variation creates a greater possibility of false-positive and false-negative classification; however, our results replicate earlier findings reported in the literature (e.g., Verdejo-García et al., 2007a), which strengthens our notion that decision making may be impaired in cocaine and methamphetamine abusers.

To conclude, SDI appear to have poor working memory and shifting skills. The impairments in executive functioning appear most pronounced in the domain of effective decision making, thus in situations when there is no easy answer. In a review,

Volkow and Fowler (2000) presented an interesting theory, demonstrating that addiction is the result of the interplay between different neural circuits associated with reward processing, motivation, memory, and learning and cognitive/executive control. Volkow and Fowler (2000) argued that the disruption of the PFC leads to loss of self-directed behavior in favor of more automatic sensory-driven behavior. An interesting avenue for future research would be to examine how manipulating reward values can alter SDI's performance on PFC functions. If performance in different domains of executive functioning can be influenced by reward values, then this might provide important insight for treatment programs. Future research is necessary to replicate our findings and to assess the relevance of sex-specific differences in people addicted to substances.

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