Drug-Related Decrease in Neuropsychological Functions of Abstinent Drug Users

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Abstract: This article reviews neuropsychological performance in frequent users of cocaine, (meth)amphetamines, ecstasy, opiates, alcohol, and cannabis. We searched the scientific literature published in the last five years, focusing on studies that required at least 2 weeks of abstinence from drug use, and included a control group.

All substances of abuse, except cannabis, were associated with sustained deficits in executive functioning, especially inhibition. In addition, verbal memory decrements were consistently found in cocaine, (meth)amphetamines and ecstasy users, but not in heroin or cannabis users. More specific executive functioning deficits were reported depending on the substance of abuse. Cocaine was associated with diminished cognitive flexibility, whereas (meth)amphetamines were associated with worse cognitive planning functions compared to controls. Opiate studies showed lower scores on verbal fluency in opiate dependent subjects compared to controls. Working memory and visuospatial abilities were compromised in alcohol abusers. In ecstasy users, inconsistent findings have been reported across neuropsychological domains, with the exception of inhibition and verbal memory. There was little evidence for sustained cognitive impairments in adult abstinent cannabis users.

Recognition of neuropsychological problems related to different substances can help to select subjects that will benefit most from treatment. Furthermore, a better understanding of the neuropsychological impairments in drug abusing individuals could help to explain the remitting course of substance abuse disorders and to improve psychological interventions.

Keywords: Alcohol, cannabis, cocaine, cognition, ecstasy, (meth)amphetamines, neuropsychological, opiates.

INTRODUCTION

Several drugs have been associated with lowered neuropsychological functioning. Knowledge of the most prominent neuropsychological deficits related to substance use is important for clinicians who assess or treat patients with a history of drug use. Although it is unclear if lowered cognitive capacities in drug users are a cause or a consequence of drug use, or a combination of the two, lowered cognition can have serious implications for drug dependent patients in psychological treatment programs. For example, deficits in working memory and cognitive flexibility are associated with lower treatment compliance and higher relapse rates [1, 2]. This could be due to the fact that working memory and attention are required to encode and process incoming information. If information is only partially processed, behavioral change may not occur [3]. Recognition of the neuropsychological problems related to different substances can help to select the subjects that will benefit most from treatment and ideally can help to improve psychological interventions. Furthermore, understanding the neuropsychological decrements in drug abusing individuals could help explain the remitting course of substance abuse disorders.

The main goal of this review is to provide an overview of the most recent methodologically sound research on the sustained neuropsychological effects of chronic drug use in abstinent drug users. While recent reviews on the effects of a specific drug of abuse have been published [4, 5], reviews addressing multiple drugs and their sustained neuropsychological consequences after a protracted period of abstinence are lacking.

One comprehensive review by Verdejo-Garcia *et al*. (2004) provides a summary of the immediate and sustained effects of cannabis, stimulants and opiates on cognition [6]. In this review, Verdejo-Garcia *et al*. also describe the multiple methodological difficulties, e.g., the wide range of abstinent days in the different studies. Some studies ask their subjects to refrain from using drugs 24 hours before testing while others require a minimum of 2 weeks of abstinence following detoxification. Because of these differences and the great variety in research designs, subsets of the addicted populations and methodological issues such as polydrug use, it is difficult to obtain a clear picture of the specific neuropsychological functions that remain affected even after sustained abstinence.

In this review we focus on the major drugs of which frequent use has repeatedly been related to sustained neuropsychological decrements in the scientific literature: cocaine, (meth)amphetamines, ecstasy, opiates, alcohol, and cannabis.

Most drug users are polydrug users and most studies selected groups based on the primary drug of abuse. We will therefore organize the neuropsychological findings according to the subjects' primary drug of abuse. In order to keep the current overview condensed, studies will not be discussed in detail. Details, e.g., about sample size and abstinence

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duration, and main results of the studies are depicted in Tables **1-6**. The paper concludes with a general discussion of the reviewed studies, methodological difficulties of this research field, clinical implications, and future directions for neuropsychological research on substance abuse.

METHOD

Since Verdejo-Garcia *et al.* thoroughly reviewed the literature published before 2004 concerning abovementioned drugs except for alcohol, we mainly concentrated on the literature published after 2004. To rule out acute toxification effects, only studies with a period of at least 2 weeks of abstinence were included. The inclusion of a control group was required and the tested subjects had to be adults. PubMed and PsychINFO were searched to indentify relevant studies written in English, using the words: 'alcohol'; 'cannabis'; 'MDMA'; 'ecstasy'; 'amphetamine'; 'methamphetamine'; 'opiate'; 'cocaine'; 'heroin' in combination with wild cards 'neuropsycho*' and 'cogn*'. A total of 221 papers were retrieved. To optimise the interpretation of the results summarised in this review and to make it possible to link the results to general practice, we only included studies that used neuropsychological tests that are validated and applied in clinical practice. To limit our scope, we did not include neuroimaging studies. The reference lists of the retrieved studies were checked for relevant studies. A total of 41 studies fulfilled all of the above mentioned criteria and were included in this review.

STIMULANTS

Cocaine

The literature on the sustained effects of cocaine on cognition before 2006 shows a consistent picture of moderate but significant neuropsychological decrements in short-term and working memory, attention, executive functions such as abstract reasoning skills, and response speed (for a comprehensive review see Verdejo-Garcia 2004 [7]). These findings are corroborated by a quantitative review showing large ($0.50<d<1.10$) to moderate ($0.40<d>0.50$) effect sizes for measures of attention and visual memory, and working memory, respectively [8].

Table 1. Cocaine

Authors	Groups N=(Female)	Abstinence Duration (Days) Mean (SD)	Instruments	Domains
Fox *et al.* 2009	CO: 36 (20) HC: 36 (20)	14	RAVLT	Verbal learning [a] Verbal memory [a]
Woicik *et al.* 2009	st-CO: 43 (6) lt-CO:21 (8) HC: 64 (14)	3-6 15-25	COWAT (phonemic and semantic), WAIS-III (digit span and letter-number sequencing), Symbol Digit Modalities Test, TMT (A and B), WISC-III (mazes), [c]WCST, Stroop task, [c]Attention network test (alerting, orienting and conflict), [c]IGT, CVLT-II, Ekman faces, Benton Facial recognition test, FTT, Grooved pegboard	Attention [a] Executive function [a] Verbal Memory [a] Facial and emotion recognition Motor function
Pace-schott *et al.* 2008	CO: 17 (2) HC: 17 (1)	0, 4-6, and 18-20	[c]CDR (simple and choice reaction time digit vigilance, delayed word recognition, spatial and numeric working memory)	*Abstinence 0* Attention [a] Verbal recognition [a] Working memory *Abstinence 4-6 and 18-20* Attention Verbal recognition Working memory
Verdejo-Garcia *et al.* 2007b	HE: 28 (?) CO: 45 (?) AA: 8 (?) HC: 37 (2)	150	FAS letter fluency, RFFT, WAIS-III (letter number sequencing, arithmetic, digits, similarities), WMS-III (spatial span), Stroop test, [c]Go/no go task, [c]Category test, WCST, [c]Cognitive bias task, [c]IGT	Updating [a] Inhibition [a] Cognitive flexibility [a] Decision making [a]
Verdejo-Garcia *et al.* 2007a	HC: 14 CO: 12 CA: 11	25	[c]IGT	Decision making [a]
Colzato *et al.* 2009	CO: 20 (4) HC: 20 (3)	14	*Study 1* [c]WCST *Study 2* Digit span, [c]N-back task	*Study 1* Cognitive flexibility [a] *Study 2* Working memory
De Oliveira *et al.* 2009	CO: 17 Ex-CO: 24 HC: 18	1-30 days 180-1825	WMS-III, WAIS-III (digit span and digit symbol substitution test, logical memory, verbal associated pairs), verbal fluency, Stroop task, Cancellation test, TMT (A and B) ,	Verbal memory [a] Verbal learning Verbal fluency Attention Cognitive flexibility [a]

AA = alcohol abusing group; HC = healthy controls; CO = cocaine abusing group; CA: cannabis abusing group; AM = Amphetamine abusing group; HE = heroin abusing group; lt-(xx) = long term abstinent user; st-(xx) = short-term abstinent user; (?) = not reported; [a] = found significant decrement in that domain; [c] = computer task; CDR: Cognitive Drug Research Computerized Assessment System; COWAT: Controlled Oral Word Association Task; CVLT-II: California verbal leaning test II; FTT: Finger Tapping Test; IGT: Iowa Gambling Task; RAVLT: Rey Auditory verbal Learning Test; RFFT: Ruff figure fluency test; TMT: Trail Making Test; WAIS-III: Wechsler Adult Intelligence Scale III; WCST: Wisconsin Card Sorting Test; WISC-III: Wechsler intelligence Scale for Children III; WMS-III: Wechsler Memory Scale-III.

Studies since 2005 continue to report deficits in verbal learning and memory [9-12], attention [9, 11, 13], inhibition, cognitive flexibility [10, 11, 14, 15], and decision-making abilities [11, 14] in abstinent cocaine dependent individuals (for details of these studies see Table **1**). However, three out of six studies that investigated cocaine abuse tested polydrug users and not pure cocaine users [9, 11, 14]. Two of these studies used multiple regression techniques to disentangle the specific effects of cocaine use on cognitive functions [11, 14]. However, the results obtained by these studies remain hard to interpret because, even though the effects of other drugs are statistically removed, the real effect of multiple drug use on neuropsychological functions cannot be discarded. However, the reality is that drug users usually show a mixed history of drug usage. Thus focusing research on single drug users would limit generalisability of findings to the drug abusing population.

An interesting and significant finding is that current cocaine use (i.e. within 72 hours) masks neuropsychological decrements in attention, executive functioning and verbal memory functions present after at least one week of abstinence of cocaine use [9]. These findings emphasise the importance of evaluating abstinence duration during neuropsychological assessment of substance-dependent individuals because neuropsychological profiles can change during abstinent periods and therapy could benefit from taking these changes into account and tailor therapy to the abilities of their patients.

Only one study that considered longer periods of abstinence from cocaine and the reversibility of neuropsychological disfunctioning has been published in the last five years [10] compared current crack cocaine users with long term (6 months to 5 years) abstinent cocaine users and non users, and found a worse performance on immediate and delayed logical memory (prose recall) in both current and abstinent users. However, memory for verbal associations was not significantly different from controls. Interestingly, cognitive flexibility was worse only in the long term abstinent cocaine users. Summarising findings from earlier years shows divergence about the persistence of neuropsychological deficits in long term abstinent cocaine users [16, 17].

We conclude that the most consistent findings of recent studies in abstinent cocaine users are deficits in inhibition, cognitive flexibility and verbal memory.

Amphetamine/Methamphetamine

In a thorough review, covering the literature from the early 1960's to 2004, decrements in memory and learning, psychomotor speed and information processing were found in short-term (ranging from 5 to 14 days) abstinent methamphetamine abusing individuals [18].

A recent meta-analysis regarding the effects of (meth)amphetamine use reported evidence for deficits on a wide range of neuropsychological functions. The largest effect sizes were reported in the domains of learning (d=-0.66), executive functions (d=-0.63) and episodic memory (d=-0.59). In addition, medium effect sizes were found for information processing (d=-0.52) and motor skills (d=-0.48). Smaller effect sizes were found in visuoconstructional functions (d=-0.39), working memory (d=-0.37) and language (d=-0.34) [19].

Recent studies also found lower performance on immediate and delayed verbal memory tasks in chronic (meth)amphetamine users [20-22]. In addition, decrements in visual immediate recall and delayed memory were also reported [21-23]. However, Woods *et al.* (2005) found that worse visual memory in methamphetamine users compared to controls were not necessarily due to mnemonic dysfunction but may have resulted from ineffective strategies in encoding, organizing and retrieving information [23]. This is consistent with other findings of aberrant executive functions in (meth)amphetamine-dependent subjects [24, 25]. Diminished cognitive planning and poorer immediate and delayed pattern recognition were still present in former amphetamine users abstinent for more than one year (mean 8 years) [24] compared to controls. On the other hand, the abstinent drug user group in this study was comprised of individuals who had suffered from a stimulant or opiate dependence or a combination of both. Therefore, it is uncertain whether these abovementioned long-term effects can be mostly ascribed to amphetamine use alone or to a combination of amphetamine and other drug use.

Another study focusing on long-term abstinent methamphetamine users found decrements in cognitive control functions in methamphetamine users abstinent for three weeks to six months compared to controls, but not in former methamphetamine users who were abstinent for more than one year [25]. Consistent with this finding, another study following a group of abstinent methamphetamine users for more than a year indicated that participants who were able to remain abstinent performed similar to non users on neuropsychological tests, whereas at baseline these long term abstainers had shown diminished global and motor functioning [21]. In addition, Rapeli *et al.* (2005) reported that amphetamine users abstinent for more than one year showed lower verbal memory performance but no decrements in executive functions and fluid intelligence compared to a non-using control group [26]. However, another study among methamphetamine users abstinent for more than one year showed evidence of impaired visual memory, but not verbal memory compared to non-using controls [27]. The authors suggested that the visual memory test also evaluated planning and organizing abilities of the subjects, and hence these visual memory deficits could be explained by executive function deficits [23-25]. However, methodological issues such as a small number of subjects and unclear demographical information about the tested ex-users, compromises the interpretability of the findings reported by Moon *et al.* 2008 [27]. Furthermore, others found no evidence of planning and organising dysfunctions, measured with the same task in methamphetamine users abstinent for more than one year, but also this study was limited by a small number of participants (n=12) [26]. In addition, cognitive control functions were also found to be intact in methamphetamine-dependent individuals after one year of abstinence [25], suggesting that executive functioning at large seem to diminish after longer periods of abstinence from (meth)amphetamine. On the other hand, it is conceivable that intact executive functions protect against

Table 2. (Meth)amphetamines

Authors	Groups N=(Male)	Abstinence Duration (Days) Mean (SD)	Instruments	Domains
Woods *et al.* 2005	MA: 87 (27) HC: 71 (29)	120 (105)	HVLT-R	Retention [a] Recognition discrimination Verbal learning Semantic clustering [a] Retrieva [a]
Rapeli *et al.* 2005	AM: 12 (7) HC: 12 (7)	1260 (687)	WMS-R (digit span and logical memory), Stroop task, [c]PASAT, RAVLT, BVRT, RFFT, CFIT	Attention Memory [a] Executive functioning
Salo *et al*. 2009	MA: 38 (19) Ex-MA:27 (18) HC:33 (11)	90-182 >365	Stroop task	Inhibition [a]
Ersche *et al.* 2006	AM: 25 (11) OP: 42 (9) ex-poly: 26 (12) HC: 27 (13)	0 0 >365	[c]TOL, [c]CANTAB (Paired Associated Learning and delayed pattern recognition)	Cognitive planning [a] Learning [a] Delayed pattern learning [a]
Hoffman *et al.* 2006	MA: 41 (10) HC: 41 (11)	195 (189)	Shipley Vocabulary, RCFT, Babcock Story Recall, RAVLT, TMT (A and B), Grooved pegboard, Stroop task, [c]WCST	Premorbid IQ Visual spatial functioning Immediate and delayed verbal recall [a] Verbal memory and learning [a] Attentional/ Psychomotor speed Inhibition [a] Cognitive flexibility
Moon *et al.* 2007	MA: 19 (0) HC:18 (0)	653 (489)	RAVLT, RCFT, WAIS-III (block design)	Verbal memory Visual memory [a]
Cherner *et al.* 2010	MA: 54 (?) HC: 46 (?)	128.8 (99.5)	BVMT-R, HVLT-R, PASAT, WAIS-III (letter number sequencing symbol search, digit symbol) TMT (A and B), Stroop task, Halstead category test WCST, FAS letter fluency, category fluency, Grooved Pegboard test	Verbal learning [a] Verbal memory [a] Working memory [a] Processing speed [a] Cognitive flexibility Verbal fluency Motor functioning [a]
Iudicello *et al.* 2010	Ecstasy: 58 (5) Ex-Ecstasy: 25 (6) HC: 38 (7)	*Baseline* 40.2 (20.1) 54.8 (28.5) *1-year follow up*	Halstead category test, WCST, TMT (A and B), Stroop task, HVLT-R, BVMT-R, grooved Pegboard test, WAIS-III (digit symbol and symbol search test, letter number sequencing test), COWAT-FAS letter fluency, PASAT	*Baseline* Executive functioning [a] Verbal learning [a] Memory Motor functioning [a] Processing speed [a] Verbal fluency Working memory *1-year follow up* Executive functioning [a] Verbal learning [a] Memory Motor functioning [a] Processing speed [a] Verbal fluency [a] Working memory [a]

HC = healthy controls; MA = Methamphetamine abusing group; AM = amphetamine abusing group; OP = opiate abusing group; ex-(xx) = ex-user; poly = polydrug abusing group; [a] = found significant decrement in that domain; [c] = computer task; BVRT: Benton Visual Retention Test; CANTAB: Cambridge Neuropsychological Test Automated Battery; CFIT: Culture Fair Intelligence Test; COWAT: Controlled Oral Word Association Task; HVLT-R: Hopkins Verbal Learning Test-Revised; PASAT: Paced Auditory Serial Addition Task; RAVLT: Rey Auditory Verbal Learning Test; RCFT: Rey-Osterrieth Complex Figure Test; TMT: Trail Making Test; TOL: Tower of London; WAIS-III; Wechsler Adult Intelligence Scale III; WCST: Wisconsin Card Sorting Test.

relapse into drug use. Hence, one serious limitation of these cross-sectional studies is that the causality of the neuropsychological impairments can not be assessed. It is possible that certain neuropsychological deficits found in abusing individuals are not an effect of drug abuse but a pre-existing vulnerability enhancing the probability of drug abuse in these individuals. Thus, neuropsychological decrements in long-term abstinent drug abusers may not necessary point to sustained deficits caused by drug abuse itself, but rather to an inherent risk factor or vulnerability to the misuse of drugs. For details about the discussed studies, see Table **2**.

Altogether, verbal memory decrements and executive functions, specifically inhibition and planning seem to be the most consistently reported deficits after an abstinence period ranging form 2 weeks to 4 months [20-24]. There are indications that after protracted abstinence (longer than a year) of (meth)amphetamine use executive functioning normalises [25, 26].

DEPRESSANTS

Heroin and Methadone

In a review by Gruber *et al.* (2007), neuropsychological effects of opiate use were discussed and they concluded that long term opiate use was associated with decrements in attention, concentration, visual and verbal recall, and visual spatial skills [28].

More recently, lower cognitive functioning associated with opiate use were found in the domain of executive functions such as inhibition [29, 30], cognitive flexibility [30] and working memory [29, 30]. Verdejo-Garcia *et al*. (2007) investigated the neuropsychological differences between abstinent cocaine and heroin polysubstance users, and found that cocaine polysubstance users preformed worse than heroin users and normal controls on measures of inhibition and cognitive flexibility, but both groups preformed worse compared to normal controls [11]. In another study by Verdejo-Garcia and colleagues (2007), cognitive inhibition and decision-making abilities were tested in abstinent cocaine users, heroin polysubstance users, and healthy controls. They found that cocaine but not heroin polysubstance users had significant deficits on several measures of response inhibition compared to controls. In contrast, both cocaine and heroin polysubstance users showed poorer performance on decision-making compared to controls [31]. One limitation of these studies is that the neuropsychological deficits could be explained by excessive drug use by itself because participants all used multiple drugs independently of being categorised as preferred heroin or cocaine users. It is however interesting that diverging neuropsychological profiles can be discovered when categorising drug-dependent individuals into groups of their preferred drugs of use. As discussed before, these findings are valuable for clinical practice because treatment clinics for substance dependent patients usually encounter patients with a polysubstance dependent history. For specifics about the discussed studies see Table **3**.

The duration and reversibility of these neuropsychological decrements is still largely unknown. Abstinent opiate-dependent subjects on methadone maintenance (free from illicit drug use for at least 18 months) and complete abstinent opiate-dependent subjects (i.e., not on methadone) showed similar cognitive deficits on fluid intelligence, working memory and design fluency compared to control subjects [32]. Notably, substitution therapy with methadone maintenance treatment may itself be linked to decrements in several cognitive functions, possibly extending deficits attributable to long-term opiate abuse [6, 33, 34]. It is out of our scope to go into the specific effects of all different opiate substitution therapy's, but buprenorphine

Table 3. Heroin and Methadone

Authors	Groups N=(Male)	Abstinence Duration (Days) Mean (SD)	Instruments	Domains
Brand *et al.* 2008	HE:18 (4) (of which 7 ME) HC: 18 (5)	14.38 (7.41)	DemTec, MCST, FAS letter fluency, Tower of Hanoi, Stroop test, Leistungs-Prüfsystem (subtest reasoning), Theory of mind eye test	General cognitive status [a] Cognitive flexibility [a] Verbal fluency Cognitive planning Inhibition [a] Abstract reasoning
Prosser *et al.* 2008	ME:29 (6) ex-ME: 27 (7) HC: 28 (8)	540 (illicit drugs). 180	WAIS-R (vocabulary), Stroop task, COWAT, BVRT	Abstract reasoning [a] Inhibition [a] Verbal fluency [a] Visual memory [a] Visual construction [a]
Prosser *et al.* 2006	ME: 29 (6) Ex-HE: 27 (7) HC: 29 (8)	0 180	WAIS-R (vocabulary), Stroop test, COWAT, BVRT	Abstract reasoning [a] Inhibition [a] Verbal fluency [a] Visual memory [a] Visual construction [a]
Verdejo-Garcia *et al.* 2007	CO: 12 (0) HE: 11 (0) HC: 14 (0)	25	Stroop task, [c]Go/No go task, [c]IGT	Inhibition [a] Decision making[a]

HC = healthy controls; ME = methadone maintenance group; CO = cocaine abusing group; HE: Heroin abusing group; ex-(xx) = ex-user; [a] = found significant decrement in that domain; [c] = computer task; BVRT: Benton Visual Retention Test; COWAT: The Controlled Oral Word Test; MCST: Modified Card Sorting Test; RFFT: Ruff figure fluency test; WAIS-III: Wechsler Adult Intelligence Scale III.

has been indicated to have less detrimental neuropsychological effects than methadone [35].

In conclusion, the most consistent findings in abstinent (1 to 4 weeks) opiate-dependent subjects include aberrant executive functioning, such as lowered inhibition, verbal fluency and decision-making skills [11, 30, 31], which persist from six up to 52 weeks [32, 33]. So far, it is not clear whether opiate-related deficits will recover after longer periods of abstinence. In addition, as with other cross-sectional studies, it is not clear if these found differences are a direct consequence of heroin abuse or a pre-existing vulnerability to the development of heroin dependence.

Alcohol

Severe chronic use of alcohol has been consistently associated with lower performance on tasks measuring attention, short term memory, visuospatial abilities, and executive functions (such as problem solving, mental flexibility, judgment, working memory, response inhibition and decision-making) [36]. In severe cases, chronic alcohol use can lead to Wernicke's encephalopathy [37], Korsakoff's syndrome [38] and alcohol-related dementia [39].

More recent studies have focused on specific executive function deficits and deviancies in social cognition in individuals with alcohol problems. Uekermann and colleagues [40] investigated the role of theory of mind and humour processing, and its relation to executive functions in abstinent alcohol-dependent subjects. They found lower working memory performance in addition to deficits in affective humour processing in alcoholics in comparison with controls. Decision-making abilities, measured with the Iowa Gambling task [41], showed more disadvantageous choice behaviour [42] and worse cognitive flexibility [43, 44] in abstinent alcohol-dependent subjects compared to controls. These decrements in complex executive functions and social cognition seem to contribute to interpersonal problems and are thus of relevance to rehabilitation of these persons.

Neuropsychological improvements have been documented after a period of 1 week to more than several years of abstinence. Recoveries after short-term abstinence are mainly reported in domains of working memory, visual spatial functioning, and attention [45]. After 1 month of abstinence, Manning *et al.* found significant improvements in working memory and verbal fluency performance, but not in cognitive flexibility and planning [45]. These findings are consistent with a recent study of Moriyama *et al*. [46] and with studies before 2005 [47-53]. The study by Moriyama *et al.* (2006) is also interesting in relation to the effect of familiar history of alcohol dependence. The authors investigated groups of alcohol dependent individuals with and without a family history of alcoholism and found that alcohol-dependent participants with a positive history of alcoholism had more severe executive function deficits than non-familial alcohol-dependent participants.

Studies with longer abstinence durations suggest that recovery or substantial improvements in executive functions can occur. For example, Fein and colleagues (2006) found that in long-term (more than 6 years) abstinent alcoholics, performance on almost every domain was similar to controls, except for a small difference in the spatial domain [54]. Pitel *et al*. (2009), found memory [55] and executive functioning deficits [56] in short-term abstinent alcohol-dependent subjects compared to controls, while after 6 months of abstinence no differences between these groups were found [57]. However, Davies and colleagues [58] tested a group of clinically healthy long-term (more than 2 years) abstinent alcohol dependent subjects and controls and found evidence of worse executive function and lower performance on verbal immediate and delayed recall in the abstinent alcohol group compared to controls.

These findings of persistent executive functioning deficits could point to permanent damage due to alcohol use, or else suggest that executive dysfunctioning is not merely a direct result of alcohol toxicity but could be indentified as a vulnerability to the development of alcohol dependence. This idea is supported by studies investigating risk factors for development of alcohol abuse disorders in adolescents, which repeatedly reported higher impulsivity and aberrant decision-making abilities compared to adolescents who did not develop alcohol abuse disorders [i.e., 59, 60].

In conclusion, chronic alcohol use is associated with decrements in working memory, verbal memory, visuospatial abilities, and inhibition after an abstinence period of 1 to 3 weeks [40, 42-44, 46, 55, 56]. Although during protracted (more than a year) abstinence, these functions may recover [54], but there are indications that decrements in executive functions are persistent [57, 58] and could be designated as a risk factor for the development of alcohol dependence disorders.

PSYCHEDELICS

Ecstasy

Studies before 2005 reported cognitive decrements in chronic ecstasy users ranging from deficits in memory, executive functions, abstract reasoning and semantic recognition [61].

More recent studies replicate these findings, with the most consistent finding being a negative effect of ecstasy use on verbal memory. In a recent meta-analysis, Kalechstein *et al*. (2007) reported medium to large effect sizes for the association between ecstasy exposure and verbal (d=0.73) and nonverbal learning (d=0.58) [62], findings consistent with a similar meta-analyses by Zakzanis *et al.* [63]. This was corroborated by a follow-up study in which recreational users performed worse on semantic word fluency task compared to controls. Additionally, after two years of continued use, these ecstasy users showed persistent deficits in verbal fluency, but also in working memory and processing speed [64]. However, these results must be interpreted with caution because the abstinent duration of participants were not assessed, although participants were asked to refrain from drug using up to 72 hours before testing. Recreational ecstasy users in Hong Kong also performed worse than non-users on verbal and non verbal memory, and on verbal fluency, but they were better on figure fluency relative to their non-users counterparts [65]. In addition, cumulative ecstasy consumption correlated negatively with neuropsychological performance [65].

Table 4. Alcohol

Authors	Groups N=(Male)	Abstinence Duration (Days) Mean (SD)	Instruments	Domains
Uekermann *et al.* 2006	AA: 29 (6) HC: 29 (10)	75 (50)	WMS-III (letter number sequencing), TMT (A and B), Stroop task	Inhibition [a] Cognitive flexibility Working memory [a]
Fein *et al*. 2006	AA: 48 (23) HC: 28 (23)	2446 (2263)	NART, COWAT, PASAT, Stroop task, TMT (A and B), RCFT, symbol digit modalities, WAIS-R (block design), Short category test, Fregly Ataxia Battery, IGT, [c]MicroCog	Cognitive flexibility Attention Working memory Immediate verbal memory Delayed verbal memory Motor functioning Visual spatial functioning [a] Verbal skills
Hildebrandt *et al.* 2006	AA: 29 (7) HC: 20 (10)	19	Leistungs-Prüfsystem (abstract reasoning, word/non word discrimination), CVLT, TAP (alertness, response alternation, inhibition), Phonological word fluency, Semantic word fluency, CANTAB (shift learning), IGT	Abstract reasoning Verbal memory Inhibition [a] Verbal fluency Cognitive flexibility [a] Decision making
Loeber *et al.* 2009	AA: 48 (21) HC : 35 (13)	15.65 (6.69)	WST, Reduced WAIS-III, RAVLT, BVRT, TMT (B), WCST, IGT	Vocabulary Intelligence Verbal learning Visual learning Cognitive flexibility [a] Decision making
Miranda *et al.* 2009	AA: 22 (0) AA+ASPD: 17 (0) HC: 21 (0)	30	[c]IGT	Decision making [a]
Pitel *et al.* 2009	AA: 14 (?) HC: 54 (?)	180	Free and Cued Selective Reminding Test, Letter fluency, Categorical fluency, Verbal span and spatial span, [c]TAP	Inhibition [a] Verbal memory [a] Executive functions [a]
Pitel *et al.* 2007	AA: 40 (7) HC: 50 (30)	11.57	Free and Cued Selective Reminding Test, Letter fluency, Categorical fluency, Stroop task, [c]TAP, [c]N-back task	Verbal memory [a] Inhibition [a] Cognitive flexibility [a] Verbal fluency [a] Working memory [a]
Pitel *et al.* 2007	AA: 20 (?) HC: 20 (?)	11.57	Verbal span and spatial span, Letter fluency, Categorical fluency, Stroop task, N-back task	Working memory [a] Verbal fluency Inhibition [a]
Moriyama *et al.* 2006	AA-fam: 19 (0) AA-nfam: 20 (0) HC: 15 (0)	Test 1: 13.4 (2.9) Test 2: 48.5 (3.8)	TMT (A and B), WAIS-R (symbol digit modalities, block design)	*Test 1:* Cognitive flexibility [a] Processing speed [a] Visual construction [a] *Test 2:* Cognitive flexibility [a] Visual construction [a] Processing speed
Davies *et al.* 2005	AA: 43 (9) HC: 58 (17)	94±169	WAIS-R (vocabulary, Arithmetic, picture arrangement, block design, digit symbol), TMT (A and B), WMS (Immediate recall, 30-min recall), RCFT	Vocabulary [a] Attention [a] Cognitive flexibility [a] Working memory [a] Visual memory [a]

AA = alcohol abusing group; HC = healthy controls; ASPD = anti social personality disorder; AA-fam = alcohol abusing group with family history of alcohol dependence; AA-nfam = alcohol abusing group without family history of alcohol dependence (?) = not reported; [a] = found significant decrement in that domain; [c] = computer task. BVRT: Benton Visual Retention Test; CANTAB: Cambridge Neuropsychological Test Automated Battery; COWAT: Controlled Oral Word Association Test; CVLT-II : California verbal leaning test II; IGT: Iowa Gambling Task; MicroCog: Assessment of Cognitive Functioning; NART: National Adult Reading Test; PASAT: Paced Auditory Serial Addition Task; TAP: Test battery on Attentional Assessment; TMT: Trail Making Test; RAVLT: Rey Auditory Verbal Learning Test; RCFT: Rey-Osterrieth Complex Figure; WAIS-III/R: Wechsler Adult Intelligence Scale III/Revised; WCST: Wisconsin Card Sorting Test; WIP: Reduced Wechsler Intelligence Scale; WMS-III: Wechsler Memory Scale-III; WST: vocabulary test (Wortschatztest).

Table 5. Ecstasy

Authors	Groups N=(Male)	Abstinence Duration (Days) Mean (SD)	Instruments	Domains
de Sola Llopis *et al.* 2008	Ecstasy+CA: 37 (18) CA: 23 (15) HC: 34 (25)	3	WAIS-III (vocabulary, corsi block tapping), [C]CALCAP, TOL, Word fluency, Symbol digit modalities, CVLT-II, RCFT, WMS-III (letter number sequencing)	*Initial examination:* Attention Working memory Verbal memory Visual memory Verbal fluency[a] Cognitive planning Processing speed *Follow-up (after 2 years):* Attention Working memory [a] Verbal memory Visual memory Verbal fluency [a] Cognitive planning Processing speed [a]
Bedi *et al.* 2008	Ecstasy: 45 (21) CA+poly: 48 (22) HCLD: 40 (19)	79.2 10-425	RAVLT, RCFT, BADS, COWAT, WAIS-III (digit span forward and backwards)	Verbal learning Verbal memory [a] Visual memory Verbal fluency Working memory
Schilt *et al.* 2008	Stratified drug using group: 67 (27)	> 14	PASAT, WAIS-R (digit span), RAVLT, Memory for Design, Mental Rotation Task, [c]JoLO	Attention Working memory Verbal memory [a] Visual memory Visual spatial functioning
Quednow *et al.* 2007	Ecstasy: 19 (0) CA: 19 (0) HC: 19 (0)	17.4 (14.6) 7.1 (4.7)	[c]Go/Nogo task, Matching Familiar Figures test, [c]IGT	Inhibition [a] Impulsivity [a] Decision making[a]
Hoshi *et al.* 2007	Ecstasy: 25 (?) Poly (excl Ecstasy): 29 (?) Ex- Ecstasy: 28 (?) HC: 27 (?)	27-560 Ex-users: >2000	RBMT, BSRT, [c]Go/no go task, Semantic and phonemic verbal fluency task, TMT (A and B), [c]CANTAB (spatial working memory, Stockings of Cambridge, Gibson's spiral maze)	Verbal learning [a] Verbal memory [a] Inhibition [a] Working memory Cognitive flexibility Executive functioning
Roiser *et al.* 2007	Ecstasy: 30 (15) Poly: 30 (15) Ex- Ecstasy: 20 (10) HC 30 (15)	75 (79) ? 1021 (1018)	[c]CANTAB (tile manipulation test, mental rotation test, decision making task, pattern recognition memory, delayed match to sample)	Memory Executive functioning [a] Impulsivity Decision making Visual spatial functioning
Ward *et al.* 2006	Ecstasy: 31 (19) Ex- Ecstasy: 30 (9) HC: 30 (20)	7 730	WMS-III	Immediate verbal recall [a] Immediate visual recall [a] Delayed verbal memory [a] Delayed visual memory [a] Working memory [a]
Schilt *et al.* 2010	Ecstasy: 17 (7) Poly: 16 (9) HC: 20 (10)	537 (833) 2842-(1484)	PASAT, WAIS-R (digit span), RAVLT, Memory for Design, Mental Rotation Task, [c]JoLO	Attention Working memory Verbal memory [a] Visual memory Visual spatial functioning
Yip and Lee 2005	Ecstasy: 100 (50) HC: 100 (50)	67 (15)	FDST and BDST, RAVLT (immediate, delayed, recognition), AFLT, Stroop task, CTT, Symbol digit modalities test, verbal fluency, RFFT	Working memory Verbal memory [a] Visual memory [a] Attention [a] Verbal fluency [a] Figural fluency [a]

HC = healthy controls; CA = cannabis abusing group; HCLD = healthy controls with legal drug use; Ecstasy = ecstasy abusing group; ex-(xx) = ex-user; *-heavy = heavy using individuals; *-light = lightly using individuals; ASPD = anti social personality disorder; poly = poly drug using group; (?) = not reported; [a] = found significant decrement in that domain; [c] = computer task; AFLT: Aggie figures learning test; BADS: Behavioural Assessment of Dysexecutive syndrome; BDST: Backward Digit Span Test; BSRT: Buschke Selective Reminding Task; CANTAB: Cambridge Neuropsychological Test Automated Battery; CALCAP: California Computerized Assessment Package; CTT: Color Trails Test; COWAT: Controlled Oral Word Association Test; CVLT-II; California Verbal Learning Test-II; FDST: Forward Digit Span Test; IGT: Iowa Gambling Task; JoLO: Judgment of Line Orientation; PASAT: Paced Auditory Serial Addition Task; RBMT: Rivermead Behavioural Memory task; RAVLT: Rey Auditory Verbal Learning test; RCFT: Rey-Osterrieth Complex Figure Test; RFFT: Ruff Figure Fluency Test; TMT: Trail Making Test; TOL: Tower of London; WAIS-R: Wechsler Adult Intelligence Scale Revised; WMS-III: Wechsler Memory Scale III

Experimental studies on chronic, but abstinent ecstasy users also showed deficits in memory updating and long-term memory [66, 67], decision-making [68, 69] and working memory [70]. Conversely, a study by Bedi and Redman (2008) tested executive functioning in abstinent ecstasy users and found no significant group differences after they controlled for confounding factors such as cannabis and other drug use by including two groups who either used cannabis and legal drugs (i.e. alcohol) [71]. However, a regression analysis did show a significant negative relationship between lifetime dose of ecstasy and verbal memory performance, although the variance explained was small (1 to 6%). In another study that also controlled for other drugs, multiple regression analyses showed a negative effect of ecstasy on verbal memory with a medium (d>0.5) effect size [72]. In addition, a study that compared ecstasy users with polydrug users and drug-naïve controls on a variety of neuropsychological tests, showed a significantly worse performance on a verbal immediate and delayed memory test in the ecstasy group in comparison with both the polydrug group and the controls [73].

A special challenge in ecstasy research is that of the delimitation of the effects associated with other co-abused substances, mainly cannabis. Because of this important issue, multiple studies discussed above [69-74] have investigated the differential effects of both substances by comparing groups of combined ecstasy/cannabis users with cannabis users or polydrug users, and drug-naïve controls. Interestingly, most results from these studies point to ecstasy induced selective decrements after controlling for cannabis co-abuse. However, the variability in the results may be associated with differences between studies on drug histories and patterns of drug consumption of the included participants.

Altogether, there is tentative evidence that chronic ecstasy use can lead to sustained decrements mainly in memory functions, with emphasis on verbal memory, after an abstinent period of at least one week [65, 67, 70, 73] to six months or even more than one year [64, 66, 67]. It is not clear whether full recovery is possible.

CANNABIS

Reports on the long-term effects of pure cannabis use, after a protracted period of abstinence, on the matured brain are scarce (for a review see [4]). Furthermore, a meta-analysis of studies up to 2002 demonstrated no significant detrimental effects of cannabis on neuropsychological functions [75]. An overview of the discussed studies investigating cannabis use is provided in Table **6**.

The short-term effects of cannabis on cognitive functions consist of deficits in attention, working memory, verbal fluency and cognitive flexibility [76]. These deficits are also found in frequent cannabis users after seven days of abstinence [77]. After two weeks of abstinence, cannabis users performed worse on measures of verbal memory and inhibition than healthy controls [78]. However an important question remains, whether cannabis use produces residual cognitive deficits after protracted periods of abstinence. The only study investigating the residual effect of former cannabis use was performed by Pope *et al.* [79]. They found that cannabis users who abstained for 28 days were indistinguishable from former heavy users or non-using controls. This was corroborated by a recent study investigating a group of cannabis users who were abstinent for at least 5 weeks, which also found no evidence of cognitive impairment in working memory, verbal fluency and associative learning [80]. Thus the persistence of neuropsychological impairments due to cannabis use seems to be limited.

One methodological limitation of these studies is that there was no control for other psychiatric disorders, which could explain some of the differences between cannabis users and controls.

In conclusion, in the past years little evidence is provided that indicates profound long-term negative effects of cannabis use on the matured brain.

DISCUSSION

We reviewed the literature published in the past five years on the sustained effects of cocaine, (meth)amphetamines, ecstasy, opiates, alcohol, and cannabis on neuropsychological functions in abstinent drug users. All these substances, except for cannabis, were associated with sustained deficits in executive functioning, especially inhibition. This common finding must be interpreted with some caution, as the term inhibition, like the overarching concept of executive functioning, is subject to discussion. The cerebral areas involved in inhibition may differ depending on the tasks used [81]. Nevertheless, this

Table 6. Cannabis

Authors	Groups N=(Male)	Abstinence Duration (Days) Mean (SD)	Instruments	Domains
Fisk *et al.* 2008	CA: 46 (?) HC: 45 (?)	35 – 252	Semantic fluency, Chicago word fluency test,	Verbal fluency
McHale *et al.* 2008	CA:12 (3) Ex-CA: 25 (12) HC: 23 (15)	1 7	Verbal fluency, Doors and people test, The shapes test, RBMT (belonging)	Verbal fluency [a] Visual recognition [a] Perspective memory [a]
Lamers *et al.* 2006	Ecstasy +CA: 11 (4) CA: 15 (5) HC:15 (6)	228 15	RAVLT, RCFT, [c]WCST, Stroop task, TMT (A and B), [c]IGT	Verbal memory [a] Visual memory Inhibition [a] Decision making[a]

HC = healthy controls; CA = cannabis abusing group; Ecstasy = Ecstasy abusing group; ex-(xx) = ex-user; (?) = not reported; [a] = found significant decrement in that domain; [c] = computer task; HVLT: Hopkins Verbal Learning Test; IGT: Iowa Gambling Task; TMT: Trail Making Task; RAVLT: Rey Auditory Verbal Learning Test; RBMT: Rivermead Behavioural Memory Test; RCFT: Rey-Osterrieth Complex Figure Test; WCST: Wisconsin Card Sorting Test.

characteristic of disinhibition in all substance abusers could be explained by a variety of addiction models in which disinhibition is thought to represent a state during which top-down control mechanisms that ordinarily suppress automatic or reward-driven responses are inadequate to meet current demands [82, 83]. Moreover, higher impulsivity and poor inhibition are thought to be a risk factor for the development of substance abuse disorders [84, 85].

Lower performance on verbal memory tasks was related to all substances, except for opiates. However, verbal memory has not been well investigated in opiate users yet. With respect to protracted periods of abstinence (more than one year), executive functions seem to normalise in (meth)amphetamine users. However, results about the reversibility of deficits in cocaine, opiates, alcohol, and ecstasy users are inconsistent.

Depending on the drug of abuse, different underlying neural and pharmacological mechanisms can be distinguished. These different mechanisms could be related to more specific neuropsychological profiles depending on the drugs of abuse. The action mechanism of cocaine is predominately blockage of the monoamine transporters, inhibiting the reuptake of dopamine, serotonin and norepinephrine. On the long term this can lead to attenuated dopamine receptor levels [86, 87]. These receptors are abundant in mesolimbic and mesocortical regions, and they are crucial for reward processing and cognitive control, respectively [88]. Congruently, we found that in cocaine studies, the most consistent cognitive deficits are those in the executive domain, mostly deficits in cognitive flexibility [9, 11].

In methamphetamine studies, executive functions such as cognitive planning and semantic clustering were found to be compromised [23, 24]. Methamphetamine blocks the dopamine reuptake, which eventually can lead to a depletion of dopamine and to a lesser extend of serotonin [for a review; 18]. Studies using functional and structural MRI have found abnormalities in prefrontal, cingulate, limbic and paralimbic cortices [89, 90], which are highly innervated by dopamine and serotonin.

Opiates such as heroin, stimulate the opiate receptor system, and chronic opiate abuse has been associated with density changes of the μ-opioid receptor throughout the brain [91, 92]. In addition, by reducing the inhibitory effect of GABA in the ventral tegmental area, dopamine levels are indirectly decreased on the long term. However, structural and functional abnormalities in opiate users are less specific than those observed for example in amphetamine users [93]. Our literature search indicated that individuals abusing heroin are found to have specific executive problems in verbal fluency [29, 32].

During chronic alcohol exposure, transmission in glutamatergic systems is facilitated both through increased NMDA receptor sensitivity [94] and increased glutamate turnover [95], resulting in partial tolerance to alcohol's sedative effects. Following withdrawal from alcohol, the glutamatergic system continues to be overactive [95], while NMDA receptor function remains elevated [94]. Especially the amygdala [96] and frontal brain regions [36] have been found to be sensitive to the toxic effect of alcohol and also to withdrawal from alcohol [96]. Our findings indicate that alcohol abuse leads to working memory problems and visuospatial decrements, which are indeed dependent on frontal brain regions [40, 46, 54-57].

Deficits related to ecstasy use are reported in the verbal memory domain [71-73]. Aberrancies in other executive functions, however, are less consistently reported in ecstasy users. Ecstasy reduces serotonin transporters in mesolimbic and mesocortical regions which also disrupts its complex interplay with dopamine functioning. Interestingly, the hippocampal area, that plays an important role in verbal memory, seems especially vulnerable to ecstasy use [97, 98]. Imaging studies in animals have shown changes in the hippocampal and (pre)frontal lobes after exposure to ecstasy [99, 100].

Lastly, little evidence exists for the presence of protracted cognitive impairments in adult abstinent cannabis users [80]. The acute effects of cannabis are produced by the interaction of the substance with cannabinoid receptor 1 [101]. This receptor is distributed throughout the brain similar to the dopaminergic receptor, with high concentrations in the basal ganglia, hippocampus and cerebellum, but it can also be found in the prefrontal cortex [102]. Although this subject is beyond the scope of our review, the effect of frequent cannabis use during adolescence seems to have a more crippling effect on brain development with possible long-term neuropsychological impairments as a consequence [76].

Unfortunately, interpretation of the neuropsychological literature remains difficult due to a number of factors. First, although the focus on studies requiring two weeks of abstinence is needed to rule out acute toxification effects, this criterion could also introduce a selection bias. It is conceivable that participants, who are able to refrain from drug use for two weeks or more, actually would like to stop using the substance (as it's difficult to get non-treatment seekers willing to stop for that long). Moreover, those who are able to remain abstinent might have better executive functions. Conversely, those who want to stop or cut down use might be the people who experience particularly adverse outcomes after drug use. Second, because of the cross-sectional nature of most studies, it is impossible to determine whether the identified deficits are a consequence of drug use, or are related to pre-existing vulnerabilities, or a combination of both. However, this methodology is necessitated by ethical considerations; we cannot administer large doses of drugs over time to participants and then test the effect on their neuropsychological functioning. Furthermore, prospective and longitudinal studies are very costly and entail large logistical difficulties. Third, both the demographic and drug use characteristics of the participants in the studies show large variability. For example, duration of drug dependence, other substances used and amount of drugs taken by the subjects differed significantly between studies. Fourth, because of the variability of neuropsychological tests used and the different neuropsychological domains they tap into, the possibility of comparing studies is limited. In addition, it should be kept in mind that some tests could be more sensitive to indicate neuropsychological differences between abuser groups and controls than other tasks. For example computerized tests, measuring reaction time with

high accuracy (in milliseconds) instead of manual stop watch timing, could be more sensitive in indicating group differences because timings are as exact as possible. Fifth, neuropsychological deficits could also be a consequence of characteristics of lifestyle frequently accompanying use of drugs. Incidences such as overdoses, head injuries, and malnutrition are phenomena that are known to cause neuropsychological deficits and are often encountered in the clinic [103-105]. These characteristics are hard to control for in experimental studies, but should be acknowledged and kept in mind while interpreting these findings. Sixth, drug users usually use multiple drugs simultaneously or at different occasions. The effects of polydrug use are interesting since both additive neurotoxicity and mutual neuroprotection could occur. For example some studies have shown milder or no cognitive decrements in populations that used cannabis as well as ecstasy [73, 106]. However, more severe neuropsychological decrements in polydrug users compared to single drug users have also been reported [107]. These difficulties are known challenges in addiction research and a growing amount of studies have taken these facts into account.

An elegant way of correcting for other substances of abuse and investigating the effects of one specific drug is to include control groups that use similar amounts of drugs except for the relevant drug. Some studies have employed this type of design and have found more specific neuropsychological decrements compared to the often broad range reported deficits when these groups were contrasted to controls [64, 71]. Another possibility is the use of multiple regression analysis, which is helpful in disentangling more specific deficits of drug effects in polydrug users [11, 31, 73]. One should, however, realize that this latter strategy is only possible if the correlations between the use of the various drugs are not too strong to cause multicollinearity. Another possibility is to look at correlations between total amount of drug used and neuropsychological performances. Although dose-response relationships in neuropsychological performance seem to be intuitively evident, some findings are at odds with these relationships [108]. Perhaps it does not matter how much drugs are used above a certain threshold. An explanation for the absence of a dose–response relationship might be that individuals differ in genetic vulnerability [109], or that the study samples have been too small to detect a dose–response relationship. Most interesting are prospective studies on the effects of drugs on neuropsychological functions since these studies rule out the confounding role of pre-existing neuropsychological differences and give insight into the causal direction of the neuropsychological decrements that are found with cross-sectional studies [i.e., 74]. Unfortunately, these prospective studies are a rarity because of the timely and costly nature of this type of research design.

Neuropsychological impairments can have a negative effect on treatment compliance and the potential benefit of cognitive behavioral therapy in drug dependent patients [1, 110]. For example, Aharanovich *et al.*, [1] found that cocaine dependent treatment dropouts showed poorer attention, memory and spatial ability than treatment completers. The strongest relationship was found between attention and treatment retention, suggesting that patients who have difficulty focusing and sustaining attention are less likely to remain in treatment. Another study in cocaine dependent patients showed that individuals that failed to benefit from feedback and repeated mistakes were more likely to discontinue treatment early [111]. In addition, decreased learning capacities might predict relapse in treated cocaine dependants [12]. Also in marijuana users, cognitive functioning was related to treatment compliance, dropouts showing poorer abstract reasoning than treatment completers [112]. Passetti and colleagues (2008) reported that decision-making abilities predicted clinical outcome after three months in recently abstinent (range from 7 to 60 days) opiate-dependent subjects [2]. They concluded that intact decision-making processes may be crucial to achieve and maintain abstinence. All of these findings indicate that neuropsychological functioning is important in overcoming a drug addiction. Thus, hypothetically, rehabilitation programs targeted to restore or compensate neuropsychological deficits could increase treatment success. Unfortunately, as far as we know, no research exists that have investigated the effect of cognitive rehabilitation on treatment success in drug users. Future research is needed to clarify if substance abusing individuals benefit more from treatment in combination with neuropsychological rehabilitation than from treatment alone.

GLOSSARY NEUROPSYCHOLOGICAL EXPRESSIONS

Domains	Explanation
Abstract reasoning	The ability to analyze information and solve problems on a complex level
Attention	Cognitive process of selectively concentrating on one aspect while ignoring other irrelevant information
Cognitive flexibility	The ability to switch between tracks, tasks or mind sets
Cognitive planning	One of the executive functions that involves the formulation, evaluation and selection of a sequence of thoughts and actions to achieve a desired goal
Decision making	Cognitive process resulting in the selection of a course of action among several alternatives
Delayed pattern learning	The ability to retrieve information about learned patterns from memory
Delayed verbal recall	The ability to retrieve verbal stimuli (i.e., words or word pairs) previously learned from memory
Executive function	An overarching concept including e.g. inhibition, planning, flexibility, working memory, fluency
Facial and emotion recognition	The ability to recognize faces and facial expressions of emotions
Figural fluency	The rate at which someone can produce a set of figures, evaluates nonverbal cognitive flexibility
Immediate verbal recall	The ability to directly reproduce previously learned verbal information
Impulsivity	The tendency to initiate behavior without adequate forethought as to the consequences of the actions
Inhibition	The ability to deliberately inhibit dominant, automatic, or prepotent responses

Motor functioning	Usually hand motor function measured by finger tapping or putting pins in pegboards
Prospective memory	The ability to remember what has to be done in the future, it is self-initiated and does not operate directly on external stimuli
Premorbid IQ	IQ before the development of a disease or disorder
Processing speed	A measure of cognitive efficacy that involves the speed task performance
Psychomotor speed	The amount of time it takes a person to process a signal, perpetrate a response and execute the reponse
Recognition discrimination	The ability to recognise familiar stimuli between un-familiar stimuli
Retention	The ability to retain facts and figures in memory
Retrieval	The process of recalling information that is stored in memory
Semantic clustering	The ability to organise information on a semantic level
Updating	Rrequires monitoring and coding of incoming information and appropriately revising the items held in working memory by replacing no-longer-relevant information with new, more relevant information
Verbal fluency	The rate at which someone can produce words associated with cognitive flexibility
Verbal learning	Learning that involves the use of language, ranging from learning to associate two nonsense syllables to learning to solve complex problems presented in verbal terms.
Verbal memory	Memory of words, word-pairs, stories and other abstractions involving language
Verbal recognition	The recognition of previous learned verbal stimuli
Verbal skills	A general category referring to various language related abilities such as reading, writing and organization of sentences and syntax
Visual construction	The ability to copy or reproduce visual constructions such as block designs or drawings
Visual memory	Part of memory preserving some characteristics of our senses pertaining to visual experience
Visual spatial functioning	Pertaining to the perception of the spatial relationships between objects in one's field of vision
Vocabulary	Knowledge of words
Working memory	The ability to actively hold information in the mind, required to carry out complex cognitive tasks such as learning, reasoning, and comprehension

Key Learning Objectives:

Cocaine, (meth)amphetamines, ecstasy, opiates, and alcohol use is associated with sustained deficits in executive functioning, especially inhibition. Cocaine, (meth)amphetamines, ecstasy, and alcohol are associated with long lasting verbal memory decrements. There is insufficient evidence for residual cognitive deficits in abstinent cannabis users. Depending on the drug of abuse, some evidence of more specific neuropsychological profiles exists. Neuropsychological impairments can have a negative effect on treatment compliance and the potential benefit of cognitive behavioral therapy in drug dependent patients.

Future Research Questions:

Studies taking into account longer periods of drug abstinence are needed to verify if drug-related deficits persist over time. More prospective study designs are considered necessary. Future research is needed to clarify if substance abusing individuals benefit more from treatment in combination with neuropsychological rehabilitation than from treatment alone.

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