Neuropsychology Review
https://doi.org/10.1007/s11065-018-9395-3

REVIEW

A Patient-Tailored Evidence-Based Approach for Developing Early Neuropsychological Training Programs in Addiction Settings

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Received: 27 January 2018 / Accepted: 16 November 2018

Abstract

Substance use disorders (SUDs) are associated with impairments of cognitive functions, and cognitive training programs are thus rapidly developing in SUD treatment. However, neuropsychological impairments observed early after withdrawal (i.e., early impairments), that is, approximately in the first six months, may be widespread. Consequently, it might not be possible to train all the identified early impairments. In these situations, we propose that the priority of cognitive training should be given to the early impairments found to be associated with early dropout or relapse (i.e., relapse-related impairments). However, substance-specific relapse-related impairments have not been singled out among all early impairments so far. Using a systematic literature search, we identified the types of established early impairments for all SUDs, and we assessed the extent to which these early impairments were found to be associated with relapse-related impairments. All cognitive functions were investigated according to a classification based on current neuropsychological models, distinguishing classical cognitive, substance-bias, and social cognition systems. According to the current evidence, demonstrated relapse-related impairments in alcohol use disorder comprised impulsivity, long-term memory, and higher-order executive functions. For cannabis use disorder, the identified relapse-related impairments were impulsivity and working memory. For stimulant use disorder, the identified relapse-related impairments were attentional abilities and higher-order executive functions. For opioid use disorder, the only identified relapse-related impairments were higher executive functions. However, many early impairments were not explored with respect to dropout/relapse, particularly for stimulant and opioid use disorders. The current literature reveals substance-specific relapse-related impairments, which supports a pragmatic patient-tailored approach for defining which early impairments should be prioritized in terms of training among patients with SUDs.

Keywords Cognitive remediation · Substance-use disorders · Alcohol · Cannabis · Stimulants · Opioid · Relapse · Treatment dropout · Cognitive impairments

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11065-018-9395-3) contains supplementary material, which is available to authorized users.

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Introduction

"Substance use disorders" (SUDs) is the official diagnostic label for substance addictions (American Psychiatric Association, 2013). SUDs constitute a set of chronic psychological and brain disorders, which are defined by criteria including the progressive loss of control upon the use of a psychoactive substance, as well as the chronic health and social consequences resulting from this uncontrolled use (Leshner, 1997; Volkow, Koob, & McLellan, 2016; Volkow & Li, 2004). Among these consequences, patients presenting with SUDs have substance-specific or general impairments in a large range of neurocognitive abilities. Such deficits have been repeatedly reported for "classical" cognitive functions

Published online: 03 January 2019

(e.g., attention, memory, and executive functions, Baldacchino, Balfour, Passetti, Humphris, & Matthews, 2012; Broyd, van Hell, Beale, Yücel, & Solowij, 2016; Spronk, van Wel, Ramaekers, & Verkes, 2013; Stavro, Pelletier, & Potvin, 2013), but more recent studies have also identified cognitive biases (i.e., preferential processing of addiction-related stimuli) as well as social cognition impairments (i.e., modified processing of interpersonal signals) in these populations. Changes in these different cognitive subsystems have been identified as key processes for the development and maintenance of addictive disorders, particularly in view of their role in relapse (Cui et al., 2015; Czapla et al., 2016; Gossop, Stewart, Browne, & Marsden, 2002; Le Berre, Fama, & Sullivan, 2017; Verdejo-Garcia et al., 2014).

Consequently, targeting neuropsychological impairments could constitute a promising short- and long-term strategy for treating SUDs as an adjunctive treatment approach in addition to the usual treatment procedures (e.g., pharmacological treatments or motivational therapy). While this research field has emerged recently, preliminary studies have suggested that training the impaired neuropsychological functions among patients with SUDs might result in improved treatment outcomes, better social functioning, and enhanced quality of life (Domínguez-Salas, Díaz-Batanero, Lozano-Rojas, & Verdejo-García, 2016; Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014). Despite the currently limited evidence regarding the actual efficiency of such programs in naturalistic clinical contexts, these promising insights have led to the expansion of neurocognitive training programs in addiction treatment (Fadardi, Cox, & Rahmani, 2016; Franken & van de Wetering, 2015). Thus far, however, the neuropsychological programs tested have been scattered regarding both the types of cognitive abilities targeted and the experimental tools used to measure them, and few structured cognitive training programs have actually been theoretically and empirically validated in patients with SUDs. As a consequence, no integrative and coherent neuropsychological perspective is currently available for treating SUDs, and many issues remain unsolved on how to practically organize treatment schemes (Rezapour, DeVito, Sofuoglu, & Ekhtiari, 2016).

A central concern currently hampering the emergence of integrated programs is that, as mentioned above, the range of neuropsychological dimensions impaired in patients with SUDs is generally quite broad. Implementing exhaustive training sessions (i.e., covering all affected cognitive dimensions) through classical neuropsychological remediation programs (e.g., Brady, 1994; Rupp, Kemmler, Kurz, Hinterhuber, & Fleischhacker, 2012) would thus be complex and would require substantial amounts of time, money, and human resources. For both organizational and financial reasons, this extensive training approach might not be suitable for a vast majority of addiction settings. Moreover, this would also be highly time-consuming and demanding for patients presenting limited cognitive resources, potentially leading to high dropout rates. Furthermore, and centrally, it has been demonstrated that many neuropsychological impairments associated with SUDs are reversible with prolonged abstinence, independently of any clinical intervention (Allen, Lee, Koob, & Rivier, 2011; Schulte et al., 2014), and might thus not be a central concern for neuropsychological training. In terms of overall efficiency, the a priori relevance of training all impaired neurocognitive functions in all patients should thus be questioned at practical and financial levels, and it is important to propose, based on the currently dispersed literature, a theoretically consistent and experimentally valid neuropsychological training algorithm that can apply the most efficient and tailored program to each patient with SUDs in each clinical setting. To optimize the currently growing proposals for neuropsychological treatment in SUDs, it is thus important to rationalize treatment schemes and to ensure that they are (1) clinically relevant with regard to priority treatment outcomes (e.g., relapse/dropout prevention); (2) affordable given the organizational resources of clinical settings; and (3) suitable given the time and cognitive resources of the patient.

The main aim of the present paper is to fill the gap between the current neuropsychological studies and the actual needs of clinical practice. Two key statements drive this integrative approach. First, we propose that the aims of the cognitive training for patients with SUDs should be focused on the main clinical objectives when treating such patients, which are (1) supporting the maintenance of substance use cessation, and (2) fostering treatment adherence by supporting patients in the recovery process. Second, we suggest organizing the neuropsychological treatment timing and priorities of the early post-withdrawal period by focusing on the cognitive deficits that are simultaneously present in the early post-withdrawal stages and identified as facilitators of treatment dropout (i.e., patients leaving the hospital before the end of the initial detoxification process, encompassing withdrawal and post-withdrawal periods) or relapse (i.e., re-consumption or re-appearance of SUDs criteria after the withdrawal process). A systematic literature search was thus conducted to identify (1) the neuropsychological impairments observed early after withdrawal (i.e., early impairments); and (2) among these substance-specific early impairments, those which are associated with early relapse and/or treatment dropout (i.e., relapse-related impairments).

Capitalizing on this literature review, we propose a rationale (illustrated in Fig. 1) for structuring neuropsychological training programs in patients with SUDs after substance withdrawal. This rationale is based on a two-stage approach separating short-term and long-term requirements for cognitive training. We postulate that the short-term requirements approximately correspond to the first

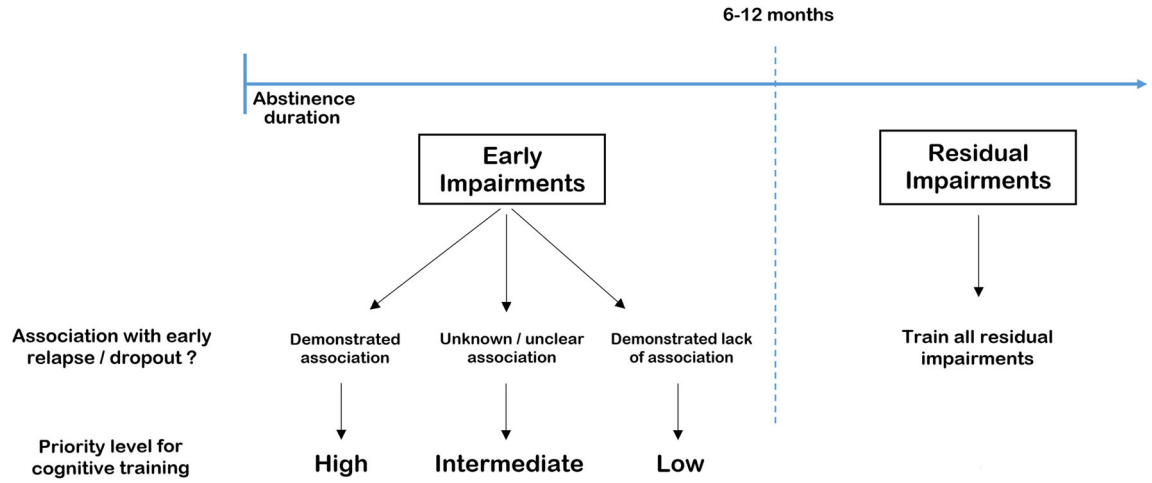

Fig. 1 Graphic summary of the proposed priority determination algorithm for identifying and rehabilitating neurocognitive impairments in clinical settings

six months after withdrawal. Indeed, while this six-month timeframe is quite long and encompasses several abstinence steps (e.g., withdrawal, post-detoxification) presenting distinct characteristics (e.g., changes in psychological/psychiatric treatments), it is usually considered as the period with the highest relapse risk (Zywiak, Westerberg, Connors, & Maisto, 2003; Zywiak et al., 2006) and it is the most frequently used cut-off for defining long-term abstinence (Nandrino et al., 2016; Pitel et al., 2009). Moreover, many early impairments have spontaneously recovered after six months of abstinence, even in the absence of neuropsychological intervention (Schulte et al., 2014). For all these reasons, we propose to retain this six-month post-withdrawal cut-off as the period during which priority should be given to the relapse-related impairments.

The therapeutic scheme proposed is thus based on three successive steps (Fig. 1): (1) a comprehensive post-withdrawal neuropsychological assessment of patients with SUD to individually measure the early impairments from a patient-tailored perspective; (2) a selection, among the identified early impairments, of those on which early neuropsychological training sessions should focus in priority (i.e., relapse-related impairments) and thereby the initiation of individualized remediation programs; (3) a re-assessment and training, after the first-stage treatment period (i.e., six months), of the residual neuropsychological impairments that have not been addressed by initial remediation, to go beyond the initial priority treatment outcomes and to further improve other disease-related factors (e.g., social rehabilitation, quality of life or well-being). Based on this rationale, the aim of this work is thus to examine, for all SUDs and each cognitive system, the relapse-related impairments that should be screened and trained by neuropsychological rehabilitation programs, before further elaborating on the proposed rationale and its implementation in clinical settings.

Methods

Theoretical Framework for Systems' Classification

To offer an exhaustive approach of the cognitive subsystems considered, a theoretically anchored classification of neuropsychological abilities at stake in SUDs has been developed. As mentioned above and in view of earlier studies exploring the key factors involved in the emergence and perpetuation of addictive disorders, three main categories of neurocognitive systems have been identified: classical cognitive functions, substance-related bias, and social cognition systems. The focus on these three systems is first justified by the fact that the distinction between classical cognitive and substance-bias systems is at the core of the currently dominant theoretical proposals on addictive disorders, i.e., dual-process models, conceptualizing addictions as an imbalance between under-activated cognitive/reflective (mostly relying on prefrontal regions) and over-activated substance-related/reflexive (mostly related to subcortical limbic regions) systems (Mukherjee, 2010; Stacy & Wiers, 2010). These models have been largely supported by empirical works showing that these two systems rely on distinct brain networks and are differentially involved in a disease course (Lindgren et al., 2018). The social cognition system has been added following the recent expansion of studies in this domain, which underlined at the conceptual level that social cognition constitutes an independent system (e.g., Happé, Cook, & Bird, 2017) and demonstrated the specific presence of social cognition deficits in addictive states as well as their influence on disease-related variables (see, e.g., Bora & Zorlu, 2017 for a review).

First, the classical cognitive system regroups cognitive functions related to information processing, which have been shown to be impaired in addictive disorders for decades. We maintained the largely accepted distinctions to differentiate the sub-functions associated with this system (e.g., Stavro

et al., 2013) by separating: (a) visuo-spatial and motor abilities (i.e., perceiving the stimuli coming from the environment and producing an efficient motor response); (b) attentional abilities (i.e., mobilizing, distributing and shifting attentional resources to process incoming stimuli); (c) long-term memory (i.e., encoding, storing, and retrieving episodic or semantic information); and (d) executive functions (i.e., using high-level abilities to select and monitor one's behaviors, when confronted with new contexts, to achieve determined goals). Because executive functions represent a large and diverse set of abilities, we separated them in four subsets following the influential theoretical model proposed by Diamond (2013): (1) inhibition/impulse control; (2) working memory/updating; (3) mental flexibility; and (4) higher-order executive functions (i.e., more complex and multi-determined abilities such as planning, decision making, or problem-solving).

Second, the substance-bias system relates to the preferential processing for substance-related stimuli found among patients presenting SUDs, independent of their cognitive impairments. The impairments associated with this system are linked to craving (Ekhtiari, Nasseri, Yavari, Mokri, & Monterosso, 2016) and are centrally characterized by attentional, approach, and memory biases toward substance-related stimuli, which are usually beyond the control of cognitive abilities (Coskunpinar & Cyders, 2013).

Third, the social cognition system regroups abilities related to the efficient perception of and reaction to interpersonal signals sent by other human beings, and is essential for adapted social behaviors and integration (Fiske & Taylor, 2013). Here again, we decided to classify the subcomponents of this system using a recent theoretical proposal (Happé et al., 2017) that distinguishes: (1) social imitation (i.e., identifying the action performed by another individual and correctly reproducing it); (2) empathy/emotion recognition (i.e., determining the cognitive or affective state presented by another individual, and adopting the same state or correctly reacting to it); and (3) theory of mind (i.e., representing and integrating one's own mental states and those presented by others).

Literature Search Procedure

For each main class of substance abuse, i.e., alcohol, cannabis, stimulants (cocaine and amphetamine), and opioids, a literature search was conducted with a two fold objective: (1) identifying substance-specific early impairments. This preliminary step was already undertaken in previous substance-specific systematic reviews (see Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Schulte et al., 2014); and (2) determining, among the early impairments, the relapse-related impairments related to all categories of SUDs.

The search was conducted on the Medline database. Because this search simultaneously pertained to different research domains, different keyword algorithms were used to find the appropriate literature. For each substance and each question, a complete list of keyword algorithms used, as well as the resulting literature selected, are provided in the Supplementary Fig. 1. When a recent systematic review or a meta-analysis was found regarding one of the questions listed above, we used it as a reference for the question. When no qualitative or quantitative review was available, we used the relevant original studies on the topic. We only selected original studies that measured (1) a classical cognitive system through validated neuropsychological tasks as defined in reviews/meta-analyses (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Stavro et al., 2013); (2) a substance-bias system through the gold-standard tasks (centrally approach-avoidance, dot-probe or modified Posner paradigms); (3) a social cognition system through tasks previously used in other psychiatric/neurological populations and considered by recent reviews (Bora & Zorlu, 2017; Le Berre et al., 2017) as reliably evaluating the targeted processes. Moreover, to be selected in this review, studies had to fulfill the following inclusion criteria: being conducted among adult participants (i.e., above 18 years of age), including a matched control group (for studies exploring early impairments), performing a diagnosis of severe substance-use disorder / substance-dependence based on DSM-IV, DSM-V or ICD-10 criteria.

Evaluation and Scoring of the Results Obtained

For each substance and each predefined category of cognitive functions, we reviewed whether this category was significantly impaired after withdrawal and significantly associated with relapse/dropout. The level of evidence of these associations was scored as follows: (1) "+++" for a significant association based on a meta-analysis or systematic review involving at least two congruent controlled studies; (2) "++" for a significant association based on at least two convergent controlled studies; (3) "+" for a significant association based on one controlled study; (4) "±" for inconsistent findings; (5) "–" for a lack of association found in one controlled study; (6) "––" for a lack of association found in at least two convergent controlled studies; and (7) "– – –" for a lack of association found in a meta-analysis or systematic review involving at least two congruent controlled studies. "Controlled" studies means that the studies used a control group, or a control condition (e.g., before/after). "Significant association" is to be understood as a statistically significant association.

We assessed the quality of each study, meta-analysis, or systematic review included in the final literature collected. Systematic reviews and meta-analyses were scored using the number of quality criteria of the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA statement), which provided an overall quality score with a maximum score of 27 (Moher et al., 2009). Observational studies

were scored using the 'Strengthening The Reporting of Observational studies in Epidemiology' (STROBE statement, von Elm et al., 2007), which provided an overall quality score with a maximum score of 34. Finally, interventional studies were assessed with the 'Risk of Bias' (ROB 2.0) tool of the Cochrane consortium (https://training.cochrane.org/resource/rob-20-webinar) for randomized studies, and the 'Risk of Bias In Non-randomized Studies' (ROBINS-I) for non-randomized studies (https://methods.cochrane.org/news/risk-bias-assessment-tool-non-randomised-studies-interventions). Narrative reviews were not scored. The process of study scoring was conducted independently by two different authors, with a third author involved in case of a mismatch. The resulting note (A-B-C) of each study is presented in Table 1.

Results: Early Cognitive Impairments and Treatment Outcomes in SUDs

The results are synthesized in Table 1. For each category of SUD, early impairments (i.e., impairments presented by patients early after withdrawal) and relapse-related impairments (i.e., impairments directly associated with increased relapse or dropout) are successively presented according to each neurocognitive system. Studies on early impairments mostly used cross-sectional approaches (with a low proportion of longitudinal exploration) while relapse-related impairments have been investigated almost exclusively by follow-up or longitudinal studies. As relapse evaluation tool and criteria strongly varied across experimental studies, the procedure used in each study to evaluate relapse/dropout is presented in Supplementary Table 1. The detailed scoring for quality of each study is presented in Supplementary Table 2.

Alcohol Use Disorder (AUD)

Classical Cognitive System

Early impairments: Participants with AUD exhibit a wide range of early neuropsychological impairments. Reduced visuo-spatial and motor abilities, long-term memory abilities, and executive functioning (including flexibility, inhibition, updating and decision-making) have been repeatedly reported (Le Berre, Fama, & Sullivan, 2017), and confirmed in a meta-analysis of good quality (Stavro et al., 2013). Conversely, the early post-withdrawal impairment of attentional abilities in AUD is less consistent (Stavro et al., 2013).

- Relapse-related impairments: Long-term memory abilities (Le Berre et al., 2017), inhibition/impulsivity (Czapla et al., 2016; Domínguez-Salas et al., 2016; Rupp et al., 2016), and high-order executive functions (Bowden-Jones et al., 2005; Domínguez-Salas et al., 2016; Rupp et al., 2016; Stevens et al., 2014) have been consistently found to be associated with early relapse or treatment dropout, in studies that were mostly presenting good quality (see Supplementary Table 2). By contrast, visuo-spatial abilities (Czapla et al., 2016), working memory, updating, and cognitive flexibility (Domínguez-Salas et al., 2016; Moriyama et al., 2002) were found to be not significantly associated with early relapse or treatment adherence in studies or meta-analyses of good quality.

Substance-Bias System

Early impairments: Attentional biases toward alcohol-related pictures have been recurrently found in recently detoxified AUD participants in studies of good or intermediate quality (Field & Cox, 2008; Snelleman et al., 2015).

Relapse-related impairments: Contradictory findings have been produced with regard to the role of cognitive biases toward alcohol-related stimuli in early relapse (Cox et al., 2002; Garland et al., 2012; Snelleman et al., 2015) or treatment adherence (Christiansen et al., 2015). Overall, the quality of the studies were found intermediate or good.

Social Cognition System

Early impairments: Post-withdrawal impairments in empathy, emotion recognition, and theory of mind have been consistently found among participants with AUD in studies presenting good quality (Bora & Zorlu, 2017; Castellano et al., 2015; Le Berre et al., 2017; Sanvicente-Vieira et al., 2017). Possible early impairments in imitation have not been explored so far.

Relapse-related impairments: While only limited findings had suggested that deficits in social cognition could foster drinking relapse or treatment dropout by showing that patients frequently reported to relapse when confronted with interpersonal difficulties (Zywiak et al., 2003), a recent study of good quality directly confirmed this important association (Rupp et al., 2017).

Cannabis Use Disorder (CUD)

Classical Cognitive System

Early impairments: Participants with CUD have been found to consistently display early impairments in long-term memory abilities and higher-order executive functions, with a quality level of the studies ranging from low to intermediate (Broyd et al., 2016; Crean et al., 2011; Grant et al., 2003). By contrast, no early visuo-spatial or motor disability was found in these participants (Grant et al., 2003). Moreover, inconsistent findings have been reported regarding early impairments in attentional abilities, inhibition and impulsivity, working memory,

Table 1 Synthesis of the literature listing the neuropsychological impairments observed early after withdrawal in the different types of substance use disorders, and the dropout/relapse related impairments

		Classical Cognitive System							Substance-bias System		Social Cognition System		
					Executive Functions								
		VM Ab.	Att. Ab.	LTM	Inh/Imp	WM/U	Flexibility	HEF	At. Bias	Ap. Bias	Imitation	E/ER	ToM
AUD	Early impairments	+++ (A) [Stavro et al., 2013]	± (A) [Stavro et al., 2013]	+++ (A) [Stavro et al., 2013]	+++ (NS-A) [LeBerre et al., 2017; Stavro et al., 2013]	+++ (NS-A) [LeBerre et al., 2017; Stavro et al., 2013]	+++ (A) [Stavro et al., 2013]	+++ (A) [Stavro et al., 2013]	+++ (B-A) [Field & Cox, 2008; Snelleman et al., 2015]	?	?	+++ (A-A-A) [Bora & Zorlu, 2017; Castellano et al., 2015; Sanvicente-Vieira et al., 2017]	+++ (NS) [LeBerre et al., 2017]
	Relapse-related impairments	– (A) [Czapla et al., 2016]	?	+ (NS) [LeBerre et al., 2017]	++ (A-A-B) [Czapla et al., 2016; Domínguez-Salas et al., 2016; Rupp et al., 2016]	– – (A-A-B) [Czapla et al., 2016; Domínguez-Salas et al., 2016; Moriyama et al., 2002]	– – (A-A-B) [Czapla et al., 2016; Domínguez-Salas et al., 2016; Moriyama et al., 2002]	++ (B-A-B) [Bowden-Jones et al., 2005; Domínguez-Salas et al., 2016; Rupp et al., 2016]	± (B-A-B-A) [Christiansen et al., 2015; Cox et al., 2002; Garland et al., 2012; Snelleman et al., 2015]	?	?	+ (A) [Rupp et al., 2017]	?
CUD	Early impairments	– – – (B) [Grant et al., 2003]	± (B-C) [Broyd et al., 2016; Crean et al., 2011]	+++ (B-C-B) [Broyd et al., 2016; Crean et al., 2011; Grant et al., 2003]	± (B-C) [Broyd et al., 2016; Crean et al., 2011]	± (B-C) [Broyd et al., 2016; Crean et al., 2011]	± (B-C) [Broyd et al., 2016; Crean et al., 2011]	+++ (B-C-B) [Broyd et al., 2016; Crean et al., 2011; Grant et al., 2003]	+++ (B-A) [Broyd et al., 2016; Norberg et al., 2016]	?	?	+ (B-A) [Bayrakçı et al., 2015; Platt et al., 2010]	+ (B) [Roser et al., 2012]
	Relapse-related impairments	?	?	?	+ (C) [Crean et al., 2011]	+ (C) [Crean et al., 2011]	?	± (A-B-B) [Domínguez-Salas et al., 2016; Peters et al., 2011; Stevens et al., 2014]	– (B) [Carpenter et al., 2006]	?	?	?	± (B) [Papinczak et al., 2017]
StUD	Early impairments	+++ (A) [Spronk et al., 2013]	± (A-A) [Potvin et al., 2014; Spronk et al., 2013]	+++ (A) [Potvin et al., 2014]	+++ (A) [Potvin et al., 2014]	+++ (A) [Potvin et al., 2014]	± (A-A) [Potvin et al., 2014; Spronk et al., 2013]	+++ (A) [Spronk et al., 2013]	+++ (A) [Leeman et al., 2014]	?	?	++ (B-A-B-A-A) [Henry et al., 2011; Hulka et al., 2014; Kim et al., 2011; Preller et al., 2014 ; Woicik et al., 2009]	+++ (B-B-A-A) [Henry et al., 2011; Kim et al., 2011; Sanvicente-Vieira et al., 2017; Verdejo-García et al., 2013]
	Relapse-related impairments	?	+ (B) [Clark et al., 2014]	?	– – – (A-A-A) [Domínguez-Salas et al., 2016; Kennedy et al., 2014; Streeter et al., 2008]	?	?	+++ (B-A-B-A-A) [Adinoff et al., 2016; Nejtek et al., 2013; Stevens et al., 2014; Turner et al., 2009 ; Verdejo-García et al., 2014]	± (B-A-A-A) [Carpenter et al., 2006; Domínguez-Salas et al., 2016; Kennedy et al., 2014; Levy-Bolin et al., 2017]	?	?	?	?
OUD	Early impairments	– – – (A) [Baldacchino et al., 2012]	± (A-B-B) [Biernacki et al., 2016; Wang et al., 2013; 2014]	± (A) [Baldacchino et al., 2012]	+++ (A-B) [Baldacchino et al., 2012; Passetti et al., 2013]	+++ (A-B) [Baldacchino et al., 2012; van Holst, & Schilt, 2011]	+++ (A-B) [Baldacchino et al., 2012; Wang et al., 2014]	+++ (A-B) [Biernacki et al., 2016; Stevens et al., 2014]	++ (B-B-B) [Constantinou et al., 2010; Garland et al., 2013; Waters et al., 2012]	?	?	+ (B-C) [Crapanzo et al., 2016; Kornreich et al., 2003]	?
	Relapse-related impairments	?	?	?	– – – (A-B) [Domínguez-Salas et al., 2016; Stevens et al., 2014]	– – – (A-B) [Domínguez-Salas et al., 2016; Stevens et al., 2014]	?	± (A-B-B-B) [Baldacchino et al., 2012; Passetti et al., 2008; 2011; Stevens et al., 2014]	++ (B-B-B-B) [Charles et al., 2015; Constantinou et al., 2010; Garland et al., 2013; Stevens et al., 2014]	?	?	?	?

Abbreviations and symbols:

+++	A positive association has been found in a meta-analysis or systematic review involving at least two congruent controlled studies
++	A positive association has been found in at least two convergent controlled studies
+	A positive association has been found in one controlled study
±	Inconclusive results have been found in the different studies and/or in a meta-analysis
–	A lack of association has been found in one controlled studies
– –	A lack of association has been found in at least two convergent controlled studies
– – –	A lack of association has been found in a meta-analysis or systematic review involving at least two congruent controlled studies
?	No Available study
A	A systematic review or meta-analysis, observational study, or interventional study with a good quality score, i.e., 19 or more out of 27 using the PRISMA criteria for systematic reviews and meta-analyses, 23 or more out of 34 using the STROBE criteria for observational studies, or low risk of bias using the ROB 2.0 statement.
B	A systematic review or meta-analysis, observational study, or interventional study with an intermediate quality score, i.e., between 9 and 18 out of 27 using the PRISMA criteria for systematic reviews and meta-analyses, between 12 and 22 out of 34 using the STROBE criteria for observational studies, or intermediate risk of bias using the ROB 2.0 statement.
C	A systematic review or meta-analysis, observational study, or interventional study with a low quality score, i.e., 8 or less using the PRISMA criteria for systematic reviews and meta-analyses, 11 or less using the STROBE criteria for observational studies, or high risk of bias using the ROB 2.0 statement.
NS	Not scored studies
AUD	Alcohol Use Disorder
CUD	Cannabis Use Disorder
StUD	Stimulant Use Disorder
OUD	Opioid Use Disorder
VM Ab.	Visuospatial and Motor Abilities
Att. Ab.	Attentional Abilities
LTM	Long-Term Memory
Inh/Imp	Inhibition / Impulsivity
WM/U	Working Memory / Updating
HEF	Higher-order Executive Functions
At. Bias	Attentional Bias
Ap. Bias	Approach Bias
E/ER	Empathy / Emotion recognition
ToM	Theory of Mind

and flexibility among participants with CUD (Broyd et al., 2016; Crean et al., 2011).

Relapse-related impairments: Impairments in inhibition/impulsivity and working memory/updating are the two types of CUD-related early impairments in the classical cognitive functions that have been reportedly associated with relapse or treatment adherence so far (Crean et al., 2011), and inconsistent results have been reported as to whether these functions are actually impaired in CUD. By contrast, mixed findings have been obtained regarding the association between higher-order executive functions (which appear to be consistently impaired among participants with CUD) and treatment outcomes (Domínguez-Salas et al., 2016; Peters et al., 2011; Stevens et al., 2014). Moreover, the relationships with relapse or treatment adherence have not yet been explored in CUD for attentional disabilities, long-term memory, and flexibility.

Substance-Bias System

Early impairments: Attentional bias toward cannabis-related stimuli was recurrently found among participants with CUD in intermediate or good level studies or meta-analyses (Broyd et al., 2016; Norberg et al., 2016).

Relapse-related impairments: One study of intermediate quality found that the intensity of the interference provoked by marijuana-related words in a Stroop task was not associated with treatment outcome in CUD (Carpenter et al., 2006).

Social Cognition System

Early impairments: After cannabis withdrawal, early deficits in empathy and emotion recognition (Bayrakçı et al., 2015; Platt et al., 2010) as well as deficits in theory of mind (Roser et al., 2012) have been reported in participants with CUD. Possible early impairments in imitation have not been explored so far.

Relapse-related impairments: the impairments in theory of mind among participants with CUD have recently been associated with reduced treatment seeking but not directly with treatment adherence or early relapse in a study presenting intermediate quality (Papinczak et al., 2017). Other functions of social cognition, i.e., imitation, empathy, and emotion recognition, have not been studied in participants with CUD with regard to the risk of early relapse or early treatment dropout.

Stimulant Use Disorder (StUD)

Classical Cognitive System

Early impairments: StUD is associated with early impairments in visuo-spatial and motor abilities (Spronk et al., 2013), long-term memory abilities (Potvin et al., 2014), and, among executive functions, with early impairments of inhibition/impulsivity (Potvin et al., 2014), working memory/updating (Potvin et al., 2014), and higher-order executive functions (Spronk et al., 2013). By contrast, early impairments in attentional abilities and flexibility have been inconsistently found in StUD (Potvin et al., 2014; Spronk et al., 2013). All these studies were found to display a good quality level.

Relapse-related impairments: An association between early StUD relapse and attentional impairment was found in a single previous study of intermediate quality (Clark et al., 2014), whereas impairments in higher-order executive functions were found to be associated with relapse or treatment adherence (Adinoff et al., 2016; Nejtek et al., 2013; Turner et al., 2009; Stevens et al., 2014; Verdejo-Garcia et al., 2014). By contrast, impulsivity and response inhibition were found not to be associated with relapse in StUD in several previous publications (Domínguez-Salas et al., 2016; Kennedy et al., 2014; Stevens et al., 2014), while they might be related to treatment adherence (Streeter et al., 2008). The involvement of visuospatial and motor abilities, long-term memory abilities, working memory, updating, and flexibility has, to the best of our knowledge, never been investigated in StUD.

Substance-Bias System

Early impairments: It is well established that participants with StUD exhibit attentional bias toward stimulants-related stimuli (Leeman et al., 2014).

Relapse-related impairments: Attentional bias toward stimulants-related stimuli did not appear to be associated with relapse in several previous observational studies (Domínguez-Salas et al., 2016; Kennedy et al., 2014). However, one study (of intermediate quality) found that interference effects for cocaine-related stimuli during a Stroop test were associated with poorer treatment outcomes (Carpenter et al., 2006). Moreover, in a recent clinical trial that we assessed as presenting a low risk of bias, a reduction of attentional bias toward cocaine-related stimuli was positively associated with a concurrent reduction in cocaine use (Levi-Bolin et al., 2017).

Social Cognition System

Early impairments: Repeated results have found that participants with StUD display early impairments in empathy and emotion recognition (Henry, Mazur, & Rendell, 2009; Hulka et al., 2014; Kim et al., 2011; Preller et al., 2014a, 2014b; but see Verdejo-García et al., 2013; Woicik et al., 2009), as well as deficits in theory of mind (Henry et al., 2009; Kim et al., 2011; Sanvicente-Vieira et al., 2017). These studies were of intermediate or good quality.

Relapse-related impairments: The impact of possible impairments in social cognition on early relapse or treatment adherence has not been assessed in StUD.

Opioid Use Disorder (OUD)

Classical Cognitive System

Early impairments: Despite the relative scarcity of studies, OUD has been found to be associated with early impairments in several dimensions of the classical cognitive functions, particularly in all types of executive functions, i.e., inhibition/impulsivity (Baldacchino et al., 2012; Passetti et al., 2013), working memory/updating (van van Holst & Schilt, 2011), flexibility (Wang et al., 2014), and higher-order executive functions (Biernacki et al., 2016; Stevens et al., 2014). By contrast, visuospatial and motor abilities were not found to be affected by OUD (Baldacchino et al., 2012), while contradictory findings were reported for attentional (Biernacki et al., 2016; Wang et al., 2014; Wang et al., 2013) and long-term memory (Baldacchino et al., 2012) abilities. All these studies showed intermediate or good quality.

Relapse-related impairments: Limited evidence is available on the association between classical cognitive functions and early relapse or treatment adherence in OUD. Inconsistent associations have been found between treatment outcomes and higher-order cognitive functions (Baldacchino et al., 2012; Passetti et al., 2011; Passetti et al., 2008; Stevens et al., 2014), while no significant association has been found with inhibition impairment/impulsivity and working memory/updating (Domínguez-Salas et al., 2016; Stevens et al., 2014). No previous study has explored the role of possible early impairments in attentional abilities, long-term memory, and flexibility on treatment adherence or relapse risk.

Substance-Bias System

Early impairments: An important number of studies of intermediate quality have been conducted on the attentional bias toward opioid-related stimuli, all finding an important attentional bias in users of either illicit or prescription opioid drugs (Constantinou et al., 2010; Garland et al., 2013; Waters et al., 2012).

Relapse-related impairments: Even though mixed findings have been obtained by studies investigating interference control over drug-related stimuli (Stevens et al., 2014), attentional bias was consistently found to be associated with relapse and treatment dropout risk in OUD (Charles et al., 2015; Constantinou et al., 2010; Garland & Howard, 2014).

Social Cognition System

Early impairments: Two studies have found deficits in emotion recognition among participants with OUD (Craparo et al., 2016; Kornreich et al., 2003), even though Kornreich et al. (2003) showed a low quality score. Imitation and theory of mind have never been explored in this population.

Relapse-related impairments: The association between impairments in social cognition and treatment outcomes has never been investigated in OUD, to the best of our knowledge.

Discussion

Our approach for defining which neurocognitive training programs should be proposed to early-detoxified patients with SUDs is based on prioritizing the early impairments that have been found associated either with early relapse or early dropout. Once a sustained cessation of substance use has been achieved, that is, after six months to one year, we propose to reassess the entire neurocognitive functioning of the patient and to refocus the training program on all the residual deficits.

According to this approach, the current evidence suggests that the type of early impairments that should receive priority treatment for early post-detoxification training are (1) for AUD: inhibition/impulsivity, higher-order executive functions, and long-term memory (with a lower level of evidence); (2) for CUD: Inhibition/impulsivity and working memory/updating; (3) for StUD: attentional abilities and higher-order executive functions; and (4) for OUD: higher-order executive functions. By contrast, the early impairments found to be not associated with relapse and which should thus not be trained at early stages are (1) for AUD: working memory/updating, flexibility, and visuomotor abilities; (2) for CUD: higher-order executive functions; (3) for StUD: inhibition/impulsivity; and (4) for OUD: inhibition/impulsivity and working memory/updating. However, and importantly, the potential effects of early training are still poorly understood for many impaired neuropsychological functions. Accordingly, the results of a similar literature-based selection on which early impairments should be trained in priority could thus be different in a few years. For this reason, this work should be considered as an essential first step for developing early neuropsychological training programs in addiction settings.

Overall, it appears that the early impairments involved in early relapse are specific to the type of SUD. For example, whereas inhibition impairments and impulsivity have been consistently found to be associated with increased relapse rates in both AUD and CUD, the same association was found to be negative in studies on StUD and OUD. Similarly, deficits in higher-order executive functions have been consistently found to be associated with relapse in AUD and StUD, but the evidence are far less convincing in CUD and OUD. It thus appears that the key neuropsychological prognostic factors are not identical for the different substances. The heterogeneity across substances claims to abandon general training programs and to evolve towards a patient-tailored, substance-

specific approach to define the neurocognitive training schemes within addiction settings. This heterogeneity also raises questions regarding the neuropsychological evaluation/training rationale that should be proposed in polysubstance abusers. As, to our knowledge, no previous study has directly compared mono-substance and poly-substance abusers regarding early cognitive impairments and their association with relapse, it is currently difficult to determine clear clinical guidelines for those populations. However, as it is impossible to simultaneously address all the early impairments related to multiple SUDs in current clinical settings, it might be proposed as a general principle that initial neuropsychological training should focus on the impairments associated with the primary drug of choice, with a particular emphasis on the impairments involved in both SUDs at stake in a specific patient (e.g., inhibition/impulsivity training in patients simultaneously presenting AUD and CUD).

Another important point resulting from our review is that the impact of SUDs on some specific types of neuropsychological impairments are still completely unexplored, particularly for social imitation abilities. Moreover, for some substances, the impact of established early impairments on clinical outcomes has not been investigated so far. For example, in CUD, whereas long-term memory deficits have recurrently been found, it has never been studied whether this category of impairment could affect relapse in cannabis use or retention in treatment. Regarding the substance-bias system, attentional biases toward substance-related stimuli are frequently reported for all SUDs in clinical and sub-clinical populations (e.g., approach tendencies toward alcohol in heavy compared to light drinkers; Field, Kiernan, Eastwood, & Child, 2008; Field, Caren, Fernie, & De Houwer, 2011a; Field et al., 2011b), and these biases appear related to impulsivity (Leung et al., 2017) underlining their role in these addictive states. Nevertheless, their association with relapse or dropout, while being demonstrated in OUD, remains controversial in other SUDs. This applies to the approach bias for all SUDs. In the same vein, the role of early impairments in social cognition on relapse has only been suggested in AUD (Rupp et al., 2017), and remains unexplored in other SUDs.

All these gaps of knowledge should be addressed in future neuropsychological research on SUDs and future cognitive training. Moreover, in this article, the already-existing cognitive training programs for SUDs-related early impairments have not been reviewed, although studies on such programs have been quickly growing in recent years. Recent works (Snider et al., 2018; Wiers, 2018) have notably suggested that specific training programs, known to effectively reduce the early impairments related to the classical cognitive system, could also substantially reduce relapse or treatment dropout rates. Much more effort has to be made regarding the substance-bias system. Indeed, while cognitive bias modification has a small but robust clinical effect in AUD when combined with classical treatments (Wiers, Boffo, & Field, 2018), the available results are still limited to AUD, and sounder clinical trials are needed to determine the exact impact of these interventions in SUDs (Cristea, Kok, & Cuijpers, 2016; Jones & Sharpe, 2017). This also applies to the social cognition system because, to the best of our knowledge, no specific training programs have been used in SUDs, while encouraging results have been obtained with already-existing interventions in patients suffering from schizophrenia (Horan et al., 2017; Kurtz & Richardson, 2012). Importantly, future clinical trials assessing such programs should definitively incorporate these important addiction outcomes in their overall assessment.

As previously pointed out, a major limitation of our approach is the important level of scarcity of the previous literature on which early impairments have been found associated with relapse, particularly for StUD and OUD, which requires caution at this stage with many of the reported findings. Moreover, whereas the quality of the studies, meta-analyses, and systematic reviews collected in our own review was generally very good for AUD, and to a lesser extent, for StUD, it was mostly intermediate for CUD and OUD (See Table 1 and Supplementary Table 2). A great deal of caution is thus warranted regarding the conclusions on these two specific SUDs. Furthermore, many concepts have not reached a consensus in the current literature. In particular, in the studies on relapse-related impairments, the concept of relapse is commonly defined by resuming any use of substance, although a few studies have focused on the re-occurrence of the DSM criteria of SUD (See Supplementary Table 1 for a description of the relapse evaluation in each study). This highlights the need for future studies to standardize the criteria used to determine the different clinical outcomes. Similarly, many studies exploring the various early impairments among the different SUDs did not assess psychiatric comorbidities or potential sociodemographic factors, and could therefore not adjust their findings according to these potential biasing factors. Although this can alter the results of Table 1 regarding early impairments, we believe however that this limitation does not affect the findings on relapse-related impairments and thus does not compromise our main conclusions on which cognitive functions should be trained in every specific SUD.

A possible other limitation of our approach is that we did not consider the likelihood that the primary training of early impairments that were found not to be associated with early relapse or retention could, in fact, be useful for enhancing the probability that these early impairments regress, compared to the probability of regressing without intervention. Although no study has ever explored this, we admit that this could be another important justification for involving these early impairments in cognitive training programs. Once again, our approach is proposed to guide the therapeutic decision-making, particularly when early impairments are too widespread to be trained simultaneously in the same participant.

In conclusion, the current literature on addiction-related impairments has identified a significant association with relapse or treatment dropout in only a part of the widespread cognitive impairments observed early after substance withdrawal. For both clinical and economic reasons, we suggest that neuropsychological training programs might increase their efficiency by initially focusing on these impairments, having an early post-withdrawal impact on relapse or treatment dropout, but future studies should be conducted to support this assumption. In practice, this means that the initial neuropsychological assessment conducted in clinical addiction settings should give priority to the cognitive impairments with which a link with relapse and/or dropout has been found, for example inhibition/impulsivity or higher executive functions in AUD, inhibition/impulsivity and working memory in CUD, attentional abilities and high executive functions in StUD, or attentional bias in OUD. This approach is simple and personalized, and aims to be progressively enriched with new evidence coming from new studies. As the recently emerging training programs for patients with SUDs have been found to be both affordable and well-accepted, we believe that developing these programs, guided by our rationale, is a pragmatic and efficient approach for both clinics and research, which places the emerging concept of neuropsychological interventions for SUDs directly in line with the clinical expectations of the medical teams.

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