Risk of neuropsychological impairment in Therapeutic communities' residents at entry: which profile should alert us?

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Simon Deniel[a], Marion Delarue[a], Louise Quételard[b], Maïlys Miquel[c], Stéphane Lozé[b], Marie Dumont[b], Christophe Rimbaud[c], Carole Rousseau[c], Susie Longbottom[d], Nicolas Kenens[d], Nicolas Bourguignon[e], Jonathan Rayneau[e], Marine Gaubert[e], Juliette Dupuis[e], Ludivine Ritz[a] and Hélène Beaunieux[a]

[a] Caen Normandy Psychology Laboratory, Caen Normandy University, Caen, France

[b] Therapeutic Community of the Sauvegarde du Nord, Le Cateau-Cambrésis, France

[c] Therapeutic Community of the Fleuve, CEID Addictions, Barsac, France

[d] Therapeutic Community of Aubervilliers, Aurore Association, Aubervilliers, France

[e] Addiction Federation, Paris, France

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Abstract

Introduction: Substance Use Disorder (SUD) has been linked to neuropsychological impairment (e.g., executive functions, working and episodic memories, visuospatial abilities, and ataxia). These disorders can hinder the benefits of the addiction treatment. The understanding of cognitive impairments in SUD has led to a modification of addictology treatment in detox centres. However, little is known about Therapeutic Communities (TCs) where cognitive disorders have not been investigated yet, as well as about the respective impact of risk factors that could interfere with cognition.

Methods: 56 TCs residents underwent interviews and filled in questionnaires relative to social, medical and substance use data and were given a neuropsychological screening (BEARNI: Brief Evaluation of Alcohol-Related Neuropsychological Impairment). The risk of cognitive deficits in TCs residents was compared with that of an abstainer control group (HC).

Results: TCs residents were mostly polysubstance users with frequent medical history. For all subtests assessed, the residents' global risk of neuropsychological impairments was higher compared to HC. Most of the sample had moderate to severe risks of impairment. Liver history was a significant predictor since it increases the risk of having moderate to severe risk of cognitive impairment by three times on the BEARNI total score.

Discussion/Conclusion: TCs patients seem to have a high risk of cognitive impairment at the time of entry that may represent a barrier in their addiction care pathway in TCs. The results obtained highlight the need to give careful consideration to liver history since it could be a red flag indicating an increased cognitive risk of impairment. These highlights point out the significance of assessing cognition in TCs to better tailor the addiction treatment and thus to limit the daily impact of cognitive disorders.

Introduction

Substance Use Disorder (SUD) is widespread internationally and represents health and social challenges. In Europe, alcohol consumption remains an important preventable cause of mortality with 41,000 deaths in France each year, followed by illicit drugs use which can lead to health complications or overdoses [1]. Given the medical, social, and psychological issues experienced by chronic users, SUD is a major public health issue [2].

A growing body of literature drawn from studies conducted in addiction hospital centres has improved the characterization of the neuropsychological profile of SUD patients, with alcohol being the most studied substance [3]. In Alcohol Use Disorders (AUD) patients, deficits affecting executive functions lead to disabilities in adapting to newness, inhibition, and represents a barrier to decision-making [4,5]. Working memory is also impaired with the subject being unable to maintain and manipulate information in short-term memory [6]. Impairment also encompasses encoding, learning and retrieval processing in verbal episodic memory [7]. Visuospatial impairments [8] have also been evidenced. A link has been established between ataxia, which results in motor gait and balance impairments, and the neurotoxic consequences of alcohol on the cerebellum, which was shown to be a severity marker of the cerebral damage related to low cognitive functioning [9]. These patterns of cognitive disorders are also reported in other substances, but with varying severity degrees depending on the substance used (e.g., cannabis, psychostimulants, opioids, or ecstasy) [10]. This observation was found in studies focusing on both monosubstance use and polysubstance use, which is a frequent pattern in SUD [11]. Disorders affecting executive functions, episodic and working memory, visuospatial abilities and ataxia are also reported in polysubstance users and seem to overlap, which makes it challenging to disentangle the specific effects of each substance separately [12].

Regardless of the substance use pattern, the aforementioned neuropsychological disorders can have a deleterious impact on daily functioning, whether it be in professional or social areas [10]. Cognitive impairment can interfere with readiness to change behavior [13] and hamper the benefits of addiction treatment for patients [14]. The treatment of SUD requires being receptive, being ready to take in new information and being able to integrate it and translate it into behavioral changes [15]. To fully benefit from the therapy, the patients must rely on cognitive functions, such as episodic memory, and executive functions [16]. The prevalence of cognitive impairment in people received in SUD outpatient settings is high and has been estimated to be in the order of 30% to 80% [17]. Cognitive screening is thus essential to make the appropriate clinical decisions regarding the nature and timing of the treatment. The BEARNI tool (Brief Evaluation of Alcohol-Related

Neuropsychological Impairment) [18] allows to rapidly assess the risk of cognitive and motor impairment in AUD. The BEARNI screening tool enables the treatment to be adjusted to the risk of neuropsychological deficits and leads to an extensive neuropsychological assessment if necessary.

These advances in detecting neuropsychological disorders in users and in understanding their deleterious effects have led to a modification of addiction treatment in detox centres. Nevertheless, the Therapeutic Communities (TCs) have not yet invested this clinical field of practice and research.

TCs are residential treatment facilities welcoming people with SUD willing to initiate a dynamic change [19]. The original aspect of this support is based on the relation with peers, their help, and the intervention of professional staff. It allows the residents to benefit from their advanced expertise in the development of their care plans, to assimilate social norms and to develop their interaction abilities.

Despite the promising results of TCs in terms of physical improvements and quality of life for the residents, the relapse and socio-professional reinsertion rates remain unsatisfying. Notwithstanding the accuracy of the TC model, the rate for relapse cases is of 49% according to studies [20]. A possible explanation is that most TCs residents experienced multiple treatment failures in other treatment system [21]. Another explanation is that neuropsychological disorders are not systematically investigated in TCs. However, there is a strong likelihood that these residents develop neuropsychological impairment, that may reduce the efficiency of the treatment. Executive functions, episodic and working memory disorders previously depicted may have deleterious effects on social cognition functioning [22,23], whereas it is highly solicited in TCs where the main therapeutic tool is based on social interactions and group support.

Few studies were led on the neuropsychological functioning of TCs residents. The prevalence of the cognitive impairment risk was investigated in a study led in Mexico TCs, that reports that around 50% of the sample is affected by objective cognitive impairment [24]. Executive functioning was investigated the most and reported as being frequently impaired in polysubstance users enrolled in TCs, with shifting, planning and multi-tasking impairment [25,26]. However, studies investigating other cognitive functions are scarce. To date, only one recent retrospective study has focused on a broader cognitive computer-based assessment, where executive functions, attention, response speed, memory, and emotion recognition impairments are reported [27]. This is the first study led in a substantial male residents' sample, and that calls for confirmation of its results and for the identification of the risk factors of those cognitive disorders. However, the computer-based design is only partially helpful in understanding cognitive functioning and cannot substitute for a cognitive competence assessment, as is done in clinical practice. Further data is therefore needed to enhance

the neuropsychological functioning characterization of TCs residents with a view to tailoring the addiction treatment.

Beyond considering the cognitive consequences of SUD, it is worthwhile to be able to identify clinical risk factors that could influence the nature and severity of neuropsychological disorders as early as possible. A few epidemiological studies led in TCs pinpointed that polysubstance use and medical, psychiatric comorbidities added to SUD are frequent [28,29]. While the direct deleterious cognitive effects of SUD are well documented, the potential additive effect of other variables on cognition remains unclear. The heterogeneity of clinical, socio-demographical and substance use profiles of TCs residents makes it necessary to disentangle the effect of these various parameters on cognitive impairment. A study conducted in AUD patients identified that biological and clinical variables (i.e., thiamine, malnutrition, long-term alcohol use, complex withdrawal, altered liver function) could represent important risks of developing neuropsychological impairment [30,31]. In opiate dependent patients, former head injuries and depression were linked to lower cognitive performance [32]. Beyond SUD, the effect of psychopathological states on cognitive performance was investigated, with depression being a risk factor of impairment [33] and psychiatric comorbidities as well [34]. Studies identifying other biopsychosocial risk factors of cognitive impairment are scarce, despite the clinical relevance to identify at risk profiles to adjust the patients' treatment to their neuropsychological strengths and weaknesses at an early stage in the care process. A limitation of these studies is that they do not always consider the factors as a whole to disentangle their respective impact on cognition. Still, there is a growing body of literature focusing on the risk factors of low treatment outcomes and relapse in SUD [35]. The risk factors for cognitive impairment were also linked to pessimistic prognoses as regards addiction treatment (e.g., characteristics of substance use, medical comorbidities, cognitive factors, polysubstance use), but also to the social and economic status [36]. The employment status was reported as being a strong predictor of mental health and preserved cognitive functioning in older workers [37], which was confirmed in psychotic patients for whom unemployment was linked to more severe symptoms and lower cognitive functioning [38]. A similar pattern was found for housing stability, with a correlation between homelessness and poor cognitive functioning being reported [39].

Given the multiplicity of the risk factors, their respective impact on cognition should be assessed in the same sample of patients. Hence, the heterogeneity of the TCs residents' profiles is an advantage to test all these factors. Consequently, as in [27], we chose to include all volunteer residents regardless of their profile. The objective is not only to study their risk of developing

neuropsychological impairments, but also the clinical factors that add to the degree of risk to get as close as possible to the reality of clinical settings.

For the first time, the present study aimed at (1) estimating the nature and severity of the risk of developing neuropsychological disorders and (2) identifying the most important risk factors for those disorders in TCs residents. Based on the literature, we first expected to observe a high level of risk of neuropsychological impairments (i.e., executive, visuospatial, working memory, episodic memory impairments and ataxia) in residents. Second, we expected the combination of the three categories of variables (i.e., substance use, social and medical history data) would represent potential risk factors of cognitive disorders, as it has been previously studied separately and in other populations of interest.

Materials and Methods

Procedure and participants

This study was part of an ongoing larger research program (Neuropsychology of Addictions in Therapeutic Communities, NEUROADDICT), exploring the efficacy of a neuropsychological approach in TCs on the relapse rate and social-professional insertion. Fifty-six volunteer residents, recruited from 3 French partner TCs, were included in the 15 days following their entry in TCs. They underwent ad hoc designed interviews about their consumption habits, filled in questionnaires, and underwent neuropsychological screening, in separated appointments. All participants, aged between 20 to 57 years, presented SUD, were native French speakers, and had at least seven years of formal education. The performance and characteristics of the TC group have been compared to a healthy controls (HC) group, drawn from [31]. The participants in the HC group did not meet the criteria for alcohol use disorder (AUDIT score < 7 for men and < 6 for women; m = 3.33; sd = 1.65; p = < .001), tobacco dependence (Fagerström: m = 0.55; sd = 1.33; p = < .001) nor for any other substance use disorder. They did not suffer from any cognitive disorder and did not have any medical and psychiatric history. HC were selected to match to TCs residents for age (m = 42.98; sd = 8.31; p = .37), sex (p = .11), and education (m = 11.24; sd = 1.33; p = .46).

Ethics

Data were gathered from January 2021 to January 2022. In accordance with the Declaration of Helsinki, all participants were informed about the study aim, prior to their participation and then provided their informed consent. This study was integrated to the classical support as proposed in TCs.

Measures

All relevant TCs resident-related measures are reported in Table 1.

Table 1. Sample characteristics of Therapeutic Communities residents (*n* = 56)

	% of total	**Mean ± standard deviation**
Variables		
Demographics and social data		
Sex ratio (men/women)	80.36 / 19.64	_
Age (in years)	_	41.51 ± 10.09
Range		*20-57*
Years of schooling	_	11.50 ± 2.15
Range		*7-17*
Living environment (stable/precarious)	67.86 / 32.14	_
Employment before care began (yes/no)	21.43 / 78.57	_
Substance Abuse		
Tobacco		
Users/Abstainers (last 12 months)	98.21 / 1.79	_
Onset	_	14.60 ± 3.66
Range		*8-27*
Fagerström	_	5.50 ± 2.88
Range		*0-10*
Alcohol		
Users/Abstainers (last 12 months)	89.29 / 10.71	_
Onset	_	14.62 ± 3.74
Range		*7-28*

Severity of disorder* (no disorder/mild/moderate/severe)	14.30 / 0 / 1.79 / 83.91	_
AUDIT	_	27.60 ± 8.66
Range		*3-39*
Cannabis		
Users/Abstainers (last 12 months)	62.50 / 37.50	_
Onset	_	14.79 ± 1.99
Range		*10-18*
Severity of disorder* (no disorder/mild/moderate/severe)	51.79 / 3.57 / 3.57 / 41.07	_
CAST	_	10.62 ± 6.43
Range		*0-21*
Benzodiazepines		
Users/Abstainers (last 12 months)	50 / 50	_
Onset	_	27.76 ± 9.17
Range		*14-49*
Severity of disorder* (no disorder/mild/moderate/severe)	67.86 / 5.36 / 8.92 / 17.86	_
Cocaine		
Users/Abstainers (last 12 months)	37.50 / 62.50	_
Onset	_	21.05 ± 6.40
Range		*15-41*
Severity of disorder* (no disorder/mild/moderate/severe)	73.21 / 7.14 / 1.79 / 17.86	_

Heroin		
Users/Abstainers (last 12 months)	12.50 / 87.50	_
Onset	_	22.29 ± 5.09
Range		*15-30*
Severity of disorder* (no disorder/mild/moderate/severe)	89.29 / 0 / 1.79 / 8.92	_
Polyconsumption (yes/no)	83.93 / 19.07	_
Number of substances used (1/2/3/4)	16.07 / 32.15 / 35.71 / 16.07	_
Medical history		
Liver history (yes/no)	41.09 / 58.91	_
Neurological history (yes/no)	67.86 / 32.14	_
HIV (yes/no)	1.79 / 98.21	_
Psychiatric history (yes/no)	85.71 / 14.29	_
Psychopathological state		
Anxiety (HADS-A)	_	10.27 ± 4.69
Range		*2-21*
Depression (HADS-D)	_	6.07 ± 3.54
Range		*0-15*

Note. *The characteristics "severity of substance use disorder" was defined according to the DSM-V criteria checklist classification.
AUDIT: Alcohol Use Disorders Identification Test; CAST: Cannabis Abuse Screening Test; HADS: Hospital Anxiety and Depression Scale.

Social and medical variables

Age, sex, years of education, native language, living environment and employment status were collected in ad hoc interviews led by TCs clinicians. The medical history variable was recorded by physicians (e.g., liver, neurological, psychiatric histories, and HIV). The participants' current psychopathological state (e.g., anxiety and depression) was assessed using the Hospital Anxiety Depression Scale (HADS) [40].

Substance use-related variables

Ad hoc designed interviews relative to substance use were oriented towards alcohol, tobacco, cannabis, ecstasy/MDMA, cocaine, heroin, and benzodiazepines. For each substance, its use over the last twelve months and the age of onset of substance use were recorded. The severity of substance use was defined according to the DSM-V criteria checklist classification: on a total of 11 criteria, the presence of 2/3 criteria indicates a mild SUD, 4/5 a moderate SUD and 6 and more a severe SUD [41]. Polysubstance use, i.e., 2 or more substances simultaneously- except tobacco- was also recorded. Specialized questionnaires were added for alcohol use, with the French version of the Alcohol Use Disorders Identification Test (AUDIT) [42], cannabis use with the Cannabis Abuse Screening Test (CAST) [43] and tobacco dependence with the Fagerström Test for Nicotine Dependence [44].

Neuropsychological screening - BEARNI

The risk of neuropsychological impairment was assessed using the BEARNI [18]. This screening tool was specifically designed to screen risk of cognitive and motor deficits in patients with AUD (i.e., episodic memory, working memory, executive functions, visuospatial abilities and ataxia). It includes five subtests: a verbal episodic memory subtest (maximum score: 6 points), an alphabetical span subtest assessing verbal working memory (maximum score: 5 points), an alternating verbal fluency subtest assessing flexibility abilities (maximum score: 6 points), a five complex figures subtest assessing visuospatial abilities (maximum score: 5 points), and an ataxia assessing balance (maximum score: 8 points). The BEARNI yields six scores: five subscores and a total score (maximum score: 30 points).

Data analysis

First, the descriptive statistics of the variables were analyzed (i.e., means, standard deviations, and frequencies). To compare neuropsychological profiles between groups (TCs residents and HC), independent student *t* tests were performed. To do so, the participants' raw BEARNI scores were transformed into z scores based on mean and standard deviation from the HC group (i.e., mean scale scores of zero and standard deviations of one). A negative z-score represents a poor performance.

Finally, we further explored the risk factors for neuropsychological impairment by carrying out a logistic regression analysis between the risk factors variables and the BEARNI total score (i.e., if the score was above or under the moderate to severe cut-offs scores, see Table 2).

Table 2. Sample characteristics of Therapeutic Communities residents (*n* = 56)

Variables	Dichotomous selection
Social variables	
Sex	Male = 1; Female = -1
Living environment	Stable = 1; Precarious = -1
Employment status	Employed = 1; Unemployed = 0
Medical history and psychopathological state	
Neurological history	Yes = 1; No = 0
Psychiatric history	Yes = 1; No = 0
Liver disease history	Yes = 1; No = 0
HIV	Yes = 1; No = 0
HAD-A pathological score	If A score > 7*, then Yes = 1; No = 0
HAD-D pathological score	If D score > 7*, then Yes = 1; No = 0
Substance use data (in the last twelve months)	
Alcohol	Yes = 1; No = 0
Tobacco	Yes = 1; No = 0
Cannabis	Yes = 1; No = 0
Cocaine	Yes = 1; No = 0
Heroin	Yes = 1; No = 0
Benzodiazepines	Yes = 1; No = 0
Polysubstance use	Yes = 1; No = 0
Cognitive state	
BEARNI total score indicating risk of moderate to severe cognitive impairment	If $>$ 12 years of schooling and total score $\leq$ 17, then Yes = 1; No = 0

	If $\leq$ 12 years of schooling and total score $\leq$ 16, then Yes = 1; No = 0

Note. *The dichotomous selection was based on the cut-off score defined in [40]
** The dichotomous selection was based on the cut-off scores defined in [18]
HIV: Human Imununodeficiency Virus; HADS: Hospital Anxiety and Depression Scale; BEARNI: Brief Evaluation of Alcohol-Related Neuropsychological Impairment

Regarding the literature previously described, several variables have been added to the analysis: social data (i.e., sex, living environment, employment status), medical history (i.e., psychiatric, liver, neurological histories and HIV) and psychopathological state (i.e., HAD-A and HAD-D pathological scores) as well as substance use over the last twelve months (tobacco, alcohol, cannabis, benzodiazepines, cocaine, polysubstance use). The potential risk factors were included as independent variables, as well as participants status for each of these variables as dichotomous dependent variables (see Table 2 for dichotomous selection details). To determine the combination of variables that best distinguishes the impaired TCs residents from the preserved ones, a forward logistic regression has been performed on the total BEARNI score. Only the variables that were significant at $p \leq 0.10$ in a backward logistic regression were entered in the subsequent analysis to determine which variables remained independent predictors of the BEARNI total score ($p < 0.05$).

Results

TCs residents' psychosocial, medical and addictive profile at the time of TCs entry

The global characteristics of TCs residents are shown in Table 1.

The sample was characterized by a greater proportion of men, a mean age of about 41 years and 11 years of education. The living environment of 32.14% of the participants was reported as precarious, and a great proportion of the sample was unemployed before they engaged their health pathway and arrived at TCs (78.57%). The residents had various medical histories throughout their healthcare experience, most of which were of psychiatric (85.71%), neurological (67.86%), and liver nature (41.09%). The questionnaire relative to depression and anxiety questionnaire revealed an anxious symptomatology, with an anxiety mean score above the cut-off level (see Table 2). This result is supported by a high frequency of anxiety in the sample (60.71%), while depressive symptomatology was found in 26.79% of TCs residents.

Tobacco, alcohol, and cannabis were among the most used by the participants over the last twelve months, followed by benzodiazepines, cocaine, and heroin (see Table 1). Substance use onset occurred in teenage years for tobacco, alcohol, and cannabis (mean onset age of about 14-15 years old), when other substance use onset occurred later (in the participants' twenties). Polysubstance use was very frequent (83.93%) and included between 2 to 4 substances used simultaneously over the last twelve months.

Neuropsychological screening

The results of cognitive performance comparisons conducted in TCs residents and HC are set out in Table 3.

Table 3. Raw scores of BEARNI subtest performances of participants

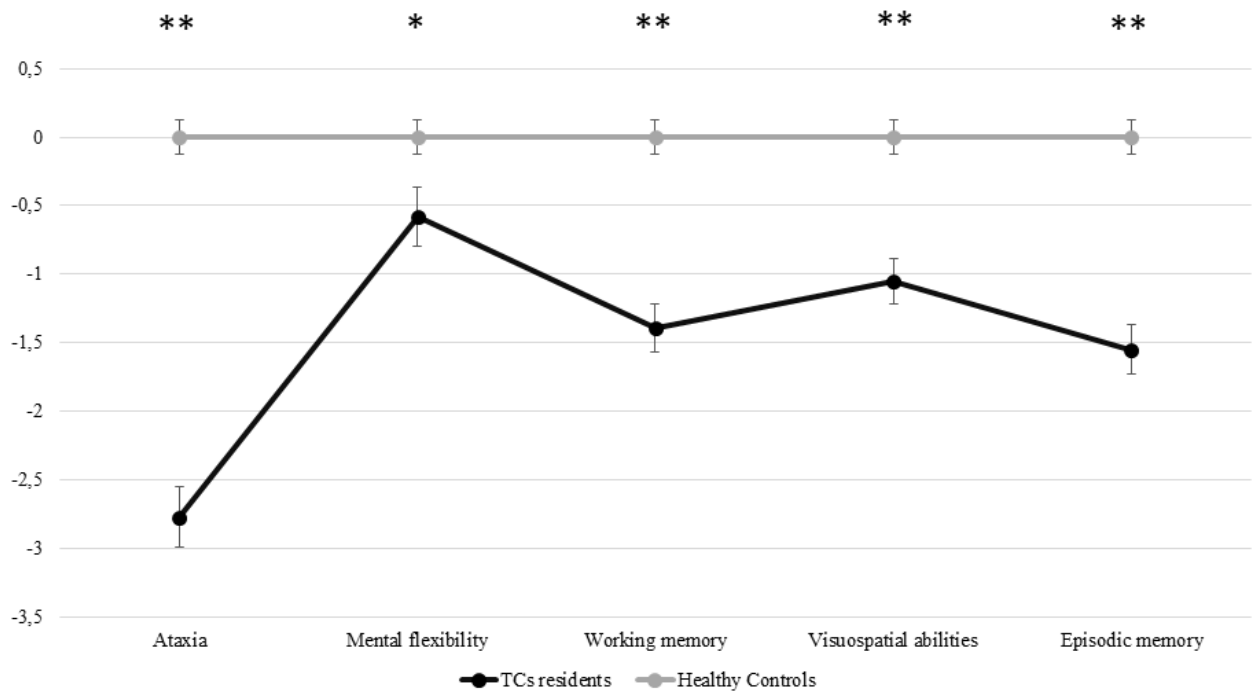
BEARNI scores	**TCs residents (*n* = 56)**	**HCs (*n* = 62)**	**Statistics**
Total score	14.47 ± 4.98	22.59 ± 1.73	$t^{(116)}$ = -12.06, p <.001*, d = -2.22,
Range	*5.5-27.5*	*19.5-26.5*	
Episodic memory *(max. score = 6)*	2.52 ± 1.38	4.09 ± 1.04	$t^{(116)}$ = -7.03, p <.001*, d = -1.29
Range	*0-5.5*	*2-6*	

Working memory *(max. score = 5)*	2.40 ± 1.03	3.47 ± 0.77	$t^{(116)}$ = -6.46, p <.001*, d = -1.19
Range	*0.5-4.5*	*2-5*	
Flexibility *(max. score = 6)*	4.41 ± 1.20	4.87 ± 0.73	$t^{(116)}$ = -2.53, p = .013*, d = -0.47
Range	*2-6*	*3-6*	
Visuospatial abilities *(max. score = 5)*	2.30 ± 1.36	3.45 ± 1.08	$t^{(116)}$ = -5.10, p <.001*, d = -0.94
Range	*0-5*	*1-5*	
Ataxia *(max. score = 8)*	2.84 ± 2.31	6.69 ± 1.41	$t^{(116)}$ = -11.06, p <.001*, d = -2.04
Range	*0-8*	*4-8*	

Note. Data are shown as mean ± standard deviation. * reports a significative result; d = Cohen's d, represents effect size (small: .20; medium: .50; large: .80)
TCs: Therapeutic Communities; HCs: Healthy Controls; BEARNI: Brief Evaluation of Alcohol-Related Neuropsychological Impairment.

The results indicate that TCs residents had a significant poorer total score compared to HCs. 87.5% of the sample had performance under the total cut-off score, with 17.86% of them being affected by a mild disorder, and 69.64% by a moderate one (see cut-offs in Table 2). These results are supported by the analysis of each of the BEARNI subscores, with lower scores compared to HCs on all the subtests (i.e., episodic memory, working memory, flexibility, visuospatial abilities, and ataxia; z-score analysis shown in Fig. 1).

Fig. 1. BEARNI subscores of Therapeutic Communities residents and Healthy Control groups.



Note. Data are shown as mean *z* scores ± standard error of mean.
** Significant difference between the TCs residents group and the HC group; $p_s < .001$.
* Significant difference between the TCs residents group and the HC group; $p < .02$
BEARNI: Brief Evaluation of Alcohol-Related Neuropsychological Impairment; TCs: therapeutic communities; HCs: healthy controls.

Predictors of the risk of neuropsychological impairment

The backward logistic regression allowed for the selection of significant variables at $p \leq 0.10$ (i.e., liver, neurological history, heroin use in the last 12 months and HAD-A pathological score). Then, a forward stepwise logistic regression analysis showed that only liver history was a significant predictor of the risk of having a moderate to severe risk of impairment on the BEARNI total score (AIC = 69.5; BIC = 73.5; McFadden $R^2 = 0.05$; Wald test = 2.96, $df = 1$, $p = .08$). The odd ratio indicates that participants having liver alterations were more than three times at risk of neuropsychological impairment ($p = .07$; Odds ratio = 3.09, 95% CI [0.85-11.15]).

Discussion/Conclusion

This was the first study conducted in French TCs with the objectives to (1) estimate the nature and severity of the risk of neuropsychological disorders and (2) identify the main risk factors. To sum up, the results first suggest that TCs residents had a globally poorer cognitive performance than HCs at the time of entry, on all the cognitive areas screened (i.e., episodic memory, flexibility, visuospatial abilities, working memory and ataxia). The majority of the TCs residents sample is at risk of

developing moderate to severe neuropsychological impairment. Second, among all the variables that could distinguish residents with preserved cognitive performance from those with a risk of moderate to severe impairment, the results pinpoint liver history as the only predictor of the risk of developing moderate to severe cognitive impairments.

The present study revealed a high level of risk of moderate to severe neuropsychological impairments in TCs resident, which was true for all the evaluated functions: executive functions, visuospatial abilities, working memory, episodic memory, and ataxia. These results are consistent with the related growing body of literature conducted in hospital contexts [45]. Ataxia was previously suggested as a severity marker of cortical atrophy [9] and is in accordance with the long-term and simultaneous exposition to psychoactive substances of TCs residents, which resonates with the low functioning of the other cognitive areas assessed. As previously depicted, all these impairment risks are fundamentally linked to the SUD treatment in general, which requires a preserved cognitive functioning. Indeed, the treatment of SUD includes a broad range of therapies, such as Motivational Enhancement Therapy, Twelve-Step Facilitation or Cognitive-behavioral therapy [15], Therapeutic Education or relapse prevention workshops [7]. In order to feel the full benefit of these therapies, the patients must implement cognitive functions such as executive functions and episodic memory. Deficits in those cognitive functions have been shown to prevent the patients from becoming aware of the negative impacts of alcohol consumption and from realizing the necessity to change [46]. This is also the case in TCs, whose particularity is to use the ability of the residents to interact in qualitative relationship with the community as a basis for care support towards recovery [47]. Even if the neuropsychological screening performed in the present study did not directly assess social cognition, all other cognitive areas that seem to be more fragile in residents at the time of entry in TCs may be involved in social functioning [22,23]. These results implications for treatment strongly suggest the necessity to consider cognitive impairment as early as possible in the residents' pathway in TCs, as this could hinder the efficacy of the treatment.

The determination of a recurrent risk of cognitive impairment (87.5%) seems to be more significant than in studies carried out in outpatient hospital setting, reporting from 30% to 80% of cognitive impairments screened [48]. This prevalence of cognitive impairment risk in TCs residents seems to be higher than in other research works, that reports around 50% of the sample having cognitive impairment [24]. This difference could be explained by methodological divergences. Studies led in SUD usually have stricter exclusion criteria, in particular as regards the presence of severe cognitive disorders or psychiatric disorders [24,48]. As in [27], we followed the opposite approach. In the current study, all variables were considered to optimally disentangle their respective influence on

the risk of developing moderate to severe impairments, and to reflect the clinical reality as much as possible. The higher proportion of cognitive disorders risk found in this work may be linked to the clinical particularities of TCs residents, who experienced long-termed, polysubstance use, and several withdrawals, that are associated with more severe neuropsychological profiles than in patients welcomed in other care settings [49]. These results support the need for TCs residents to benefit from a long-term treatment, which could facilitate potential cognitive recovery, as has already been reported in hospital settings after several months of abstinence [50]. For now, it also emphasizes the need for further analysis on variables that could be related to a higher risk of impairment.

TCs residents is a highly heterogeneous clinical population because of the singularity of the various care practices, with frequent long-term and polysubstance use, co-occurring disorders, and social differences. This study is the first one to consider all variables together to assess their respective impact on the risk of developing moderate to severe cognitive impairment. The ecological reality also highlights the scientific necessity to consider holistic profiles by unselecting residents to analyze the effect of all accurate variables that could interfere with cognitive functioning.

Surprisingly, among all the variables included in the statistical model (i.e., social data, medical history, psychopathological state, and substance use) and that were identified as risk factors of neuropsychological disorders in the literature, the only significant variable was that considering liver history. In the present case, the results are likely to differ from those achieved from other studies as they were obtained on each variable separately, and not in a same sample. Previous studies reported addictive data or polysubstance use variables as risk factors of higher cognitive impairment in addition to liver history [31], as well as psychiatric comorbidities or substance use severity on treatment outcomes [51]. It seems that liver history is the common denominator beyond the heterogeneity of profiles in our sample. The results even indicate that residents with liver history are three times more at risk of developing cognitive impairment than those who do not suffer from this affection.

It is well known that a common feature of psychoactive substances can be associated with liver injury. The prevalence of liver injury in alcohol use disorder [52], and the toxicity of other substances as opioids [53], heroin [54] and cocaine [55] have been reported. Little is known about the prevalence of liver disease in polyuser TCs residents. With 41.09% of our sample having liver history, it could be hypothesized that simultaneous substance use could fragilize the liver. This thus emphasize the need to take it into account as it may be a high-risk factor of cognitive impairment.

The issue of the link between liver disease and cognition has been frequently addressed, with studies reporting lower cognitive functioning related to liver alterations in other disorders such as non-alcoholic fatty liver disease [56]. Studies carried out in people suffering only from liver affection reported an association between liver disease and markers of white matter lesions and microbleedings [57], which is supportive of the brain-liver axis hypothesis. One piece of explanation could be that metabolic and physiopathological mechanisms such as oxidative stress or inflammatory processes are shared by the brain and the liver (this is mostly the case for hepatic and Gayet-Wernicke encephalopathies) [58]. It is possible that this axis promotes neurodegenerative processes as depicted in Alzheimer and Parkinson diseases, with liver alterations representing a high risk factor of cognitive decline [59].

Liver disease was also studied in SUD. Usually studied in severe alcohol use disorder complications such as liver encephalopathy, the deleterious effects of liver alterations on cognition have been reported, even in subacute phenotypes as classical alcohol use disorder without encephalopathy [60]. Studies focusing on other substances than alcohol are still scarce. However, at the light of the results of the present study, the potential link found in other diseases creates the opportunity to question the genesis of cognitive impairment linked with SUD. Are neuropsychological disorders in SUD originally linked to the direct effects of substances on the brain? Or are they due to a secondary effect of the substances on the liver, which is at the origin of brain alterations linked to cognitive disorders? The present study seems to indicate that liver history comes with a higher risk of cognitive impairment among other variables. Still, it cannot be interpreted as being the only responsible factor for the risk of developing cognitive impairment, since it is highlighted by odd ratio medium effect sizes (<4.25), which are known to be due to the intervention of multicomponent factors. These studies are promising, but the exhaustive and clear shared mechanisms as well as the direct effect of substances on the brain or liver remain to be further examined to better understand their cognitive impact.

Limitations

The present study has some limitations that must be acknowledged. First, even if the BEARNI serves to better qualify the risk of cognitive impairment in TCs residents, this screening tool was originally validated in AUD patients in hospital settings. Its validation was based on the AUD neuropsychological semiology [18], and its sensitivity to TCs residents' cognitive specificities remains to be clarified. This tool has multiple components and as in the case of other neuropsychological tests, some tasks require to impede several cognitive functions (such as working memory and executive functions). Moreover, it is highly possible that TCs residents could experiment social

cognition disorders, which cannot be assessed yet by the BEARNI. All these reasons justify the need for further investigations of cognitive functioning in the framework of a complete neuropsychological assessment. Moreover, results related to risk factors of cognitive disorders in TCs residents with liver history being the only significant factor are of course important need to be tempered. The variability of our sample is not optimal for the variables studied as cognitive disorders are prevalent, and a medium effect size is to consider. An interesting lead could be the impact of other variables on cognitive performance rather than that of liver history only. TCs residents have frequent co-occurring disorders, numerous socio-demographic and substance use pathways. This heterogeneity could explain the medium effect size, reflecting the impact of other variables on cognitive functioning as depicted in the literature. It is insufficient to conclude to any causality, but the results underline the need to consider this heterogeneity and adopt a holistic vision for further research avenues.

Conclusion and practical implications

TCs residents generally would be subject to a greater risk of developing cognitive impairment at their arrival, and this would be true in various areas. Neuropsychological disorders can hinder the efficacy of the treatment as it relies on preserved cognitive functioning. People with liver history are more likely to develop cognitive disorders. These results incite to consider cognitive impairment in TCs and addiction departments, with a special attention given to liver history since it could represent a red flag indicating neuropsychological disorders. These parameters are easy to identify and are required in clinical practice. This study suggests that adopting a holistic approach in scientific and clinical settings would help provide the most appropriate support for addiction recovery.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Author 1 prepared the manuscript. Authors 2, 15 and 16 reviewed and edited the manuscript. Authors 1 to 12 and 15, 16 designed the experiments. Authors 6 to 14 provided resources to conduct the research. Authors 1 to 5 gathered data and quality checked. Authors 1, 2, 15 and 16 analysed the data. All authors coordinated the project and approved the final manuscript.

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