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SHORT-TERM NEUROPSYCHOLOGICAL RECOVERY IN ALCOHOL USE DISORDER: A RETROSPECTIVE CLINICAL STUDY

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ABSTRACT

Background: Neuropsychological impairments found in recently detoxified patients with alcohol use disorder (AUD) can limit the benefit of psychosocial treatments and increase the risk of relapse. These neuropsychological deficits are reversible with abstinence. The aim of this retrospective clinical study was to investigate whether a short-term stay as inpatients in a convalescent home enables neuropsychological deficits observed in recently detoxified AUD patients to recover and even performance to return to normal.

Methods: Neuropsychological data were collected in 84 AUD patients. Five neuropsychological components were assessed before and after a three-week stay in a convalescent home offering multidisciplinary support. Baseline and follow-up performance were compared in the entire group of patients and in subgroups defined by the nature and intensity of the therapy (OCCASIONAL: occasional occupational and physical therapy; INTENSIVE: intensive occupational and physical therapy and neuropsychological training).

Results: In the entire group of patients, neuropsychological performance significantly improved between baseline and follow-up for all 5 components and even returned to a normal level for 4 of them. The ratio of patients with impaired performance was significantly lower at follow-up than baseline examination for 3 components in the INTENSIVE group only.

Conclusion: Recently detoxified AUD patients with cognitive deficits benefit from a short-term stay in an environment ensuring sobriety and healthy nutrition. Cognitive recovery may be enhanced by intensive care including neuropsychological training. Alcohol programs could be postponed in patients with cognitive deficits in order to offer psychosocial treatment when patients are cognitively able to benefit from it.

KEYWORDS: alcohol use disorder, neuropsychology, cognitive recovery, training

1 1. INTRODUCTION

2 It is well-known that alcohol use disorder (AUD), characterized by chronic and excessive
3 alcohol consumption, is associated with brain damage and cognitive deficits (Epstein, Pisani,
4 & Fawcett, 1977; Fama et al., 2019; Oscar-Berman, Shagrin, Evert, & Epstein, 1997; Parsons,
5 1977; Pitel et al., 2011). Indeed, executive functions and episodic memory abilities were
6 repeatedly reported as impaired in recently detoxified AUD patients (Le Berre, Fama, &
7 Sullivan, 2017; Oscar-Berman et al., 2014 for a review). Dysfunctions of these cognitive
8 components can alter motivation to change behavior, decision-making abilities and new
9 complex learning (Blume, Schmaling, & Marlatt, 2005; Le Berre et al., 2012), which are
10 crucial processes involved in the motivation to abandon excessive drinking behavior and to
11 engage in alcohol treatment (DiClemente, Bellino, & Neavins, 1999). Altered decision-
12 making abilities would hamper patients to modify alcohol habits in order to maintain
13 abstinence. For these reasons, it seems clinically evident that efficient cognitive abilities are
14 crucial when sobriety or reduction of alcohol consumption is considered. All together,
15 neuropsychological impairments observed early in abstinence may thus limit the benefit of
16 psychosocial treatment and increase the risk of relapse. As found in other psychopathological
17 states such as schizophrenia (Harvey, Green, Keefe, & Velligan, 2004) and depression
18 (Culpepper, Lam, & McIntyre, 2017), cognitive deficits limit the benefit of psychosocial
19 treatments and notably of cognitive behavioral therapies (CBT). In AUD patients,
20 psychoeducation, CBT or motivational interview, which are routinely proposed during the
21 first weeks of sobriety, may thus not be clinically appropriate for AUD patients with impaired
22 neuropsychological abilities (Fein, Bachman, Fisher, & Davenport, 1990; McCrady & Smith,
23 1986; Tapert, Ozyurt, Myers, & Brown, 2004).

24 It is now clear that cognitive deficits observed early after detoxification can be
25 partially or totally reversible with drinking cessation even in the absence of any stimulation.

26 Several studies indicated improvements of cognitive abilities in long-term abstinent AUD
27 patients (more than one year) and even a return to a normal level of performance (Fein,
28 Torres, Price, & Di Sclafani, 2006; Reed, Grant, & Rourke, 1992; Stavro, Pelletier, & Potvin,
29 2013). However, Munro et al. (2000) highlighted that memory deficits and certain executive
30 dysfunctions were still present after a two-year period of abstinence. Similarly, Nowakowska-
31 Domagała et al. (2017) showed that executive deficits persist in AUD patients who have been
32 abstinent for one year. Regarding medium-term abstinence (several months), some studies
33 showed that six months without alcohol consumption allow neuropsychological functions to
34 recover (Ioime et al., 2018; Loeber et al., 2010). Pitel et al. (2009) even highlighted that
35 patients abstinent for six months perform on par with controls regarding memory and
36 executive functions. On the opposite, other studies only found partial or nonsignificant
37 improvement during the first year of abstinence (Ros-Cucurull et al., 2018; Stavro et al.,
38 2013). With regard to the effects of short-term abstinence (several weeks), results are also
39 inconsistent. Some studies reported that one month of sobriety is sufficient to recover from
40 alcohol-related cognitive deficits (Kish, Hagen, Woody, & Harvey, 1980; Mann, Günther,
41 Stetter, & Ackermann, 1999) while other investigations showed that neuropsychological
42 impairments can still be observed after the first weeks of sobriety (Mulhauser, Weinstock,
43 Ruppert, & Benware, 2018; Stavro et al., 2013). Manning et al. (2008) and Petit et al. (2017)
44 both found that working memory recovers after three weeks of abstinence while executive
45 dysfunction persists.

46 The discrepancies in these results may be related to different factors modulating the
47 neuropsychological recovery. Indeed, the number of previous detoxifications could influence
48 the recovery of flexibility abilities (Loeber et al., 2010). It is also important to take account of
49 the smoking status of AUD patients as non-smoker AUD patients seem to better recover than
50 smoker patients (Durazzo, Mon, Gazdzinski, Yeh, & Meyerhoff, 2015). The age of drinking

51 cessation can also explain the heterogeneity in the findings (Munro et al., 2000; Ros-Cucurull
52 et al., 2018). A slowdown in the dynamics of cognitive recovery, which may be related to
53 decreased brain plasticity, has been described in older AUD patients. Cognitive recovery may
54 also be affected by the concurrent use of benzodiazepines (Manning et al., 2008; Petit et al.,
55 2017). Further studies including AUD patients without psychotropic drugs are thus required.
56 In addition, because of the heterogeneity in the cognitive profile of AUD patients, the use of
57 cross-sectional design comparing patients with different lengths of abstinence (e.g.
58 Nowakowska-Domagala et al., 2017) yields less reliable results than longitudinal studies that
59 investigate the same group of patients over the course of abstinence (e.g. Ioime et al., 2018).
60 Finally, several studies suggest that neuropsychological recovery can be influenced by
61 cognitive training. After three months of cognitive training, AUD patients had higher memory
62 and learning abilities than after three months of working therapy (Bell, Vissicchio, &
63 Weinstein, 2016). In the same vein, Rupp et al. (2012) showed that 12 sessions of cognitive
64 stimulation during six weeks favor cognitive improvement in certain executive functions and
65 memory components compared to conventional treatments. All together, these results are
66 encouraging since they suggest that psychosocial treatments could be postponed in AUD
67 patients with neuropsychological deficits in order to offer psychoeducation, CBT or
68 motivational interview when patients are cognitively able to benefit from them (McCrary &
69 Smith, 1986, for review).

70 The main purpose of this retrospective clinical study was thus to investigate, in recently
71 detoxified benzodiazepine-free AUD patients, whether a short-term stay as inpatients in a
72 convalescent home enables neuropsychological deficits to recover and even performance to
73 return to normal. In a more exploratory perspective, an additional objective was to examine,
74 in a clinical setting, the effect of intensive and multidisciplinary care including
75 neuropsychological training compared to occasional physical and/or occupational therapy.

76 Finally, the present study also explored the relations between recovery on the one hand and
77 demographic and clinical data on the other hand.

78

79 2. MATERIAL AND METHODS

80 2.1. *Patients*

81 For this retrospective study, data were collected for 84 AUD inpatients (71 men and 13
82 women) through clinical practice in Caen University Hospital and the convalescent home
83 Korian Côte Normande at Ifs from 2011 to 2018. The inclusion criteria were the presence of
84 the DSM IV criteria for alcohol dependence (American Psychiatric Association, 1994) or
85 DSM 5 criteria for AUD (American Psychiatric Association, 2013). Patients were included
86 when they had performed a neuropsychological assessment (in the Addiction department of
87 Caen University Hospital) both before and after a short-term stay in a convalescent home
88 (Korian Côte Normande at Ifs). Alcohol history is presented in Table 1. Because they reflect
89 the reality of the population in addiction departments in France, patients who presented
90 comorbidities were included when clinicians hypothesized that these comorbidities would not
91 hinder them to benefit from the therapies proposed in the convalescent home. Nine patients
92 presented psychiatric comorbidities (4 bipolar, 4 anxiety syndrome, and 1 major depression)
93 and 15 patients had previous neurological history including head injuries, stroke, and glioma.
94 However, patients with intelligence quotient below 70 as well as patients with suspicion of
95 neurodegenerative disorders, Korsakoff's syndrome or fetal alcohol spectrum disorder were
96 excluded. Fifty-nine patients were smokers and 10 had consumed other substances before
97 alcohol detoxification (benzodiazepines, cannabis, buprenorphine). All patients were free
98 from psychotropic medication during the follow-up period, except for those who already had
99 a stable mood regulator treatment (5 out of the 9 patients with psychiatric comorbidities).

100

101

Table 1 about here

102

103

104 2.2. Study Design

105 The overall design of the study is illustrated in Fig. 1. Patients followed a symptom-
106 triggered detoxification protocol at Caen University Hospital consisting of monitoring
107 patients and providing long-acting benzodiazepines only when symptoms of alcohol
108 withdrawal developed. Symptoms were identified with a validated assessment tool, the
109 Cushman score (Cushman, Forbes, Lemer, & Stewart, 1985). A baseline neuropsychological
110 assessment was administered to AUD inpatients at least 48 hours after the detoxification
111 program (ie no physical symptoms of alcohol withdrawal and no benzodiazepine when they
112 were assessed). The neuropsychological status was examined through five neuropsychological
113 components: episodic memory, working memory, flexibility, inhibition and processing speed.
114 When at least one neuropsychological component was impaired, patients were offered to stay
115 in the convalescent home Korian Côte Normande for three weeks during which all patients
116 remained abstinent. The first objective of this stay is to favor time-dependent physical and
117 cognitive recovery. This convalescent home also offers multidisciplinary care. Physical
118 therapy, occupational therapy, and dietary advice can systematically be offered to patients
119 whereas access to neuropsychological training is limited to the scarce availability of the only
120 neuropsychologist of the convalescent home. The neuropsychological training sessions
121 consist of exercises that stimulate cognitive functions such as inhibition, flexibility, attention,
122 and working memory. Physical therapy, occupational therapy, dietary advice and
123 neuropsychological training were offered to the patients who were free to participate or not.
124 Since the beginning of the collaboration between the addiction department and the
125 convalescent home, the nature and frequency of each type of treatment were documented for
126 each patient.

127 To meet our secondary objectives, patients were *a posteriori* subdivided in two groups
128 depending on the nature and the intensity of the therapy they could benefit from. The main

129 criterion we used to split the group was the possibility to attend neuropsychological training
130 sessions or not. When we compared patients who had benefited from neuropsychological
131 training sessions (N=54) with those who could not attend neuropsychological training (N=30),
132 we found that the first group had on the overall benefited from more occupational/physical
133 therapy sessions (15.07 ± 6.01) than the second one (6.00 ± 9.62). Thus, the two groups
134 differed not only on the nature of the treatment (neuropsychological and
135 occupational/physical therapy vs occupational/physical therapy only) but also on the
136 frequency of the training sessions. The two groups were consequently named INTENSIVE
137 (N=54) and OCCASIONAL (N=30) to emphasize that given our clinical retrospective study
138 design, the present study cannot disentangle the effect of the nature versus frequency of the
139 sessions. After a short-term stay, all the patients underwent a follow-up neuropsychological
140 assessment at Caen University Hospital.

141 Figure 1 about here

142

143 2.3. Neuropsychological Assessment

144 Because data were collected retrospectively through clinical practice, neuropsychological
145 examinations sometimes included different tests classically used to assess the same cognitive
146 component. For the same reason, the sample size can vary depending on the cognitive task
147 (Figure 3).

- 148 • *Baseline examination*

149 *Episodic Memory.* A French version of the Free and Cued Selective Reminding Test (FCSRT,
150 Grober & Buschke, 1987; Van der Linden et al., 2004) or a French version of the California
151 Verbal Learning Test (CVLT, Delis, Kramer, Kaplan, & Ober, 1987; Nolin, 1999) were used.

152 For the FCSRT, performance on the 3 free recalls of learning trials was used. For the CVLT,
153 performance on the 5 free recalls of learning trials was used.

154 *Executive Functions.* Inhibition was assessed by means of the Stroop test (Stroop, 1935). The
155 time (in seconds) needed to complete the interference condition (Word-Color condition)
156 minus the time needed for the denomination condition (Color condition) was calculated.
157 Flexibility was assessed by means of the Modified Card Sorting Test (MCST, Cianchetti,
158 Corona, Foscol, Scalas, & Sannio-Fancello, 2005). The number of perseverative errors was
159 recorded.

160 *Working Memory.* Verbal working memory was assessed by means of the digit span task
161 (forward and backward, WAIS-III; Wechsler, 1997). The final score corresponded to the
162 number of correctly reported sequences. The standardized score was used.

163 *Processing speed.* Time needed to complete the denomination task (Color condition) of the
164 Stroop test (Stroop, 1935) was recorded.

165 • *Follow-Up examination*

166 Episodic memory was assessed using a parallel version of the FCSRT (Van der Linden et al.,
167 2004) to avoid a potential test-retest effect, which is particularly problematic for memory
168 assessment. The other functions were assessed using the same tasks as those administered
169 during the baseline session since no parallel forms are available for these tests, and executive
170 tasks are less affected by test-retest effect (Bachoud-Levi et al., 2001).

171

172 *2.4. Statistical analyses*

173 All neuropsychological measures were first transformed into z-scores which were
174 obtained using the mean and standard deviation of the standardized norms for each

175 neuropsychological test and each patient adjusted for age, gender, and level of education
176 when available. Regarding episodic memory, an average of the z-score for the free recall trials
177 was computed for each patient. Thus all cognitive variables were on the same scale with 0 as
178 the mean and 1 as the standard deviation of the reference population. When necessary, the
179 direction of the z-score was reversed so that all the z-scores had the same direction: the higher
180 the z-score, the better the performance.

181 Given that the sample size varied depending on the cognitive components studied and the
182 fact that some data were not normally distributed (according to Shapiro Wilk tests), we chose
183 to conduct non-parametric tests for all analyses.

184 First, in order to determine whether a short-term stay as inpatients in a convalescent home
185 enables neuropsychological recovery, we compared cognitive performance between baseline
186 and follow-up examinations by means of Wilcoxon's tests in the entire group of patients. We
187 also investigated whether the cognitive changes between baseline and follow-up were
188 clinically meaningful. To this end, both at baseline and follow-up examinations and for each
189 patient, the neuropsychological performance was classified as impaired or preserved
190 according to a binary z-score approach. The individual performance was considered as
191 impaired when a z-score was strictly below -1.65 standard deviations from the mean. The
192 proportion of patients with preserved and impaired performance was then compared between
193 baseline and follow-up using Yates corrected Chi-square tests.

194 Second, we explored whether an intensive and multidisciplinary therapy including a
195 neuropsychological training would result in better recovery than occasional physical and/or
196 occupational therapy. To this end, we first compared the INTENSIVE and OCCASIONAL
197 groups on demographic and clinical variables, as well as on the neuropsychological
198 performance both at baseline and follow-up using Mann-Whitney's tests or Yates corrected
199 Chi-square tests. We then used Wilcoxon's tests to examine neuropsychological changes

200 between baseline and follow-up in each group, and Yates corrected Chi-square tests to
201 compare the proportion of patients with preserved and impaired performance between
202 baseline and follow-up examinations in each group.

203 Last, we gauged the cognitive recovery by computing a ratio (follow-up performance -
204 baseline performance divided by the baseline performance for each patient). Spearman's
205 correlations were conducted to examine the relationships between this score of cognitive
206 recovery on the one hand and the number of days in the convalescent home, the number of
207 therapy sessions, and demographic as well as disease-related variables on the other hand.

208 We performed statistical analyses with the complete sample of patients as well as 1)
209 without patients who presented neurological comorbidities, 2) without patients who presented
210 psychiatric comorbidities, and 3) without these two samples.

211

212 3. RESULTS

213 *3.1. Comparison between neuropsychological performance at Baseline and Follow-up in* 214 *the entire group*

215 In the entire group of patients, flexibility, inhibition, and processing speed were
216 impaired (z-scores < -1.65) at baseline, whereas episodic memory and working memory
217 components were relatively preserved (z-scores > -1.65). Wilcoxon's comparisons (Fig. 2.)
218 revealed significant differences between baseline and follow-up examinations: cognitive
219 performance was better at follow-up than baseline for all components (episodic memory [$T =$
220 394, $p < 0.001$]; working memory [$T = 172$, $p < 0.001$]; flexibility [$T = 120$, $p < 0.001$];
221 inhibition [$T = 84$, $p < 0.001$]; and speed processing [$T = 96$, $p < 0.001$]). These results were
222 unchanged when patients with comorbidities were removed from the sample. Episodic
223 memory and working memory were still preserved at follow-up. Inhibition and processing
224 speed abilities were also preserved on this second assessment (z-scores > -1.65). Yet, the

225 flexibility component remained impaired ($z\text{-score} < -1.65$), whereas when analyses were
226 performed without patients who presented comorbidities, flexibility performance always
227 returned to a normal level.

228 Figure 2 about here

229 Chi-square tests showed that the proportion of patients with preserved or impaired
230 performance in the entire group was significantly different between baseline and follow-up
231 assessments for episodic memory ($X^2 = 9.31, p < 0.01$), working memory ($X^2 = 8.94, p <$
232 0.01), flexibility ($X^2 = 14.94, p < 0.001$), and inhibition ($X^2 = 5.11, p = 0.02$), indicating that
233 there were fewer patients with impaired performance at follow-up than baseline (Figure 3).

234

235 *3.2. Comparisons between demographic and clinical variables in the INTENSIVE and*
236 *OCCASIONAL groups*

237 The statistical analyses did not reveal any significant difference in terms of
238 demographic, clinical, or disease-related variables between the patients of the INTENSIVE
239 and OCCASIONAL groups at baseline (Table 1). However, patients in the INTENSIVE
240 group benefited from more therapy sessions than patients in the OCCASIONAL group ($U =$
241 $341, p < 0.001$). More precisely, the number of physical therapy sessions was significantly
242 higher in the INTENSIVE group than in the OCCASIONAL group ($U = 357, p < 0.001$) as
243 well as for the number of occupational therapy sessions ($U = 349, p < 0.001$). Only patients in
244 the INTENSIVE group benefited from neuropsychological training sessions ($5,50 \pm 3,23$).

245

246 *3.3. Comparisons between neuropsychological performance in the INTENSIVE and*
247 *OCCASIONAL groups at Baseline*

248 Analyses did not reveal any significant difference between the INTENSIVE and
249 OCCASIONAL groups at baseline, except for the flexibility component (Figure 4): patients in

250 the INTENSIVE group had lower flexibility performance than patients in the OCCASIONAL
251 group ($U = 129.5$, $p = 0.04$). When comorbid patients were excluded, the difference was no
252 more significant. However, regarding the proportion of patients with impaired performance,
253 no between-group difference was found at baseline (Figure 3).

254 Figure 3 about here

255

256 3.4. Comparisons between neuropsychological performance at Baseline and Follow-up in 257 each group

258 In the INTENSIVE group, analyses revealed a significant improvement between
259 baseline and follow-up performance for all five components (episodic memory [$T = 149.5$, $p <$
260 0.001]; working memory [$T = 40.5$, $p < 0.001$]; flexibility [$T = 43$, $p < 0.001$]; inhibition [$T =$
261 46 , $p < 0.001$]; and processing speed [$T = 50.5$, $p < 0.001$]).

262 In the OCCASIONAL group, analyses revealed a significant improvement between
263 baseline and follow-up performance for episodic memory ($T = 58$, $p < 0.01$); inhibition ($T = 6$,
264 $p < 0.01$) and processing speed ($T = 10$, $p = 0.01$) only (Figure 4).

265 Regarding the comparisons of the proportion of patients with impaired and preserved
266 performance between baseline and follow-up, Chi-square tests showed more patients with
267 preserved performance at follow-up than at baseline only in the INTENSIVE group (Fig. 3)
268 for episodic memory ($X^2 = 5.52$, $p = 0.02$), working memory ($X^2 = 6.45$, $p = 0.01$), and
269 flexibility ($X^2 = 17.08$, $p < 0.001$).

270 There were no major changes when patients with comorbidities were removed from
271 the samples, as for the two next parts.

272 Figure 4 about here

273 *3.5. Comparisons between neuropsychological performance in the INTENSIVE and*
274 *OCCASIONAL groups at Follow-up*

275 No differences were found between the two groups regarding neuropsychological
276 performance at follow-up (Figure 4).

277

278 *3.6. Relationships between neuropsychological changes and clinical variables*

279 There was no significant relationship between cognitive changes on the one hand and
280 demographic, clinical, or disease-related variables (all p values > 0.05).

281

282 4. DISCUSSION

283 The present investigation aimed at determining whether a short-term stay (three
284 weeks) as inpatients in a convalescent home enables neuropsychological deficits observed
285 early in abstinence to recover and even performance to return to normal. In accordance with
286 previous studies (Oscar-Berman et al., 2014; Pitel et al., 2007), baseline results collected early
287 in abstinence indicated that AUD patients exhibited a slowdown in the processing speed, low
288 memory performance and executive dysfunction including altered flexibility and inhibition
289 abilities. Comparisons between baseline and follow-up examinations confirm that cognitive
290 performance significantly improves during the first weeks of sobriety (Kish et al., 1980;
291 Mann et al., 1999). Contrary to Petit et al. (2017) who described persistent executive
292 impairments after 3 weeks of abstinence, we found recovery of inhibition abilities within the
293 same time period.

294 For four cognitive components (episodic memory, working memory, inhibition, and
295 processing speed), performance returned to a normal level (z -scores > -1.65) at follow-up.
296 Improvement of flexibility was not sufficient to observe a normalization of the performance at

297 follow-up (zscore<-1.65) because baseline results were very severely impaired. Regarding the
298 proportion of patients with preserved and impaired performance, there were fewer patients
299 with impaired episodic and working memory as well as executive performance at follow-up
300 than at baseline. The absence of clinically meaningful changes regarding the ratio of patients
301 with impaired and preserved processing speed performance may be related to the low
302 proportion of impaired patients at baseline. Both when considered the average performance of
303 the group or the individual results, our data suggest that neuropsychological abilities can
304 return to normal not only after several years (Rosenbloom, Pfefferbaum, & Sullivan, 2004;
305 Rourke & Grant, 1999) or several months of abstinence (Pitel et al., 2009) but also after
306 several weeks without alcohol consumption.

307 Psychosocial treatments are usually proposed early in abstinence, right at the time
308 when alcohol-related neuropsychological deficits are the most severe. Thus, the timing of
309 most psychosocial treatments may not be appropriate for patients with cognitive impairments
310 (McCrary & Smith, 1986). Our results suggest that the neuropsychological recovery observed
311 after just a few weeks of sobriety could enable AUD patients to be cognitively able to
312 effectively benefit from motivational interview, psychoeducation and CBT. After short-term
313 abstinence, efficient inhibition abilities would make patients more able to control alcohol
314 craving but the use of novel adaptative strategies in risky situations (Giancola & Moss, 1998)
315 may still be difficult because of residual flexibility deficits. Such persistent flexibility
316 impairments could reflect premorbid cognitive alterations that would make patients
317 particularly vulnerable to develop AUD (Mulhauser et al., 2018). Interestingly, when patients
318 with psychiatric and/or neurological comorbidities were excluded from the analyses,
319 flexibility performance returned to a normal level at follow-up. This result suggests that
320 cognitive impairments related to psychiatric and/or neurological diseases may slow down the

321 course of recovery (Bourne et al., 2013; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari,
322 & Lönnqvist, 2008; Whiting, Deane, Simpson, McLeod, & Ciarrochi, 2017).

323 While drinking cessation is the main factor that influences cognitive recovery, other
324 variables have been suggested to modulate its dynamics and extent. The present study does
325 not confirm the role of age (Munro et al., 2000; Ros-Cucurull et al., 2018) and smoking status
326 (Durazzo et al., 2015), and does not indicate a relationship between alcohol-related variables
327 and cognitive recovery. Diet may also support neuropsychological recovery through regular
328 and healthy meals provided in the convalescent home. Biological comorbidities including
329 malnutrition (Ritz et al., 2016) and altered thiamine metabolism (Coulbault et al., 2019) are
330 associated with neuropsychological impairments. As all patients included in the present study
331 were well-fed and benefited from nutritional monitoring during convalescence, the effect of
332 this variable could not be examined.

333 Another factor has been described to influence cognitive recovery. The concept of
334 experience-dependent recovery suggests that neuropsychological skills may indeed be
335 enhanced by the practice of cognitive tasks (Goldman, 1990). In an exploratory perspective,
336 the present study enabled us to investigate the effect of intensive and multidisciplinary care on
337 cognitive recovery. Between baseline and follow-up, the INTENSIVE group significantly
338 improved all five cognitive components, whereas the OCCASIONAL group only improved
339 episodic memory, inhibition, and processing speed performance. For flexibility, the difference
340 in the recovery of the two groups may be related to a larger margin of improvement observed
341 in the INTENSIVE group. Indeed, at baseline, the INTENSIVE group performed lower than
342 the OCCASIONAL group only on the flexibility task. However, this difference may be driven
343 by the presence of patients with psychiatric and neurological comorbidities as there was no
344 more significant difference at baseline when these patients were excluded from the analyses.
345 Our results also show that in the OCCASIONAL group, the proportion of patients with

346 preserved performance did not increase from baseline to follow-up. On the opposite, in the
347 INTENSIVE group, there were significantly more patients with preserved episodic memory,
348 working memory and flexibility performance at follow-up than at baseline. To sum up, even a
349 short-term mild intensity program based on occasional physical and occupational therapy
350 allows cognitive improvement during the first weeks of sobriety (Kish et al., 1980; Mann et
351 al., 1999). But a more intensive program including cognitive training seems to favor an
352 overall neuropsychological recovery and even a normalization of some cognitive components.
353 The present results are in agreement with those of Bell et al. (2016) and Rupp et al. (2012),
354 who showed that cognitive training programs (respectively three months and six weeks) allow
355 a better cognitive recovery than usual treatment.

356 It is worthwhile keeping in mind that the present investigation is a retrospective
357 clinical study, which does not permit to determine whether cognitive recovery is modulated
358 by the nature and/or the intensity of the program. Another limitation of this study relates to
359 the tasks used for the cognitive assessment. Performance was analyzed with
360 neuropsychological tasks classically used in routine practice. Other experimental tasks, not
361 frequently used in clinical settings, would be more sensitive to alcohol effects (Stephan et al.,
362 2017). It would thus be interesting to complete the neuropsychological assessment using
363 decision-making tasks, social cognition tasks, and more ecological tests, which would
364 probably better reflect daily life difficulties. Ideally, the use of parallel versions of the tasks,
365 when available, should also be used, not only for memory assessment, to avoid test-retest
366 effects. Moreover, given the retrospective nature of this research, the experimental design
367 (exact modalities of treatment, randomization of the different treatment options and use of
368 blind experimenters) is not as well controlled as it would be with a randomized controlled
369 trial (RCT). Further RCT are thus required to set up solid programs favoring cognitive
370 recovery and specifying whether the nature or intensity of the care matters. For a better

371 differentiation between time-dependent or treatment-dependent recovery, future studies need
372 to include non-treated comparison groups. In a more sophisticated prospective study with
373 three experimental groups, a passive control group with no treatment could be proposed to
374 measure spontaneous recovery only related to sobriety. The clinical setting in which this study
375 was conducted offering systematically occasional physical and occupational therapy, the
376 OCCASIONAL group was considered as an active control group. From a clinical perspective,
377 psychosocial treatments involving efficient cognitive abilities should be postponed in order to
378 propose programs including physical, cognitive and nutritional support that seem to favor
379 cognitive recovery of AUD patients with neuropsychological deficits. While the present
380 study was conducted in AUD inpatients, day center programs could be a relevant alternative
381 so that patients can face their daily life without alcohol. Finally, it would also be interesting to
382 examine whether the recovery observed after short-term sobriety allows AUD patients to
383 engage more actively and efficiently in psychosocial treatment ultimately decreasing the rate
384 of relapse.

385 To conclude, early detoxified AUD patients who are cognitively impaired could be
386 transferred to an environment in which they would be well-fed, alcohol would be prohibited,
387 and a multidisciplinary treatment would be offered. The cognitive improvement observed
388 during a short-term stay in such environment would enable patients to effectively benefit from
389 psychosocial programs to eventually reduce alcohol relapse.

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399

400 CONFLICTS OF INTEREST

401 The authors report no conflicts of interest.

402

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411 **Table 1.** Demographic, clinical and disease-related characteristics of the INTENSIVE and
 412 OCCASIONAL groups

Variables	ENTIRE GROUP (N=84) (M ± SD or N)	INTENSIVE GROUP (N=54) (M ± SD or N)	OCCASIONAL GROUP (N=30) (M ± SD or N)
<u>Demographic variables</u>			
Men/Women ratio	71/13	46/8	25/5
Age (years)	53,38 ± 8,57	53,04 ± 8,72	54,00 ± 8,40
Education (years)	11,31 ± 2,10	11,50 ± 2,11	10,97 ± 2,08
<u>Clinical variables</u>			
Number of days in the convalescent home	23,29 ± 7,21	22,61 ± 6,68	24,50 ± 8,05
Number of days between assessments	33,17 ± 11,90	33,50 ± 12,38	32,57 ± 11,17
Overall number of therapy sessions	11,83 ± 8,63	15,07 ± 6,01	6,00 ± 9,62 ***
Number of neuropsychological training sessions	3,23 ± 2,97	5,02 ± 2,16	--
Number of physical therapy sessions	7,54 ± 5,93	9,57 ± 4,84	3,87 ± 6,02 ***
Number of occupational therapy sessions	4,30 ± 3,78	5,50 ± 3,23	2,13 ± 3,79 ***
<u>Disease-related factors</u>			
Daily alcohol consumption (units ^a)	17,76 ± 10,35 (5MD)	18,02 ± 11,05 (1MD)	17,23 ± 8,92 (4MD)
AUD duration (years)	21,73 ± 11,66 (9MD)	21,85 ± 11,18 (6MD)	21,52 ± 12,68 (3MD)
Smokers	59 (2MD)	37 (1MD)	22 (1MD)
Polysubstance users	10 (1MD)	6 (1MD)	4
Psychiatric comorbidity	9 (1MD)	7 (1MD)	2
Neurological history	15 (1MD)	12 (1MD)	3

413 *N: sample size; M: mean; SD: standard deviation; MD: missing data*

414 ^a: an alcohol unit = 10g of pure ethanol

415 ****p* < 0.001, Mann-Whitney's tests used to compare demographic and clinical characteristics between the
 416 INTENSIVE and OCCASIONAL groups

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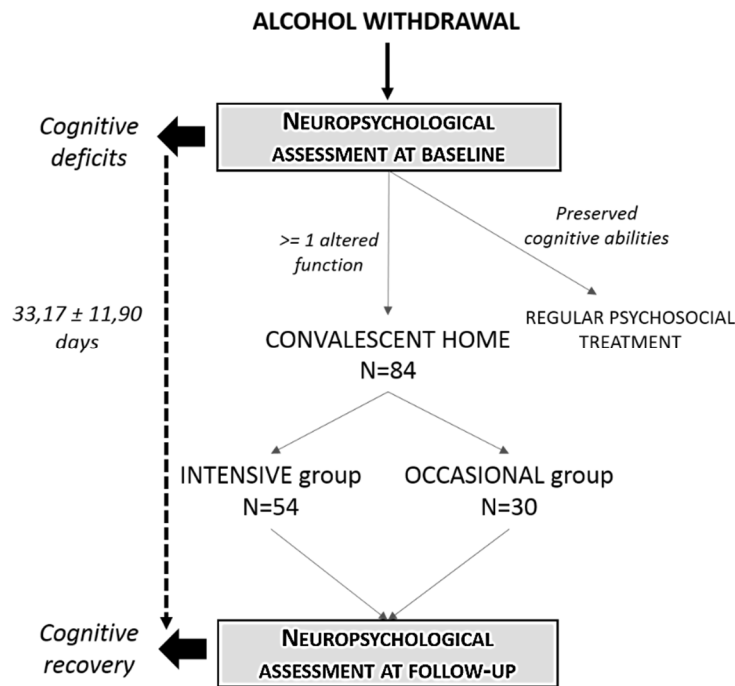
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426 **Figure 1.** Study design.

427 After alcohol withdrawal, AUD patients performed a first neuropsychological assessment.

428 When they had preserved cognitive abilities, patients attended the regular psychosocial

429 treatment, whereas when at least one neuropsychological component was impaired, they were

430 offered to stay in a convalescent home. The entire group of patients was *a posteriori*

431 subdivided in two groups (INTENSIVE versus OCCASIONAL) depending on the therapy

432 they could benefit from. One month after the first neuropsychological assessment, patients

433 underwent a follow-up assessment. In order to study the cognitive recovery, we compared

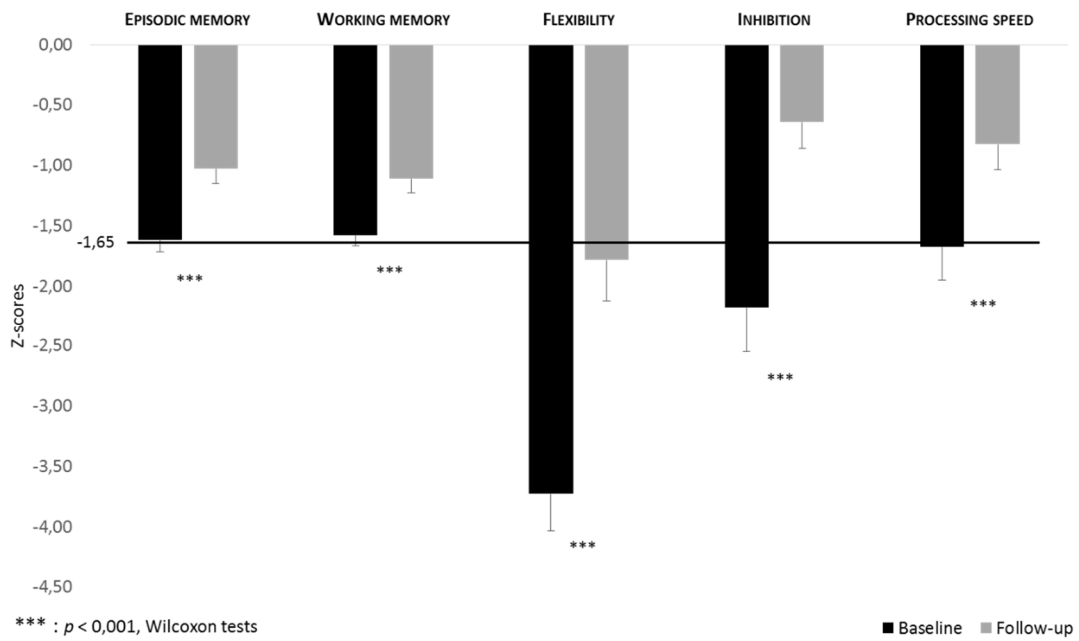
434 baseline and follow-up neuropsychological assessments in the entire group and in each group

435 separately.

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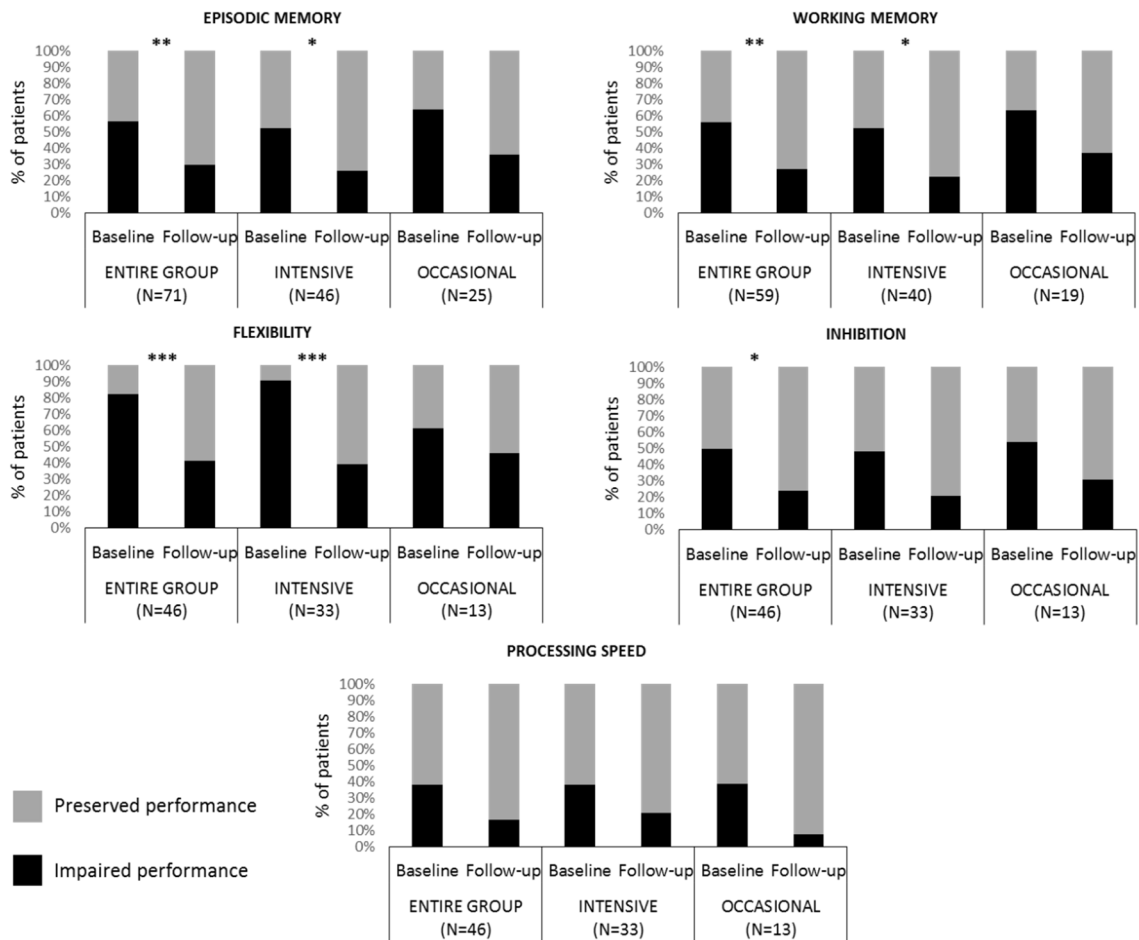
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442 **Figure 2.** Neuropsychological performance at Baseline and Follow-up.

443 ***: significant difference between baseline and follow-up performance, with a p-value
 444 strictly below 0.001 at Wilcoxon test. The black line represents the threshold for considering
 445 performance as impaired ($z\text{-score} < -1.65$) or preserved ($z\text{-score} > -1.65$).

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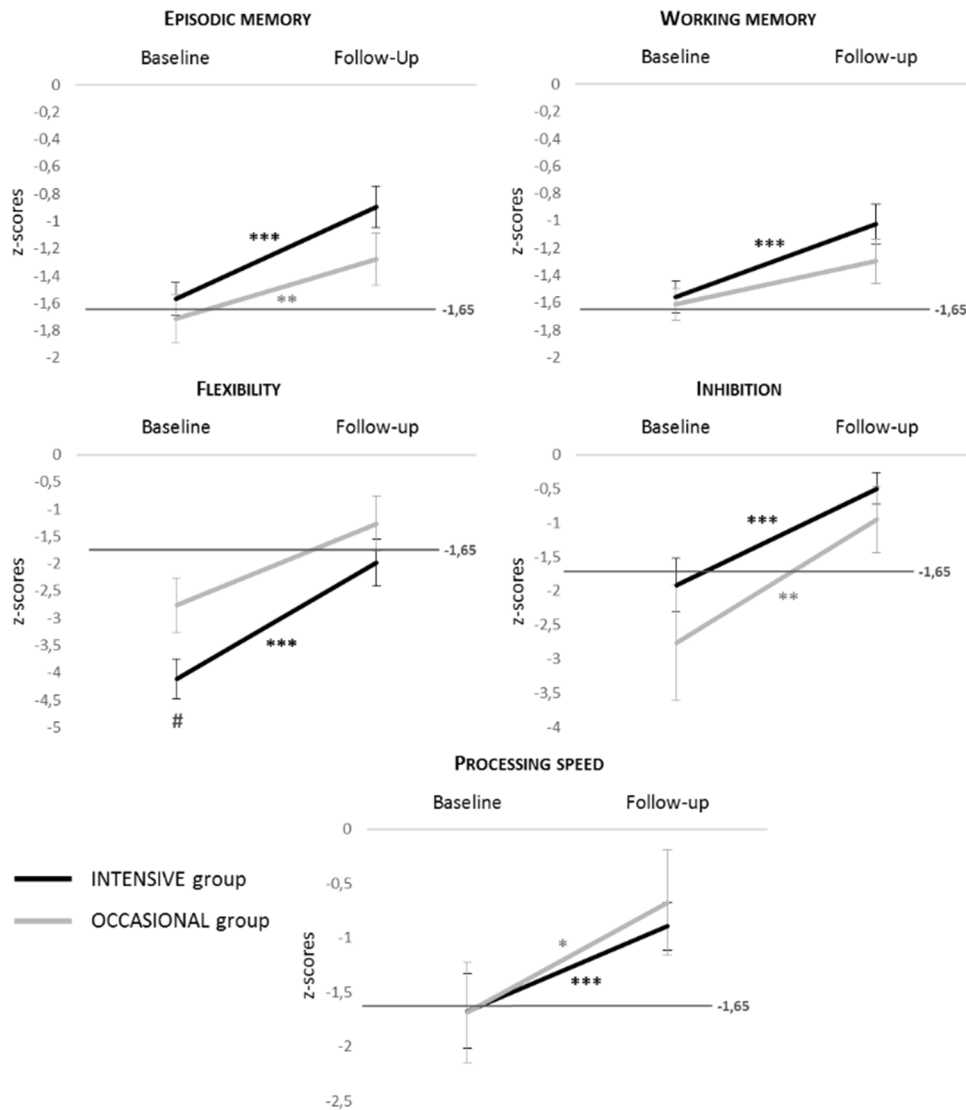
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450 **Figure 3.** Ratio of patients with preserved and impaired neuropsychological performance at
 451 Baseline and Follow-up in the ENTIRE group, as well as in the INTENSIVE and
 452 OCCASIONAL groups.

453 The performance of each patient was classified as impaired or preserved according to a binary
 454 z-score approach (Cut-off z-score: -1.65). *, **, *** represent significant differences in the
 455 proportion of patients with impaired and preserved performance between baseline and follow-
 456 up, with p-values respectively below 0.05, 0.01, and 0.001 at Chi-square tests. The proportion
 457 of patients with impaired performance differed significantly between the two groups neither at
 458 baseline nor at follow-up examinations.

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462 **Figure 4.** Neuropsychological performance at Baseline and Follow-up in the INTENSIVE
 463 and OCCASIONAL groups.

464 Means and standard errors. # represents a significant difference between the performance of
 465 the two groups at baseline, with a $p < 0.05$ at the Mann-Whitney test.

466 *, **, *** represent significant differences between baseline and follow-up performance
 467 within each group, with p-values respectively below 0.05, 0.01, and 0.001 at Wilcoxon tests.

468 The dark gray lines represent the threshold for considering performance as impaired (z-
 469 score < -1.65) or preserved (z-score > -1.65).

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