



HAL
open science

Early Identification of Alcohol Use Disorder Patients at Risk of Developing Korsakoff's Syndrome

Ludivine Ritz, Alice Lanièpce, Nicolas Cabe, Coralie Lannuzel, Céline Boudehent, Laurent Urso, Shailendra Segobin, François Vabret, Hélène Beaunieux, Anne-lise Pitel

► To cite this version:

Ludivine Ritz, Alice Lanièpce, Nicolas Cabe, Coralie Lannuzel, Céline Boudehent, et al.. Early Identification of Alcohol Use Disorder Patients at Risk of Developing Korsakoff's Syndrome. *Alcoholism: Clinical and Experimental Research*, 2021, 45 (3), pp.587-595. 10.1111/acer.14548 . hal-03118248

HAL Id: hal-03118248

<https://normandie-univ.hal.science/hal-03118248>

Submitted on 22 Jan 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Early identification of Alcohol Use Disorder patients at risk of developing Korsakoff's**
2 **syndrome**

3 Ludivine Ritz^{1,2}; Alice Laniepce²; Nicolas Cabé^{2,3}; Coralie Lannuzel^{2,3}; Céline
4 Boudehent^{2,3}; Laurent Urso⁴; Shailendra Segobin²; François Vabret^{2,3}; Hélène Beaunieux^{1,2}
5 and Anne-Lise Pitel²

6
7 ¹Normandie Univ, UNICAEN, Laboratoire de Psychologie Caen Normandie (LPCN, EA
8 4649), Pôle Santé, Maladies, Handicaps – MRSH (USR 3486, CNRS-UNICAEN), 14000
9 Caen, France

10 ²Normandie Univ, UNICAEN, PSL Research University, EPHE, INSERM, U1077, CHU de
11 Caen, Cyceron, Neuropsychologie et Imagerie de la Mémoire Humaine, 14000 Caen, France

12 ³Service d'Addictologie, Centre Hospitalier Universitaire de Caen, 14000 Caen, France

13 ⁴Service d'Addictologie, Centre Hospitalier Roubaix, 59056 Roubaix, France

14
15
16
17
18
19 Correspondence to: Ludivine Ritz, UFR de Psychologie, Bâtiment L, Esplanade de la Paix,
20 14032 Caen Cedex 5 ; ludivine.ritz@unicaen.fr

21
22 Number of words in the abstract: 215

23 Number of words in the text: 4499

24 Number of tables: 3

25 Number of figures: 3

26

27 **Abstract**

28 **Background:** The aim of the present study was to determine whether the Brief Evaluation of
29 Alcohol-Related Neuropsychological Impairments (BEARNI), a screening tool developed to
30 identify neuropsychological deficits in Alcohol Use Disorder (AUD) patients, can also be used
31 as a relevant tool for the early identification of AUD patients at risk of developing Korsakoff's
32 syndrome (KS).

33 **Methods:** Eighteen KS patients, 47 AUD patients and 27 healthy controls underwent BEARNI
34 (including five subtests targeting episodic memory, working memory, executive function,
35 visuospatial abilities and ataxia) and a comprehensive neuropsychological examination.

36 **Results:** Performance of AUD and KS patients on BEARNI subtests is in accordance with the
37 results on the standardized neuropsychological assessment. On BEARNI, ataxia and working
38 memory deficits observed in AUD were as severe as those exhibited by KS patients, whereas
39 for visuospatial abilities, a graded effect of performance was found. On the opposite, the
40 subtests involving long-term memory abilities (episodic memory and fluency) were impaired
41 in KS patients only. AUD patients with a score lower than 1.5 points (/6) on the episodic
42 memory subtest of BEARNI could be considered at risk of developing KS and exhibited the
43 lowest episodic memory performance on the neuropsychological battery.

44 **Conclusions:** These findings suggest that BEARNI is a relevant tool to detect severe memory
45 impairments, thus making early identification of AUD patients at high risk of developing KS
46 possible.

47

48 **Key words:** BEARNI, alcohol use disorder, Korsakoff's syndrome, neuropsychological
49 assessment

50

51

52 **1. Introduction**

53 Alcohol-related neuropsychological impairments have been widely described in the
54 literature. Executive functions, working memory, episodic memory, visuospatial and motor
55 abilities are, among others, indeed frequently affected by chronic and excessive alcohol
56 consumption (Maillard et al., 2020; Oscar-Berman et al., 2014, for a review). The
57 neuropsychological assessment of patients with Alcohol Use Disorder (AUD) is crucial early
58 after detoxification. In effect, efficient cognitive abilities are required to fully benefit from
59 cognitive-behavioral therapies and/or to be able to reduce alcohol drinking or to remain
60 abstinent (Bates et al., 2013, for a review).

61 Since few Addiction departments have the financial resources and qualified clinical staff
62 required to conduct an extensive neuropsychological examination, a rapid screening is essential.
63 The Brief Evaluation of Alcohol-Related Neuropsychological Impairments (BEARNI; Ritz et
64 al., 2015) is a brief screening tool especially designed to rapidly assess (in 15-20 minutes)
65 neuropsychological impairments in AUD. It is easy to administer and score and accessible to
66 non-psychologists. The aim of this screening tool is to identify AUD patients with mild or
67 moderate-to-severe neuropsychological impairments, who should be referred to a psychologist
68 for a comprehensive neuropsychological evaluation and treatment adjustments based on their
69 neuropsychological profile. Studies conducted in AUD patients without neurological
70 complications showed that BEARNI has excellent sensitivity and specificity to detect moderate-
71 to-severe neuropsychological impairments (Pelletier et al., 2018; Ritz et al., 2015) compared
72 with other brief screening tools, such as the Mini Mental State Examination (Ritz et al., 2015),
73 Mattis Dementia Rating Scale (Ritz et al., 2015) and MOCA (Pelletier et al., 2018; Wester et
74 al., 2013). A recent study compared the psychometric properties of the BEARNI and MOCA,
75 a brief screening tool already used in AUD patients (Alarcon et al., 2015; Copersino et al., 2012,
76 2009; Pelletier et al., 2018; Wester et al., 2013) but initially designed to detect cognitive decline

77 associated with Alzheimer disease or other types of dementia. The BEARNI was found to be
78 more relevant than the MOCA to identify AUD patients with moderate-to-severe impairments.
79 Patients with mild deficits and those with moderate-to-severe impairments did not differ from
80 each other on the MOCA (Pelletier et al., 2018). Result on BEARNI were also found to be
81 reliable predictors of performance on an extensive neuropsychological battery assessing
82 episodic memory, working memory, executive functions, visuospatial abilities and ataxia (Ritz
83 et al., 2015).

84 Beyond the prediction of neuropsychological performance on a more extensive
85 neuropsychological examination in AUD patients without any ostensible neurological
86 complications, BEARNI could be used to identify AUD patients at risk of Korsakoff's
87 syndrome (KS). KS is a severe neurological complication resulting from thiamine deficiency
88 and is most frequently observed in AUD patients. KS is mainly characterized by persistent
89 amnesia (Kopelman, 1995; Kopelman et al., 2009) but is also associated with executive and
90 working memory deficits, ataxia, false-recognitions, fabrications and anosognosia (Arts et al.,
91 2017; Brion et al., 2014, for a review). False-recognitions and fabrications are mainly observed
92 early after the acute episode of Wernicke's encephalopathy (WE) leading to KS or early after
93 the diagnosis, and cannot therefore be used to differentiate AUD from KS. The direct
94 comparison of AUD and KS patients revealed that the two groups share similar profiles of
95 working memory and executive deficits, while they differ regarding the severity of episodic
96 memory impairments (Pitel et al., 2008). In agreement, brain alterations are more severe in KS
97 than in AUD within the Papez circuit only (Pitel et al., 2012; Segobin et al., 2015, 2019).

98 In addition to highlighting cognitive deficits or brain alterations specifically observed in KS
99 compared with AUD, the comparison of AUD and KS makes it possible to identify AUD
100 patients at risk of developing KS. In effect, before the development of this severe and
101 debilitating disease, some AUD patients present episodic memory impairments, anterior

102 thalamic shrinkage and altered white matter integrity in the fornix and cingulum similar to those
103 observed in KS (Pitel et al., 2012; Segobin et al., 2015, 2019). It is clinically essential to detect
104 these patients at risk of KS early in order to offer them special care before the development of
105 KS. Evaluation of the severity of episodic memory disorders is crucial for the diagnosis of KS
106 and the identification of AUD patients potentially at risk of KS (Pitel et al., 2008). Moreover,
107 there are only a few clinics or shelter homes that host and appropriately take care of KS patients,
108 further reinforcing the need for a correct clinical diagnosis at the earliest. However, such
109 identification remains difficult since it requires either an extensive neuropsychological
110 evaluation or a specific MRI examination that are costly and not commonly conducted in AUD
111 patients. Only one study examined the psychometric properties of a screening tool, the MOCA,
112 for discrimination between AUD and KS patients, in comparison with an ecological battery
113 only assessing episodic memory (Rivermead Behavioral Memory Test (RBMT-3); (Wester et
114 al., 2013). Results indicated that AUD and KS patients differed from healthy controls on the
115 MOCA total score only, and no optimal cut-off score could be determined to discriminate the
116 two patient groups. BEARNI has proven to be more relevant than MOCA to discriminate AUD
117 patients with mild deficits from those with moderate-to-severe impairments (Pelletier et al.,
118 2018) and may thus be relevant to identify KS patients. The aim of the present study is to
119 determine whether BEARNI is a relevant tool for the early identification of AUD patients at
120 risk of developing KS.

121

122 **2. Material and Methods**

123 **2.1. Participants**

124 Eighteen KS patients, 47 AUD patients and 27 healthy controls (HC) were included in the
125 present study (Table 1). AUD patients and HC were matched for age, sex and education (years
126 of schooling) but KS patients were older and less educated than both AUD and HC (Table 1).

127 The sex ratio was different in the KS group. As a result, age, education and sex were included
128 as covariates in the subsequent statistical analyses (Table 1). None of the participants had a
129 history of neurological pathology (except diagnosis of KS), endocrinal or other infectious
130 (diabetes, HIV and hepatitis as confirmed by the blood analysis), mental illness (psychiatric
131 disorders assessed by the MINI (Mini International Neuropsychiatric Interview)), or other
132 forms of substance misuse or dependence (except tobacco) and none were under psychotropic
133 medication (such as benzodiazepines only used during the alcohol withdrawal) that might have
134 had an effect on their cognitive functioning. All participants were informed about the study
135 approved by the local ethics committee of the Caen University Hospital (CPP Nord Ouest III
136 n° IDRCB: 2011-A00495) prior to their inclusion and provided their written informed consents.

137 KS patients were recruited as inpatients at Caen University Hospital (N=10) and in a nursing
138 home (Maison Vauban, Roubaix, France; N=8). All KS patients were diagnosed with reference
139 to the clinical DSM-IV criteria of “amnesia due to substance abuse” and to the DSM-5 criteria
140 of “major neurocognitive disorders, confabulatory type, persistent”. All KS patients had a
141 history of heavy drinking, but it was difficult to obtain accurate information about their alcohol
142 intake due to their amnesia. The case of each patient was examined by a multidisciplinary team
143 made up of specialists in cognitive neuropsychology and behavioral neurology. A detailed
144 neuropsychological examination enabled the diagnosis of all KS patients who presented
145 disproportionately severe episodic memory disorders compared to other cognitive deficits.
146 Clinical and neuroimaging investigations (Magnetic Resonance Imaging, MRI) ruled out other
147 possible causes of memory impairments (particularly focal brain damage). Most of the KS
148 patients lived in a sheltered environment and had been diagnosed long before. Patients were no
149 longer confabulating or presenting false recognitions, and no longer had any sign of WE.

150 AUD patients were recruited by clinicians while they were receiving withdrawal treatment
151 as inpatients at Caen University Hospital. At inclusion, none of the patients presented physical

152 symptoms of alcohol withdrawal as assessed by the Cushman's scale (Cushman et al., 1985).
153 They were interviewed with the Alcohol Use Disorders Identification Test (AUDIT; (Gache et
154 al., 2005)), a semi-structured interview (Skinner, 1982) and questions accompanying the
155 Structured Clinical Interview for DSM-IV-TR (SCID; (First and Gibbon, 2004)) with measures
156 regarding the duration of misuse (in years), number of detoxifications (including the current
157 one) and daily alcohol consumption over the month prior treatment (in units, a standard drink
158 corresponding to a beverage containing 10 g of pure alcohol) (Table 1).

159 HC were recruited to match the AUD patients for sex, age and education. All HC were
160 interviewed with the AUDIT questionnaire (Gache et al., 2005) to ensure that they did not meet
161 the DSM-IV criteria for alcohol abuse or dependence (AUDIT <7 for men and <6 for women).
162 HC with neuropsychological impairments revealed during the extensive neuropsychological
163 examination (see 2.2 section) were excluded.

164

165 **2.2. Neuropsychological assessment**

166 **2.2.1. BEARNI**

167 All participants underwent the BEARNI (Ritz et al., 2015), a validated screening tool especially
168 designed to assess the cognitive and motor functions that are impaired in AUD, namely episodic
169 memory, working memory, executive functions, visuospatial abilities, and ataxia. The BEARNI
170 has high content validity and reliable diagnostic accuracy in detecting AUD patients with
171 cognitive and motor impairments (Pelletier et al., 2018; Ritz et al., 2015).

172 The *episodic memory* subtest consists of two learning trials of a 12-word list (4 words x 3
173 semantic categories). After a 20-minute interval (after the rest of the BEARNI has been
174 administered), delayed free recall is performed (one trial lasting 1 minute). The episodic
175 measure is the number of correct responses (0.5 point per response) minus the number of errors

176 (intrusions and perseverations; 0.5 point per error) during the delayed free recall task (maximum
177 score: 6 points).

178 **Working memory** is assessed with an alphabetical span subtest. Increasingly long letter
179 sequences are read out loud, and for each sequence the patient has to repeat the letters in
180 alphabetical order. Two trials are performed for each sequence. The task ends when the
181 participant fails both two trials of a sequence (0.5 point per trial; maximum score: 5 points).

182 **Executive functions** are assessed with the alternating verbal fluency subtest (120 seconds to
183 generate as many words as possible from two alternating categories (“color name” and “city
184 name”). Depending on the number of correct responses, points range from 0 to 6.

185 **Visuospatial abilities** are assessed a subtest including five complex figures, each containing
186 two separate hidden figures that the patient has to find. For each complex figure, one point is
187 provided when the patient finds both hidden figures within 1 minute (maximum score: 5 points).

188 Finally, the **ataxia** subtest requires patients to stand on each foot in turn for 30 seconds, first
189 with eyes open, then with eyes closed. There are up to two trials per condition. For each
190 condition, 2 points are awarded when patients successfully perform the task at the first trial, 1
191 point when they successfully perform the task at the second trial, and 0 point when they fail
192 both trials (maximum score: 8 points).

193 BEARNI provides six scores: five sub-scores (one for each of the subtests) and a total score
194 (maximum score: 30 points).

195

196 **2.2.2. Extensive neuropsychological examination**

197 All participants also underwent an extensive neuropsychological examination that targeted the
198 cognitive functions assessed by the BEARNI.

199 **Verbal working memory** was assessed with the backward span of the WAIS III (Wechsler,
200 2001). Regarding **executive functions**, inhibition was assessed by the Stroop task (Stroop

201 Interference - Naming, time in seconds; (Stroop, 1935)) and flexibility by the Trail Making Test
202 (TMT B-A, time in seconds; (Reitan, 1955). These executive tasks were selected since they can
203 be performed relatively briefly, limiting potential interaction with amnesia and forgetting of
204 instructions.

205 *Visuospatial abilities* were assessed by the copy of the Rey-Osterrieth complex figure (ROCF;
206 accuracy score/36 points; (Osterrieth, 1944)).

207 *Verbal episodic memory* was assessed with the French version of the Free and Cued Selective
208 Reminding Test (FCSRT; (Linden and Collectif, 2004) for all the participants, except for the
209 KS patients of the nursing home (Maison Vauban, Roubaix, France; N=8) who performed the
210 California Verbal Learning Test (CVLT; (Delis et al., 1988). Retrieval abilities in verbal
211 episodic memory were assessed with the sum of the three free recalls of the FCSRT and the
212 first three free recalls CVLT.

213 Raw performance on the neuropsychological battery is provided in Supplementary Table 1.

214

215 **2.3. Statistical analyses**

216 **2.3.1. Neuropsychological profile of AUD and KS patients on BEARNI**

217 For each participant, performance on the 5 subtests of BEARNI were transformed into z-scores,
218 based on the mean and standard deviation of the entire group of HC. Performance on BEARNI's
219 subtests was then compared with a MANCOVA (3 groups x 5 subtests, with age, sex and
220 education as covariates) followed by *post-hoc* comparisons (Tukey's tests).

221

222 **2.3.2. Is BEARNI a relevant tool to identify AUD at risk for developing KS?**

223 In order to identify AUD patients at risk of developing KS, k-means clustering classifications
224 were performed on the performance obtained on each BEARNI's subtest. We focused this
225 analysis on the subtests that were more severely impaired in KS than in AUD patients, with the

226 algorithm constrained to separate the 65 patients (AUD and KS) into 2 groups. Two main results
227 could be obtained:

- 228 - An irrelevant result with AUD and KS patients being mixed in the two clusters
- 229 - A relevant result with the identification of a cluster of AUD patients being classified
230 within the same cluster as all KS patients and being deemed as AUD patients at “high
231 risk” of developing KS. The other cluster of AUD patients would be considered as
232 presenting “low risk” of developing KS.

233 When the result of the k-means clustering classification was relevant, we used it to run a
234 Receiver Operating Characteristic (ROC) curve analysis using the raw performance on this
235 specific BEARNI subtest. Performance of the subjects belonging to the cluster including the
236 HC and AUD with “low risk” was considered as normal (=0) and that of KS and AUD with
237 “high risk” was considered as impaired (=1). Clinically, the goal was to determine the cut-off
238 score under which AUD patients could be considered at risk of developing KS. This score was
239 determined, for each subtest included in the ROC analysis, by the best balance between
240 sensitivity and specificity.

241 Then, Mann-Whitney’s tests were conducted on demographic and alcohol variables to compare
242 AUD patients with “low risk” and “high risk” of developing KS.

243

244 ***2.3.3. Predictive value of BEARNI to identify AUD patients at risk for developing KS***

245 HC, KS, AUD^{low} and AUD^{high} were then compared on the performance obtained on the
246 extensive neuropsychological battery with ANCOVAs (4 groups, with age, sex and education
247 as covariates) followed by *post-hoc* comparisons (Tukey’s tests). In order to prevent type I error
248 due to multiple comparisons, Bonferroni’s corrections were applied ($p \leq 0.01$ for 5
249 comparisons).

250

251 3. Results

252 3.1. Neuropsychological profile of KS patients on BEARNI

253 Raw BEARNI results of the three groups are provided in Table 2.

254 The MANCOVA (3 groups x 5 subtests with age, sex and education as covariates) showed a
255 significant effect of group ($F_{(2;84)}= 35.16$; $p<0.001$; $\eta^2= 0.46$; large effect size), and a significant
256 effect of age ($F_{(2;84)}= 13.64$; $p<0.001$; $\eta^2= 0.14$; large effect size), education ($F_{(2;84)}= 14.69$;
257 $p<0.001$; $\eta^2= 0.15$; large effect size) and sex ($F_{(2;84)}= 4.21$; $p=0.04$; $\eta^2= 0.05$; moderate effect
258 size) included as covariates. There was no effect of the subtest ($F_{(4;336)}= 1.03$; $p=0.39$), no
259 significant interaction subtest*age ($F_{(4;336)}= 0.65$; $p=0.62$) and subtest*education ($F_{(4;336)}= 2.00$;
260 $p=0.09$) but a significant interaction subtest*sex ($F_{(4;336)}=2.55$; $p=0.04$; $\eta^2= 0.03$; small effect
261 size) and group*subtest ($F_{(8;336)}= 2.19$; $p=0.02$; $\eta^2= 0.05$; moderate effect size).

262 Regarding the significant main effect of group, Tukey's *post-hoc* tests showed that on the
263 overall, KS patients had lower performance than both AUD patients and HC (both $p\leq 0.001$),
264 who differed between each other ($p\leq 0.001$). Regarding the significant effect of sex, men had
265 lower performance than women ($p=0.04$). Regarding the significant sex*subtest interaction,
266 women had lower performance than men only on the visuospatial subtest ($p\leq 0.001$). Regarding
267 the significant group*subtest interaction, results are depicted in Figure 1. For all BEARNI
268 subtests, KS patients had lower performance than HC (all $p\leq 0.001$). KS patients also had lower
269 performance than AUD patients for the episodic memory, executive and visuospatial subtests
270 (all $p\leq 0.001$). In AUD patients, working memory ($p=0.005$), visuospatial ($p\leq 0.001$) and ataxia
271 ($p\leq 0.001$) subtests were impaired compared to HC (Figure 1). When a MANOVA was
272 conducted (3 groups x 5 subtests without any covariate), similar results were observed and all
273 comparisons remained significant.

274 The number of days of sobriety before inclusion did not correlate with any of the BEARNI
275 scores, nor with the cognitive performance on the extensive neuropsychological battery (all p
276 values >0.05).

277

278 **3.2. Is BEARNI relevant to identify AUD patients at risk of developing KS?**

279 K-means clustering classifications were performed on the episodic memory, executive and
280 visuospatial subtests of BEARNI since these subtests were more severely impaired in KS than
281 in AUD patients. For the executive and visuospatial subtests, we found KS patients belonging
282 to the two clusters (Figure 2). Thus, these results were not considered as relevant to distinguish
283 AUD and KS. For the episodic memory subtest, two clusters were obtained. The first one
284 included only AUD patients, thus considered as presenting low risk of developing KS (N = 34;
285 mean = 3.55; standard deviation = 1.02). The second cluster (N = 31) included all the KS
286 patients and several AUD patients, thus considered as presenting high risk of developing KS
287 (mean = 0.50; standard deviation = 0.56; min = 0; max = 1.5) (Figure 2).

288 The ROC curve analysis performed on the raw results obtained on the BEARNI episodic
289 memory subtest showed that a cutoff score of ≤ 1.5 yielded the best balance between sensitivity
290 and specificity for identifying AUD patients at risk of developing KS (Sensitivity = 100.00 [CI
291 87.2-100.0]; Specificity = 93.85 [CI 85.0-98.3]; Area Under the Curve = 0.991 [CI 0.944-1.00];
292 $p < 0.001$). This cut-off score corresponds to -2 standard deviations from the mean of the first
293 cluster identified by the k-mean clustering classification on the BEARNI episodic memory
294 subtest.

295 There was no difference between AUD patients with “low risk” and “high risk” on age,
296 education, and alcohol history described in table 1 (Mann-Whitney’s tests, all p values >0.05,
297 data not shown).

298

3.3. Predictive value of BEARNI to identify AUD patients at risk for developing KS

Results of the ANCOVAs conducted to compare the performance on the extensive neuropsychological battery between the 4 groups (HC, KS, AUD with “low risk” and AUD with “high risk”) are presented in table 3. Except for flexibility abilities, a significant main effect of group was found for all cognitive functions assessed by the extensive neuropsychological battery, with large effect sizes (medium effect size for inhibition). These effects remained significant after Bonferroni’s corrections ($p \leq 0.01$), except for inhibition.

More precisely, for **retrieval abilities in verbal episodic memory**, Tukey’s *post-hoc* tests revealed a graded effect: KS had lower performance than both AUD^{high} and AUD^{low} , who differed between each other. All patient groups also had lower performance than HC.

For **verbal working memory**, performance of KS patients, AUD^{high} and AUD^{low} were similar, all of them performing poorer than HC. AUD^{high} also had lower performance than AUD^{low} .

For **visuospatial abilities**, KS patients had lower performance than both HC and AUD^{low} but did not differ from AUD^{high} .

When KS patients with less than 9 years of education ($N=4$) were excluded from the analyses, the three groups of participants were matched for education ($p=0.39$) but remained different for age ($F(2;85) = 12.96$; $p \leq 0.001$; $HC = AUD < KS$) and sex ($\chi^2 = 19.06$; $p \leq 0.001$). All the analyses conducted yielded the same results as those including all the KS patients.

4. Discussion

BEARNI (Ritz et al., 2015) is a validated screening tool that has been especially designed to detect neuropsychological impairments in AUD. Given its reliability in the detection of moderate-to-severe impairments in AUD patients without neurological complications (Pelletier et al., 2018; Ritz et al., 2015), the aim of the present study was to determine whether BEARNI is a relevant tool for the early identification of AUD patients at risk of developing KS. Overall,

324 analyses showed a significant effect of group with a graded effect of impairments: KS patients
325 had lower performance than both AUD patients and HC, who differed between each other.
326 However, analyses of the BEARNI subtests revealed three distinct profiles of performance
327 among AUD and KS patients.

328 The first profile concerned the visuospatial subtest, for which a graded effect was observed
329 between HC, AUD and KS patients. Visuospatial deficits were repeatedly reported in AUD
330 patients (Creupelandt et al., 2019, for a review; Fama et al., 2004; Sullivan et al., 2000). KS
331 patients also show visuospatial impairments (Kopelman, 1995) and a graded effect has been
332 found between KS, AUD and HC on tasks requiring visuospatial abilities (Oscar-Berman et al.,
333 2004). The pattern of performance observed in AUD and KS patients on the BEARNI
334 visuospatial subtest is thus in agreement with the literature. Deficits on visuospatial tasks in
335 AUD are also shown to be related, at least partially, to executive dysfunction (Fama et al., 2004;
336 Fox et al., 2000; Oscar-Berman et al., 2004; Ritz et al., 2015). Visuospatial deficits results in
337 loss of inhibitory control, attentional bias towards alcohol-related stimuli, emotional deficits
338 and altered long-term memory (Creupelandt et al., 2019). From a clinical perspective, AUD and
339 KS patients with visuospatial deficits may be at risk of more severe cognitive and emotional
340 impairments, that could limit the benefit of treatment.

341 The second profile, characterized by a similar level of impairments in AUD and KS patients,
342 was observed on the ataxia and working memory subtests. Ataxia of gait and balance, frequently
343 observed in AUD patients (Sullivan et al., 2000; Sullivan et al., 2009), is considered as a
344 severity index of the neuropsychological profile (Sullivan, 2003). Half of the KS patients shows
345 residual and persistent ataxia after WE (Akhouri et al., 2020). In agreement, most of the KS
346 patients included in the present study, who had been diagnosed long before, did not differ from
347 AUD patients on ataxia. Pitel et al. (2008) analyzed individual working memory results in AUD
348 and KS patients. They showed a total mixture of the two groups with performance ranging from

349 normal (at the same level of HC) to severely impaired. The authors concluded that working
350 memory deficits did not allow to distinguish KS and AUD. Brain shrinkage in the
351 frontocerebellar circuit, involved in motor and executive abilities, was also found to be similar
352 in AUD and KS (Pitel et al., 2012). The fact that AUD and KS patients do not differ on the
353 BEARNI ataxia and working memory subtests is thus in accordance with the literature.

354 The third profile is observed on the episodic memory and executive subtests. Although the
355 fluency task does not directly involve episodic memory, strategic search in long-term memory
356 is needed to generate words from the two semantic categories. On these two subtests, KS
357 patients have lower performance than both AUD patients and HC, who did not differ between
358 each other. This pattern of performance reflects the fact that KS is marked by amnesia, a
359 disproportionate impairment of episodic memory compared with other neuropsychological
360 deficits but also compared with AUD (Brokate et al., 2003; Pitel et al., 2008). The specificity
361 of deficits observed in KS on BEARNI's subtests involving memory components suggests that
362 BEARNI is particularly sensitive to severe episodic memory impairments.

363 The k-means cluster classifications revealed that performance on the BEARNI episodic
364 memory subtest (but not on the fluency subtest) makes the identification of AUD patients at
365 risk of developing KS possible. AUD patients with scores on the episodic memory subtest equal
366 or below the cut-off score of 1.5 points (/6 points) were included in the same group as all the
367 KS patients (Figure 2), suggesting that these AUD patients could be considered at risk of KS.
368 To go further, signs of WE were investigated in a sub-group of AUD patients according to the
369 method proposed by Caine (Caine et al., 1997) and used by (Pitel et al., 2011) (see
370 supplementary Material 2). All AUD patients with high risk of developing KS had signs of WE,
371 whereas AUD patients with low risk of KS presented either signs or no sign of WE. Those AUD
372 patients should benefit from particular attention and receive an extensive neuropsychological
373 evaluation and a clinical and biological assessment of their nutritional status. Preventive actions

374 should urgently be conducted with thiamine supplementation (Thomson, 2000; Thomson and
375 Marshall, 2006) to prevent the development of WE and KS. For these patients, a follow-up
376 evaluation, conducted with the parallel version of BEARNI, could enable to observe the
377 recovery of neuropsychological impairments with sustained abstinence from alcohol (Mann et
378 al., 1999; Pitel et al., 2009)

379 Performance below this cut-off score on the episodic memory subtest (1.5/6 points) of
380 BEARNI seems to be predictive of severe episodic memory deficits on the extensive
381 neuropsychological battery. On the standardized episodic memory tasks (FCRST or CVLT),
382 KS had the poorest level of performance and AUD patients with high risk of developing KS
383 had more severe episodic memory impairments than both AUD patients with low risk and HC.
384 On the opposite, the three groups of patients (KS, AUD^{high} and AUD^{low}) did not differ between
385 each other on inhibition, flexibility, verbal working memory and visuospatial abilities on the
386 extensive neuropsychological battery.

387 Individual performance of the three patient groups, reported in Figure 3 (z-scores),
388 confirmed that results on BEARNI episodic memory subtest enable the prediction of
389 performance on the extensive and standardized neuropsychological battery. On the episodic
390 memory tasks, the poorest results were observed in KS patients and most of the AUD patients
391 at high risk of KS. On the contrary, individual analyses of verbal working memory and
392 visuospatial tasks showed a total mixture between the three groups (KS, AUD^{high} and AUD^{low})
393 ranging from severe (< -2 standard deviations from mean) to moderate deficits or even
394 preserved performance.

395 To conclude, the performance of AUD and KS patients on the BEARNI subtests is in
396 accordance with the literature. This finding reinforces the relevance of using BEARNI to detect
397 neuropsychological impairments in the context of AUD. On BEARNI, ataxia and working
398 memory deficits observed in AUD were as severe as those exhibited by KS patients, whereas

399 for visuospatial abilities, a graded effect of performance was found. On the opposite, the
400 subtests involving long-term memory abilities (episodic memory and fluency) were impaired
401 only in KS patients. The selectivity of KS deficits in subtests requiring memory suggests that
402 BEARNI is sensitive to severe episodic memory deficits. AUD patients with a score lower than
403 1.5 points (/6) on the episodic memory subtest could thus be considered at risk of developing
404 KS. Those patients should receive particular attention and personalized care such as long time
405 stay in a safe and enriched environment (withdrawal from alcohol and nutritional treatment to
406 prevent WE) to favor neuropsychological recovery with abstinence. While the use of BEARNI
407 seems appropriate to screen AUD patients at risk of developing KS, it is not sufficient to
408 diagnose KS. A clinical evaluation, an extensive neuropsychological assessment associated
409 with a neuroimaging examination are required. A follow-up evaluation is also necessary to
410 ascertain the persistence of severe episodic memory impairments, even with abstinence, which
411 is a key feature of KS diagnosis.

412

413 **Acknowledgments**

414 This work was supported by the French National Institute for Health and Medical Research
415 (INSERM), the French National Agency for Research (ANR) Postdoc Return (Retour Post-
416 Doctorants, PDOC) program, the Regional council of Lower-Normandy and the Mission
417 Interministerielle de Lutte contre les Drogues Et les Conduites Addictives (MILDECA).

418

419 **Declaration of interest**

420 Authors declare no conflict of interest.

421

422

423

424 **References**

- 425 Akhouri S, Kuhn J, Newton EJ (2020) Wernicke-Korsakoff Syndrome In: StatPearls , Treasure
426 Island (FL), StatPearls Publishing.
- 427 Alarcon R, Nalpas B, Pelletier S, Perney P (2015) MoCA as a Screening Tool of
428 Neuropsychological Deficits in Alcohol-Dependent Patients. *Alcohol Clin Exp Res*.
- 429 Arts NJ, Walvoort SJ, Kessels RP (2017) Korsakoff's syndrome: a critical review.
430 *Neuropsychiatr Dis Treat* 13:2875–2890.
- 431 Bates ME, Buckman JF, Nguyen TT (2013) A role for cognitive rehabilitation in increasing the
432 effectiveness of treatment for alcohol use disorders. *Neuropsychol Rev* 23:27–47.
- 433 Brion M, Pitel A-L, Beaunieux H, Maurage P (2014) Revisiting the continuum hypothesis:
434 toward an in-depth exploration of executive functions in korsakoff syndrome. *Front*
435 *Hum Neurosci* 8:498.
- 436 Brokate B, Hildebrandt H, Eling P, Fichtner H, Runge K, Timm C (2003) Frontal lobe
437 dysfunctions in Korsakoff's syndrome and chronic alcoholism: Continuity or
438 discontinuity?. *Neuropsychology* 17:420.
- 439 Caine D, Halliday GM, Kril JJ, Harper CG (1997) Operational criteria for the classification of
440 chronic alcoholics: identification of Wernicke's encephalopathy. *J Neurol Neurosurg*
441 *Psychiatry* 62:51–60.
- 442 Copersino ML, Fals-Stewart W, Fitzmaurice G, Schretlen DJ, Sokoloff J, Weiss RD (2009)
443 Rapid cognitive screening of patients with substance use disorders. *Exp Clin*
444 *Psychopharmacol* 17:337.
- 445 Copersino ML, Schretlen DJ, Fitzmaurice GM, Lukas SE, Faberman J, Sokoloff J, Weiss RD
446 (2012) Effects of cognitive impairment on substance abuse treatment attendance:
447 predictive validation of a brief cognitive screening measure. *Am J Drug Alcohol Abuse*
448 38:246–250.

449 Creupelandt C, D'Hondt F, Maurage P (2019) Towards a Dynamic Exploration of Vision,
450 Cognition and Emotion in Alcohol-Use Disorders. *Curr Neuropharmacol* 17:492–506.

451 Cushman P Jr, Forbes R, Lerner W, Stewart M (1985) Alcohol withdrawal syndromes: clinical
452 management with lofexidine. *Alcohol Clin Exp Res* 9:103–108.

453 Delis DC, Freeland J, Kramer JH, Kaplan E (1988) Integrating clinical assessment with
454 cognitive neuroscience: construct validation of the California Verbal Learning Test. *J*
455 *Consult Clin Psychol* 56:123–130.

456 Fama R, Pfefferbaum A, Sullivan EV (2004) Perceptual Learning in Detoxified Alcoholic Men:
457 Contributions From Explicit Memory, Executive Function, and Age. *Alcohol Clin Exp*
458 *Res* 28:1657–1665.

459 First MB, Gibbon M (2004) The Structured Clinical Interview for DSM-IV Axis I Disorders
460 (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-
461 II) In: *Comprehensive Handbook of Psychological Assessment, Vol. 2: Personality*
462 *Assessment* , pp 134–143. Hoboken, NJ, US, John Wiley & Sons Inc.

463 Fox AM, Coltheart M, Solowij N, Michie PT, Fox GA (2000) Dissociable cognitive
464 impairments in problem drinkers. *Alcohol Alcohol Oxf Oxf* 35:52–54.

465 Gache P, Michaud P, Landry U, Accietto C, Arfaoui S, Wenger O, Daeppen J-B (2005) The
466 Alcohol Use Disorders Identification Test (AUDIT) as a Screening Tool for Excessive
467 Drinking in Primary Care: Reliability and Validity of a French Version. *Alcohol Clin*
468 *Exp Res* 29:2001–2007.

469 Kopelman MD (1995) The Korsakoff syndrome. *Br J Psychiatry J Ment Sci* 166:154–173.

470 Kopelman MD, Thomson AD, Guerrini I, Marshall EJ (2009) The Korsakoff syndrome: clinical
471 aspects, psychology and treatment. *Alcohol Alcohol* 44:148.

472 Linden MV der, Collectif (2004) L'évaluation des troubles de la mémoire : Présentation de
473 quatre tests de mémoire épisodique. Solal Editeurs.

474 Maillard A, Cabé N, Viader F, Pitel AL (2020) Chapter 8 - Neuropsychological deficits in
475 alcohol use disorder: impact on treatment In: Cognition and Addiction (Verdejo-Garcia
476 A ed), pp 103–128. Academic Press.

477 Mann K, Günther A, Stetter F, Ackermann K (1999) Rapid recovery from cognitive deficits in
478 abstinent alcoholics: a controlled test-retest study. *Alcohol Alcohol Oxf Oxf* 34:567–
479 574.

480 Oscar-Berman M, Kirkley SM, Gansler DA, Couture A (2004) Comparisons of Korsakoff and
481 Non-Korsakoff Alcoholics on Neuropsychological Tests of Prefrontal Brain
482 Functioning. *Alcohol Clin Exp Res* 28:667–675.

483 Oscar-Berman M, Valmas MM, Sawyer KS, Ruiz SM, Luhar RB, Gravitz ZR (2014) Profiles
484 of impaired, spared, and recovered neuropsychologic processes in alcoholism. *Handb*
485 *Clin Neurol* 125:183–210.

486 Osterrieth PA (1944) Le test de copie d'une figure complexe; contribution à l'étude de la
487 perception et de la mémoire. [Test of copying a complex figure; contribution to the study
488 of perception and memory.]. *Arch Psychol* 30:206–356.

489 Pelletier S, Alarcon R, Ewert V, Forest M, Nalpas B, Perney P (2018) Comparison of the MoCA
490 and BEARNI tests for detection of cognitive impairment in in-patients with alcohol use
491 disorders. *Drug Alcohol Depend* 187:249–253.

492 Pitel AL, Beaunieux H, Witkowski T, Vabret F, de la Sayette V, Viader F, Desgranges B,
493 Eustache F (2008) Episodic and Working Memory Deficits in Alcoholic Korsakoff
494 Patients: The Continuity Theory Revisited. *Alcohol Clin Exp Res* 32:1229–1241.

495 Pitel A-L, Chételat G, Le Berre AP, Desgranges B, Eustache F, Beaunieux H (2012)
496 Macrostructural abnormalities in Korsakoff syndrome compared with uncomplicated
497 alcoholism. *Neurology* 78:1330–1333.

498 Pitel AL, Rivier J, Beaunieux H, Vabret F, Desgranges B, Eustache F (2009) Changes in the
499 Episodic Memory and Executive Functions of Abstinent and Relapsed Alcoholics Over
500 a 6-Month Period. *Alcohol Clin Exp Res* 33:490–498.

501 Pitel A-L, Zahr NM, Jackson K, Sassoon SA, Rosenbloom MJ, Pfefferbaum A, Sullivan EV
502 (2011) Signs of preclinical Wernicke’s encephalopathy and thiamine levels as predictors
503 of neuropsychological deficits in alcoholism without Korsakoff’s syndrome.
504 *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 36:580–588.

505 Reitan RM (1955) The relation of the trail making test to organic brain damage. *J Consult*
506 *Psychol* 19:393–394.

507 Ritz L, Lannuzel C, Boudehent C, Vabret F, Bordas N, Segobin S, Eustache F, Pitel A-L,
508 Beaunieux H (2015) Validation of a brief screening tool for alcohol-related
509 neuropsychological impairments. *Alcohol Clin Exp Res* 39:2249–2260.

510 Segobin S, Laniepce A, Ritz L, Lannuzel C, Boudehent C, Cabé N, Urso L, Vabret F, Eustache
511 F, Beaunieux H, Pitel A-L (2019) Dissociating thalamic alterations in alcohol use
512 disorder defines specificity of Korsakoff’s syndrome. *Brain J Neurol* 142:1458–1470.

513 Segobin S, Ritz L, Lannuzel C, Boudehent C, Vabret F, Eustache F, Beaunieux H, Pitel A-L
514 (2015) Integrity of white matter microstructure in alcoholics with and without
515 Korsakoff’s syndrome. *Hum Brain Mapp*.

516 Skinner HA (1982) Development and validation of a lifetime alcohol consumption assessment
517 procedure. Alcoholism and Drug Addiction Research Foundation.

518 Stroop JR (1935) Studies of interference in serial verbal reactions. *J Exp Psychol* 18:643–662.

519 Sullivan EV (2003) Compromised Pontocerebellar and Cerebellothalamocortical Systems:
520 Speculations on Their Contributions to Cognitive and Motor Impairment in Nonamnesic
521 Alcoholism. *Alcohol Clin Exp Res* 27:1409–1419.

522 Sullivan EV, Rohlfing T, Pfefferbaum A (2009) Pontocerebellar volume deficits and ataxia in
523 alcoholic men and women: no evidence for “telescoping.” *Psychopharmacology* (Berl)
524 208:279–290.

525 Sullivan EV, Rosenbloom MJ, Pfefferbaum A (2000) Pattern of motor and cognitive deficits in
526 detoxified alcoholic men. *Alcohol Clin Exp Res* 24:611–621.

527 Thomson AD (2000) Mechanisms of vitamin deficiency in chronic alcohol misusers and the
528 development of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol Oxf Oxf Suppl*
529 35:2–7.

530 Thomson AD, Marshall E (2006) The natural history and pathophysiology of Wernicke’s
531 Encephalopathy and Korsakoff’s Psychosis. *Alcohol Alcohol* 41:151.

532 Wechsler D (2001) *WAIS-III: Wechsler Adult Intelligence Scale, Third Edition: Canadian*
533 *Technical Manual*. Harcourt Canada.

534 Wester AJ, Roy J, Kessels RPC, Egger JIM (2013) The Montreal Cognitive Assessment (MoCA)
535 as a measure of severity of amnesia in patients with alcohol-related cognitive
536 impairments and Korsakoff syndrome. *Clin Neuropsychiatry* 10:134.

537

538

539

540 **Figure legends**

541 Figure 1: Performance (z-scores) on each BEARNI's subtests in AUD and KS

542 Results of the significant interaction group * BEARNI subtests of the MANCOVA.

543 Data are shown as mean \pm standard error

544 HC: healthy controls; AUD patients: alcohol use disorder patients; KS: Korsakoff's syndrome patients

545 *: significant difference with HC

546 †: significant difference with AUD patients

547

548 Figure 2: Results of the k-means clustering classifications based on the performance at each

549 BEARNI subtest (raw performances) in AUD and KS

550 AUD patients: alcohol use disorder patients; KS: Korsakoff's syndrome patients.

551 The dotted line represents the separation between the two identified clusters.

552

553 Figure 3: Individual performance (z-scores) of each patient for verbal episodic memory,

554 verbal working memory and visuospatial abilities

555 The dotted lines represent the pathological z-score (-2 standard deviation from mean of HC)

556 Verbal episodic memory was assessed by the FCSRT for all the participants, except for the KS patients of the

557 nursing home (Maison Vauban, Roubaix, France) who performed the CVLT; verbal working memory by the

558 backward span task; visuospatial abilities by the Rey Osterrieth figure

559

560

561 **Tables**

562 Table 1: Main features of the participants

	KS patients	AUD patients	Healthy controls	Statistical analyses
Sample size	18	47	27	
Men/Women	8/10	42/5	25/2	Chi ² =20.54; p<0.001 ¹
Age (years)	55.72 ± 5.49	46.91 ± 9.17	43.41 ± 6.29	F _(2,89) =13.84; p<0.001 ^{2*}
Range	44-67	26-66 ⁴	31-55	(HC=AUD)<KS
Education (years of schooling)	10.39 ± 2.52	11.83 ± 2.05	12.11 ± 1.69	F _(2,89) =4.22; p=0.02 ^{*2}
Range	6-15	9-17	9-15	(HC=AUD)>KS
BEARNI total score	5.28 ± 2.48	13.78 ± 5.05	20.70 ± 2.30	F _(2,84) =34.45; p<0.001 ^{*3}
Range	2-10.5	4-22.5	16.5-26	KS<AUD<HC
AUDIT	-	28.65 ± 7.84	2.63 ± 1.60	F _(1,72) =380.10; p<0.001 ²
Range	-	9-39	0-6	AUD>HC
Days of sobriety before inclusion	-	11.89 ± 4.20	-	-
Range	-	4-24	-	-
Daily alcohol consumption during the month preceding treatment (units)	-	20.01 ± 8.68	-	-
Range	-	0-40	-	-
Duration of alcohol misuse (years)	-	22.87 ± 12.38	-	-
Range	-	5-46	-	-
Number of detoxifications	-	1.81 ± 1.52	-	-
Range	-	1-8	-	-

563 Data are shown as means ± standard deviations; -: data not applicable; KS: Korsakoff's syndrome; AUD: Alcohol

564 Use Disorder; HC: healthy controls

565 ¹ Chi² (correction of Yates applied)

566 * significant at p≤0.05

567 ² One-way ANOVA (group): Tukey's post-hoc tests

568 ³ ANCOVA (with age, sex and education as covariates), Tukey's post-hoc tests

569 ⁴ Only one AUD patients had 65 years old and only 5 had more than 60 years old

570 Table 2: Performance (raw scores) on BEARNI

BEARNI score	KS patients	AUD patients	Healthy controls
Episodic memory	0.22 ± 0.31	3.02 ± 1.40	3.55 ± 1.33
<i>Range</i>	0-1	0-5.5	1.5-5
Executive functions	2.22 ± 1.11	4.19 ± 1.15	4.93 ± 1.00
<i>Range</i>	0-4	2-6	2-6
Working memory	1.67 ± 0.80	2.39 ± 1.25	3.44 ± 0.92
<i>Range</i>	0-3.5	0-5	1.5-5
Visuospatial abilities	0.39 ± 0.61	1.78 ± 1.37	3.41 ± 1.08
<i>Range</i>	0-2	0-5	2-5
Ataxia	0.78 ± 1.40	2.38 ± 2.22	5.37 ± 1.77
<i>Range</i>	0-4	0-8	0-8

571 Data are shown as means ± standard deviations

572 KS: Korsakoff's syndrome: AUD: Alcohol Use Disorder

573

574

575

576 Table 3: Performance (z-scores) on the neuropsychological battery

Cognitive functions	KS	AUD ^{high}	AUD ^{low}	Statistics ¹	Tukey's post-hoc tests
Verbal episodic memory					
FCSRT Or CVLT ²	-4.86 ± 1.12	-2.34 ± 1.56	-1,04 ± 1.39	F _(3;85) = 34.52; p<0.001*; η ² =0.55	KS<high<low<HC
Verbal working memory					
Backward span task	-1.42 ± 0.77	-1.87 ± 0.63	-1.01 ± 0.86	F _(3;85) = 11.08; p<0.001*; η ² =0.28	KS=high<HC KS=low<HC high<low
Executive functions					
Stroop task	-4.43 ± 5.49	-3.09 ± 4.25	-1.46 ± 3.38	F _(3;85) = 3.01; p=0.03; η ² =0.10	KS<HC KS<low
Trail Making test	-9.96 ± 8.76	-6.97 ± 11.34	-3.37 ± 8.97	F _(3;85) = 2.55; p=0.06; η ² =0.08	/
Visuospatial abilities					
Rey Osterrieth figure	-4.42 ± 5.66	-2.04 ± 3.22	-0.86 ± 2.04	F _(3;85) = 6.86; p<0.001*; η ² =0.19	KS<HC KS<low

577 Data are shown as means ± standard deviations

578 Results of the ANCOVA (4 groups: KS, AUD^{high}, AUD^{low} and HC) with age, sex and education as covariates.

579 Only group effects are reported.

580 KS: Korsakoff's patients; AUD^{high}: AUD patients at high risk for developing KS; AUD^{low}: AUD patients at low risk for developing KS; HC: Healthy Controls

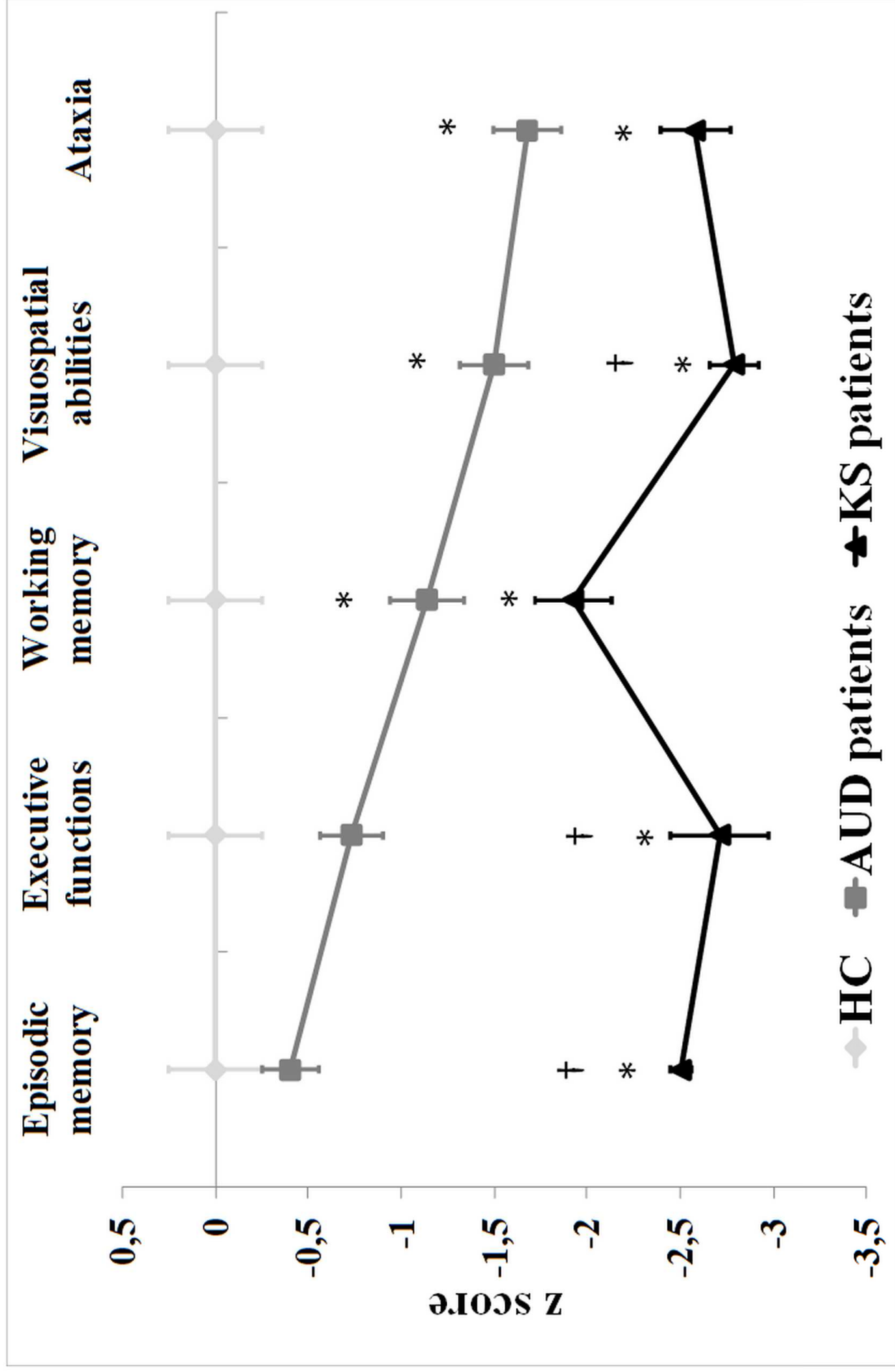
582 Z-scores of HC are: means=0 and standard deviations=1

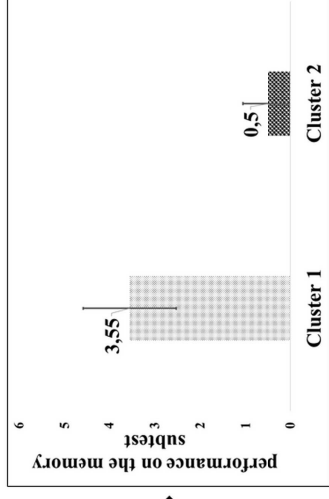
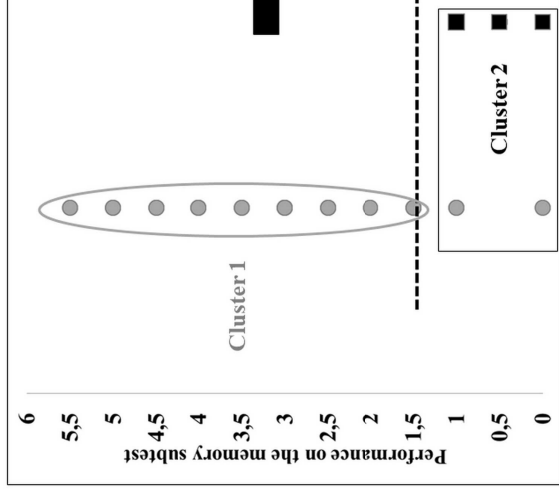
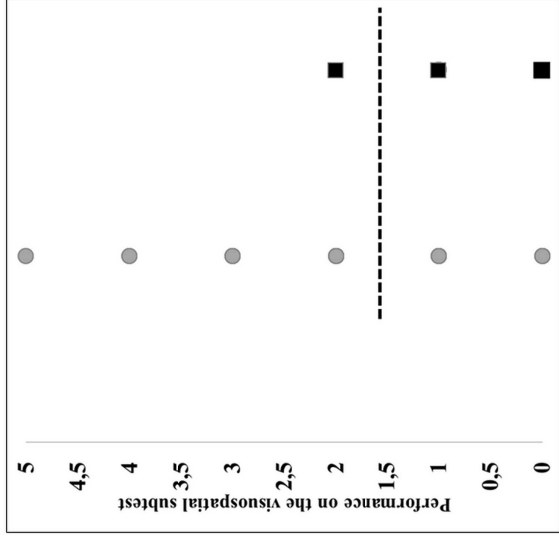
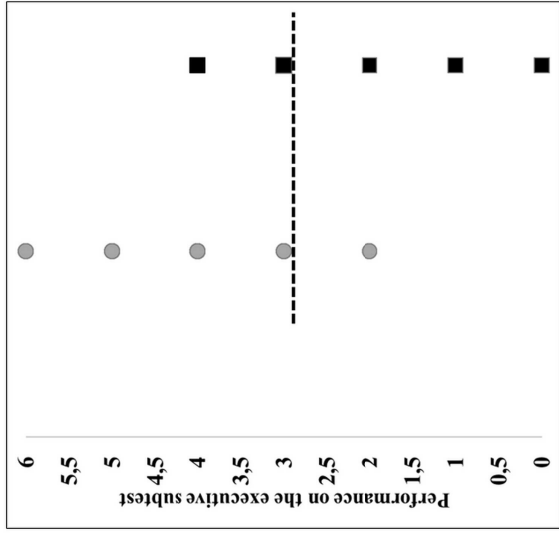
583 ¹ Statistics: Fisher's F ; p value ; partial eta-squared (η²)

584 *: significant after Bonferroni correction (p≤0.01)

585 ²: Verbal episodic memory was assessed by the FCSRT for all the participants, except for the KS patients of the nursing home (Maison Vauban, Roubaix, France) who performed the CVLT.

586





● AUD patients ■ KS patients

● AUD patients ■ KS patients

● AUD patients ■ KS patients

- KS patients
- AUD patients at high risk for developing KS
- AUD patient at low risk

