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

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Abstract

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

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

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

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

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

1. Introduction

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

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

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

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

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

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

2. Material and Methods

2.1. Participants

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

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

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

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

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

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

2.2. Neuropsychological assessment

2.2.1. BEARNI

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

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

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

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

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

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

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

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

2.2.2. Extensive neuropsychological examination

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

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

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

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

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

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

2.3. Statistical analyses

2.3.1. Neuropsychological profile of AUD and KS patients on BEARNI

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

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

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

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

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

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

Then, Mann-Whitney's tests were conducted on demographic and alcohol variables to compare AUD patients with "low risk" and "high risk" of developing KS.

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

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

3. Results

3.1. Neuropsychological profile of KS patients on BEARNI

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

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

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

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

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

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

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

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

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,

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

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

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

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

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

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

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

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

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

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

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

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Declaration of interest

Authors declare no conflict of interest.

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Figure legends

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

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

Data are shown as mean ± standard error

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

*: significant difference with HC

†: significant difference with AUD patients

Figure 2: Results of the k-means clustering classifications based on the performance at each BEARNI subtest (raw performances) in AUD and KS

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

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

Figure 3: Individual performance (z-scores) of each patient for verbal episodic memory, verbal working memory and visuospatial abilities

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

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; verbal working memory by the backward span task; visuospatial abilities by the Rey Osterrieth figure

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] Chi^2 (correction of Yates applied)
566 * significant at $p \leq 0.05$
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
Range	0-1	0-5.5	1.5-5
Executive functions	2.22 ± 1.11	4.19 ± 1.15	4.93 ± 1.00
Range	0-4	2-6	2-6
Working memory	1.67 ± 0.80	2.39 ± 1.25	3.44 ± 0.92
Range	0-3.5	0-5	1.5-5
Visuospatial abilities	0.39 ± 0.61	1.78 ± 1.37	3.41 ± 1.08
Range	0-2	0-5	2-5
Ataxia	0.78 ± 1.40	2.38 ± 2.22	5.37 ± 1.77
Range	0-4	0-8	0-8

571 Data are shown as means ± standard deviations

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

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574

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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

Data are shown as means ± standard deviations

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

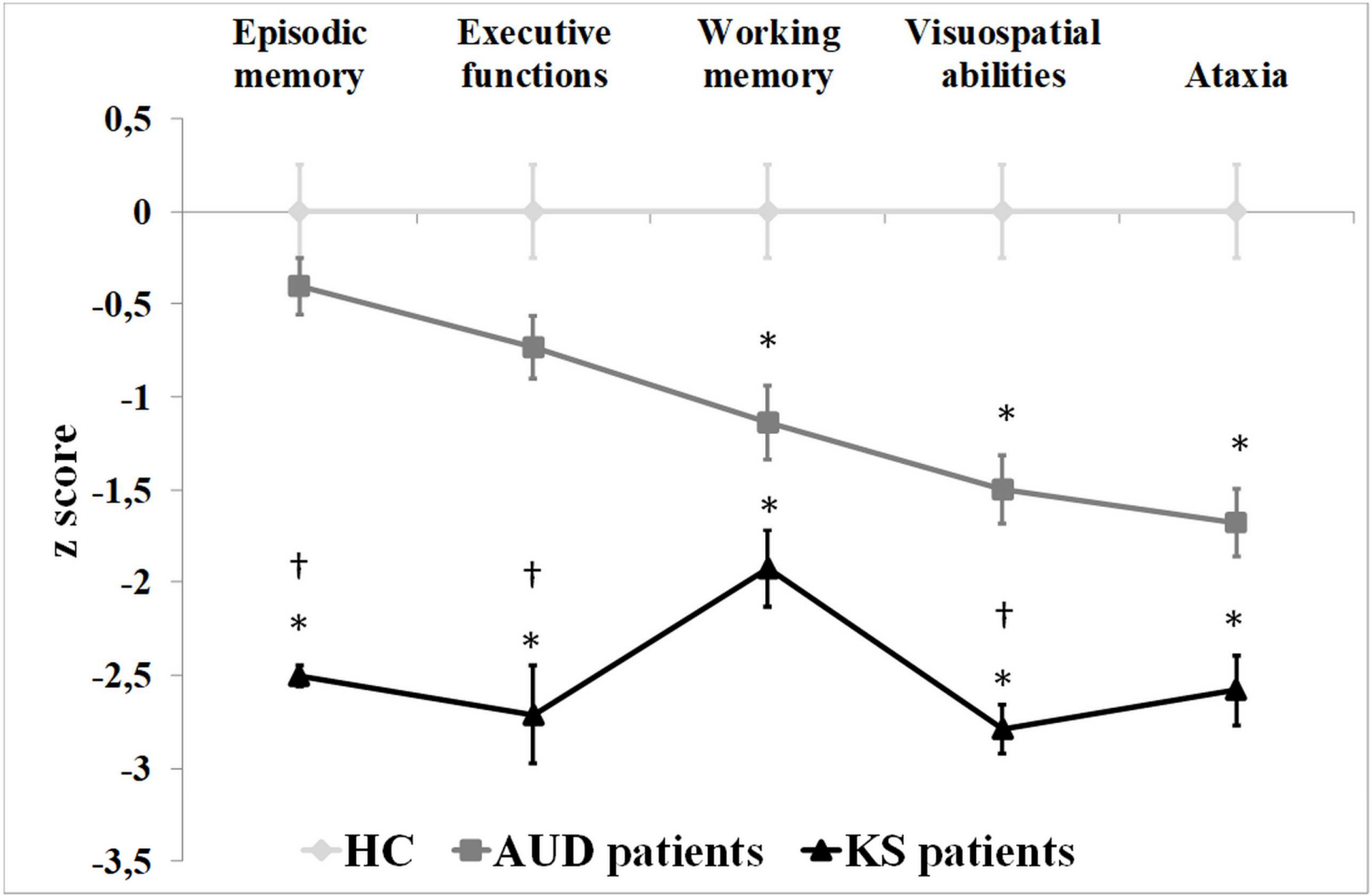
KS: Korsakoff's patients; AUD^{high}: AUD patients at high risk for developing KS; AUD^{low}: AUD patients at low risk for developing KS; HC: Healthy Controls

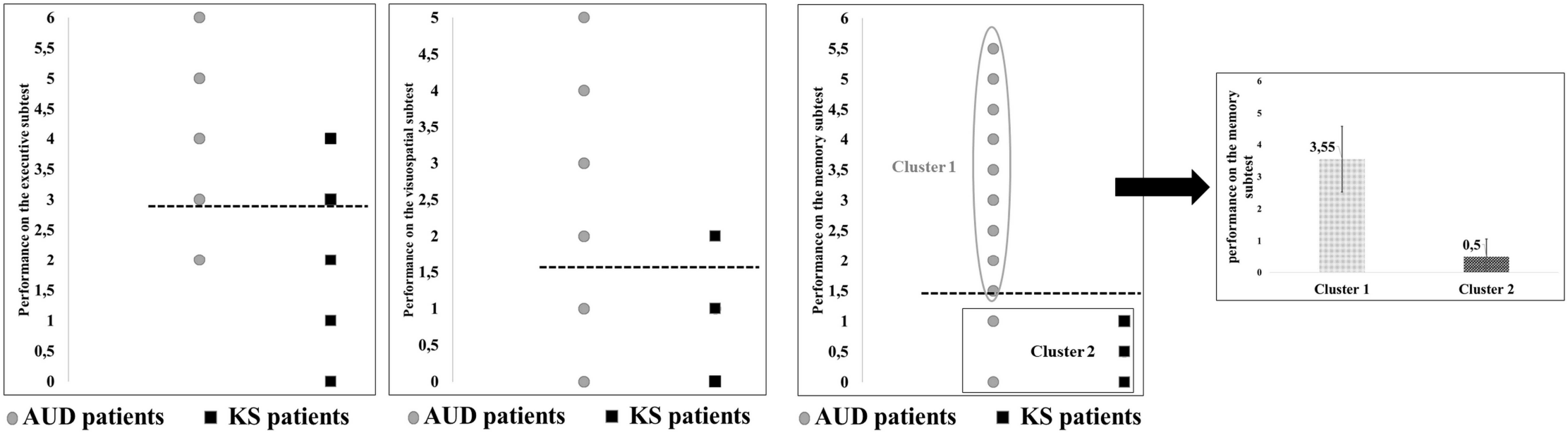
Z-scores of HC are: means=0 and standard deviations=1

[1] Statistics: Fisher's F ; p value ; partial eta-squared (η^2)

*: significant after Bonferroni correction ($p \leq 0.01$)

[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.


Episodic memory
Executive functions
Working memory
Visuospatial abilities
Ataxia
0,5
0
-0,5
-1
-1,5
-2
-2,5
-3
-3,5
z score
HC
AUD patients
KS patients


Performance on the executive subtest
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
AUD patients
KS patients
Performance on the visuospatial subtest
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
AUD patients
KS patients
Performance on the memory subtest
Cluster 1
Cluster 2
AUD patients
KS patients
performance on the memory subtest
3,55
0,5
Cluster 1
Cluster 2

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