NEUROPSYCHOLOGICAL AND NEUROIMAGING EXAMINATIONS OF SELF-REPORTED SLEEP QUALITY IN ALCOHOL USE DISORDER WITH AND WITHOUT KORSAKOFF'S SYNDROME

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Number of words in the abstract: **297**
Number of words in the body of the manuscript: **4950**
Number of figures: **5 ;** Number of color figures: **5**
Number of tables**: 3**

The authors declare no conflicts of interest. This work was supported by the French National Institute for Health and Medical Research (INSERM), the French National Agency for Research (ANR), and Conseil Régional de Basse-Normandie. Alice Laniepce's doctoral fellowship was co-funded by European Union in the framework of the ERDF-ESF operationnal programme 2014-2020 and Lundbeck Society.

ABSTRACT

Background: Alcohol Use Disorder (AUD) patients without Korsakoff's syndrome (KS) report a variable self-rated sleep quality. Their ability to accurately judge their sleep quality may be related to their alcohol-related cognitive deficits and brain damage. KS patients, who present severe brain dysfunction, may be cognitively unable to judge their sleep quality. The aim of the present study is to examine in AUD and KS patients, whether the absence of sleep complaint is associated with altered brain structure and impaired cognitive abilities within specific cerebral networks.

Methods: An assessment of subjective sleep quality was conducted in 20 healthy controls, 37 AUD and 17 KS patients. Patients were first pooled together and then classified into two groups (no-complaint^{AUD+KS} and complaint^{AUD+KS}) according to the total PSQI score. Cognitive scores, gray matter volume (GM) and white matter (WM) integrity were compared between these two groups, and then in AUD and KS patients separately.

Results: Poor sleep quality was reported by 70% of AUD and 18% of KS patients. Compared to controls, both no-complaint^{AUD+KS} and complaint^{AUD+KS} presented cortical and subcortical alterations as well as episodic memory deficits, which were more severe in patients without sleep complaint. Only no-complaint^{AUD+KS} presented executive deficits. Then, considering the clinical diagnosis, GM volume in fronto-temporal regions, WM integrity and executive functions were affected to the same extent in AUD and KS without sleep complaint.

Conclusion: Our results confirm the high prevalence of sleep complaint in AUD patients and the rare complaint in KS patients. In AUD and KS patients, the absence of sleep complaint may not indicate good sleep quality but rather reflect executive deficits and fronto-thalamic damage. Alcohol-related cognitive deficits may indeed alter the ability to self-evaluate sleep quality, suggesting that the use of sleep questionnaire should be considered with caution in patients with executive deficits.

Keywords: Alcohol Use Disorder; Korsakoff's syndrome; Neuropsychology; Neuroimaging; Subjective sleep assessment

1. INTRODUCTION

Alcohol-related neurological disorders exist principally in two clinical forms that can be distinguished based on the severity of brain dysfunction (Zahr, 2014) and cognitive deficits (Oscar-Berman et al., 2014). The more severe clinical form is the Korsakoff's syndrome (KS), which is a neurological complication related to the combination of chronic and excessive alcohol consumption and thiamine deficiency. KS is described as a severe and profound amnesia potentially associated with executive dysfunction. Alcohol Use Disorder without KS (AUD) is also characterized by episodic memory deficits and executive dysfunction, from mild to moderate in most cases up to severe in some patients at risk for KS (Pitel et al., 2008).

Chronic and heavy alcohol consumption is not only associated with neuropsychological impairments but also with major sleep disorders. Sleep disturbances are frequently present in recently detoxified AUD patients (Angarita et al., 2016) with a variable sleep complaint reported by 36 to 72% of the population. Such variability can be explained by the AUD patients' clinical features (the criteria used to diagnose AUD or alcohol abuse, the length of sobriety at the time of the sleep assessment), as well as the absence of standard definitions and measurements of sleep complaint (different sleep questionnaires with, for example, different time frames; Brower, 2001; Stein and Friedmann, 2005). While objective sleep quality seems affected in KS patients (Lairie and Pottier, 1979; Martin et al., 1986), only one study considered their subjective sleep perception (Lairie and Pottier, 1979) and suggested that KS patients would report sleeping well. This seemingly absent sleep complaint in KS patients may be related to their characteristic impaired self-awareness (Arts et al., 2017).

Even in absence of KS, altered abilities to accurately self-evaluate have been described in AUD patients regarding neuropsychological performance (overall cognitive abilities, episodic memory decoding of facial emotions) and daily recall of alcohol consumption (Kornreich, 2002; Le Berre et al., 2010; Lincoln et al., 2011; Rinn et al., 2002; Walvoort et al., 2016). The variability in the sleep complaint prevalence observed in AUD patients may thus be related to their ability to self-assess their sleep quality. Indeed, an accurate subjective sleep evaluation requires efficient episodic memory abilities to recall recent sleep periods and executive functions to interpret internal and physical states, to quantify sleep duration and to respond to a written sleep questionnaire. AUD patients with episodic

memory impairments and executive dysfunctions may not be cognitively able to correctly evaluate their sleep quality, just as it may be the case in KS patients.

The objective of the present study is to investigate subjective sleep quality in KS and recently detoxified AUD patients using a validated sleep questionnaire. We aim at examining whether the absence of sleep complaint is associated with altered brain structure and cognitive abilities within cerebral networks involved in episodic memory and executive functions. First, we hypothesize that most KS patients do not complain about their sleep while most AUD patients do. Second, we hypothesize that KS and AUD patients without sleep complaint present more severe alterations of the brain networks involved in episodic memory and executive functions than patients who complain about their sleep. Third, we hypothesize that this profile of executive dysfunction and associated brain alterations is similar in KS and AUD without sleep complaint.

2. MATERIALS AND METHODS

2.1. Participants

Seventy-four participants were included in this study: 54 patients with AUD or KS (37 AUD patients and 17 KS patients) and 20 healthy controls (HC). None of them had a history of neurological pathology (except diagnosis of KS), endocrinal nor other infectious diseases, depression (assessed using the Beck Depression Inventory (Beck et al., 1961) nor other forms of substance use disorder (except tobacco). All participants were informed about the study approved by the local ethics committee of Caen University Hospital (CPP Nord Ouest III, no. IDRCB: 2011-A00495-36) prior to their inclusion and provided their written informed consent. For KS, informed consent was collected from guardians or caregivers as well as from the patients themselves.

Clinicians recruited AUD patients while they were receiving withdrawal treatment as inpatients at Caen University Hospital. AUD patients met "alcohol-dependence" criteria according to the DSM-IV (American Psychiatric Association (APA), 2000) and "alcohol use disorder" according to the DSM-5 (American Psychiatric Association, 2013) for at least 5 years. At inclusion and evaluation, none of them presented physical symptoms of alcohol withdrawal as assessed by the Cushman's scale (Cushman et al., 1985) and were under medication by benzodiazepines. Alcohol history of the AUD patients is described in Table 1.

KS were recruited as inpatients at Caen University Hospital (n=9) 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 "major neurocognitive disorders, confabulatory type, persistent" according to the DSM-5. 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 behavioural neurology. A detailed neuropsychological examination enabled the diagnosis of all KS patients presenting disproportionately severe episodic memory disorders compared to other cognitive functions (Table 1). Clinical and neuroimaging investigations ruled out other possible causes of memory impairments (particularly focal brain damage).

HC were recruited locally and to match the demographics of the AUD patients. They were interviewed with the AUDIT to ensure that they did not meet the criteria for alcohol abuse (AUDIT < 7 for men and < 6 for woman (Gache et al., 2005)). None of the controls had a Beck Depression Inventory (BDI) > 29 (Beck et al., 1961), an MMSE score < 26 (Folstein et al., 1975), nor sleep complaint (Pittsburg Sleep Quality Index ≤ 5; Buysse et al., 1989).

-Insert Table 1-

AUD and HC were age-, sex- and education-matched (p=0.31, p=0.42 and p=0.31 respectively). KS differed from both HC and AUD in age (p< 0.001) and only from HC (p=0.03) for education. The sex ratio was also different in the KS group from that in the HC (p=0.01) and AUD groups (p=0.04). There was no difference on BMI among the three groups (Table 1).

2.2. Subjective assessment of sleep quality

All participants completed the *Pittsburg Sleep Quality Index* (PSQI; Buysse et al., 1989) during the neuropsychological examination. The PSQI is a 19-item self-assessment questionnaire that allows a measure of sleep quality and disturbances over the last month. Seven components are evaluated ranging from 0 to 3: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The total score ranges from 0 (indicating no difficulty) to 21 (major sleep difficulties). As recommended, a cut-off score of 5 was used to indicate a significant sleep complaint.

Based on the total PSQI score, patients (AUD and KS) were divided into 2 subgroups:

(i) **No-complaint^{AUD+KS} patients** corresponding to patients who did not complain about their sleep (i.e., PSQI score ≤ 5)

(ii) **Complaint^{AUD+KS} patients** corresponding to patients who complained about their sleep (i.e., PSQI score > 5).

2.3. Neuropsychological examination

For *executive functions*, a composite score was created including performance on three tests assessing manipulation of information (verbal backward spans of the WAIS-III (Wechsler, 1997)), inhibition

(Stroop Test (Stroop, 1935), time in seconds needed to complete the interference condition minus time needed for the denomination condition) and mental flexibility (Modified Card Sorting Test (Cianchetti et al., 2005), number of perseverative errors).

Episodic memory was examined through the sum of the five free-recalls of the French version of the California Verbal Learning Test (CVLT ; Van der Linden et al., 2004).

Neuropsychological data were then transformed into z-scores using the mean and standard deviation obtained from the healthy controls. The sign of all variables for which high scores were in the impaired direction (such as completion time or number of errors) were reversed so that all the z-scores had the same direction: the higher the z-score, the better the performance. Thus, all cognitive and motor variables were on the same scale. We computed a global composite score corresponding to the mean of the 3 z-scores (manipulation of information, inhibition and mental flexibility) for executive functions.

This neuropsychological examination showed graded effects of deficits for all evaluated cognitive functions with KS presenting more severe impairments than AUD patients (all p values <0.001, Table 1).

2.4. MRI Data acquisition:

Brain imaging examinations were conducted in 15 HC, 20 AUD and 17 KS patients within the same week as the neuropsychological assessment and the sleep questionnaire.

A high-resolution T1-weighted anatomical image was acquired for each subject on a Philips Achieva 3T scanner using a three-dimensional fast-field echo sequence (sagittal; repetition time, 20 ms; echo time, 4.6 ms; flip angle, 10°; 180 slices; slice thickness: 1mm; field of view, 256 x 256 mm^2; matrix, 256 x 256). Regarding Diffusion Tensor Imaging (DTI), 70 slices (thickness: 2 mm, no gap) were acquired axially using a diffusion weighted imaging spin echo sequence (32 directions at b = 1000 s/mm^2, repetition time = 10000 ms; echo time = 82 ms; flip angle = 90°, field of view = 224 x 224 mm^2, matrix = 112 x 112 and in plane resolution of 2 x 2 mm^2; one no-diffusion weighted image at b = 0 s/mm^2 was also acquired).

2.5. MRI Data processing:

178 The volumetric MRI data were analyzed using the Statistical Parametric Mapping software (SPM12;
179 Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Preprocessing
180 steps included segmentation of the MRI data into gray matter (GM) and spatial normalization to the
181 Montreal Neurological Institute (MNI) template (voxel size = 1.5 mm^3, matrix = 121 x 145 x 121).
182 The normalized GM images were modulated by the Jacobian determinants to correct for non-linear
183 warping only so that the resulting brain volumes were corrected for brain size. The resulting images
184 were smoothed by a Gaussian kernel of 8 mm full-width-at-half-maximum (FWHM). GM volume
185 density reflects cerebral macrostructure and numerically corresponds to the mean gray matter per unit
186 volume for each significant cluster.

187 The diffusion-weighted images (DWI) were first preprocessed to create Fractional Anisotropy (FA)
188 images using the FSL Diffusion Toolbox (FDT; http://fsl.fmrib.ox.ac.uk/fsl/ fslwiki/FDT) that is part
189 of FSL 5.0 toolbox for medical image analysis (Smith et al., 2004). Briefly, for each subject, the 32
190 DWI images were first corrected for distortions due to Eddy currents and aligned to the b=0 s/mm^2
191 image using rigid-body registration for motion correction (Jenkinson et al., 2002). FA images were
192 then created by fitting a tensor model to the diffusion images. Individual FA data were aligned into
193 MNI space using the nonlinear registration tool (FNIRT), which uses a b-spline representation of the
194 registration warp field (Rueckert et al., 1999). The resulting FA maps were resliced to matrix size of
195 182 x 218 x 182 and voxel size of 1 mm^3 and smoothed to 6 mm FWHM prior to voxel-based
196 statistical analyses. Numerically, FA values vary between 0 and 1. Generally, the higher the FA value,
197 the better the microstructural integrity of the fiber within that voxel. FA is assumed to be a structural
198 biomarker that depicts WM disruption involving myelin, cytoskeleton, and the axons' microtubule
199 system (Pfefferbaum et al., 2006).

200 The GM mask was obtained taking the unmodulated GM images of healthy controls (HC) normalized
201 to the MNI space, averaging them and thresholding the resultant mean image at 0.5. The white matter
202 (WM) mask was obtained by taking the FA maps of healthy controls normalized to the MNI space,
203 averaging them and thresholding the resultant mean image at 0.3. The resulting GM and WM masks
204 were applied respectively to GM and WM data analyses.

205 *2.6. Statistical analysis*

206 *2.6.1. Prevalence of sleep complaint in AUD and KS patients*

207 We first described the prevalence, severity and nature of the sleep complaint in the HC, AUD and KS
208 patients using Chi^2 tests and ANCOVAs (age, gender and Body Mass Index (BMI) used as covariates)
209 when appropriate.

210 *2.6.2. Pattern of cognitive alterations according to sleep quality*

211 Then, we pooled the AUD and KS patients together and conducted ANCOVAs (using age, gender and
212 BMI as covariates) followed by *post-hoc* comparisons (Tukey's tests) on neuropsychological data to
213 compare HC, no-complaint^{AUD+KS} and complaint^{AUD+KS} patients.

214 We also investigated whether this effect was driven by the results obtained in a specific clinical group
215 by comparing HC, complaint^{AUD}, no-complaint^{AUD} and no-complaint^{KS} patients using ANCOVAs with
216 age, gender and BMI as covariates. Given the sample size of the complaint^{KS} group (N=3), these
217 patients were not included in the statistical analysis (Table 2).

218 *-Insert Table 2-*

219 *2.6.3. Pattern of brain alterations according to sleep quality*

220 Voxel-based ANCOVAs were conducted in SPM12, with age, gender and BMI as covariates, to
221 compare HC, no-complaint^{AUD+KS} and complaint^{AUD+KS} patients on GM volume and WM integrity (FA
222 values). Results are reported at $p<0.001$ (uncorrected for multiple comparisons) with a minimal cluster
223 size (k) of 60 voxels (200 mm^3).

224 Once again, to ensure that the effect was not only due to the presence of KS patients in the clinical
225 sample, average signal values within significant clusters were extracted and *post hoc* tests (Tukey's
226 tests) were conducted to compare HC, complaint^{AUD}, no-complaint^{AUD} and no-complaint^{KS} patients.
227 Here again, given the sample size of the complaint^{KS} group (N=3), these patients were not included in
228 the statistical analysis.

Significant clusters of GM were labeled using the Harvard-Oxford cortical and subcortical structural atlases implemented in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). WM regions were manually labeled using the MRI Atlas of Human white matter (Oishi et al., 2011).

3. RESULTS

3.1. Prevalence of sleep complaint in AUD and KS patients.

Prevalence of sleep complaint: Based on the PSQI total score, poor sleep quality (PSQI total score > 5) was significantly more frequently reported in AUD patients (70.3 %) than in KS patients (17.6 %) and HC (Table 3, Fig 1).

Severity of sleep complaint: The ANCOVA revealed a significant effect of group on the PSQI total score ($F(2,68)=26,63$; $p<0.0001$; Table 3). AUD patients had higher scores than KS patients ($p<0.0001$) and HC ($p <0.0001$), these two latter groups being comparable ($p = 0.93$).

Nature of sleep complaint: ANCOVAs conducted on each PSQI subcomponent revealed significant effects of group (all F-values are reported in Table 3). Compared to HC, AUD patients reported poor subjective sleep quality ($p<0.004$), longer sleep latency ($p=0.03$) and sleep disturbances ($p=0.001$), more frequent use of sleeping medication ($p=0.03$), altered sleep efficiency ($p=0.01$) and daytime dysfunction ($p<0.03$). No difference was observed between HC and KS patients (all p values >0.05). Compared to KS patients, AUD patients reported significantly poor subjective sleep quality ($p=0.003$), shorter sleep duration ($p=0.005$), sleep disturbances ($p=0.0009$) and daytime dysfunction ($p=0.008$; Table 3).

- Insert Figure 1 and Table 3 –

3.2. Pattern of cognitive alterations according to sleep quality.

3.2.1. HC vs no-complaint^{AUD+KS} patients vs complaint^{AUD+KS} patients

The ANCOVAs revealed significant effects of group (HC vs no-complaint^{AUD+KS} vs complaint^{AUD+KS} patients) for executive ($F(2,68)=7.69$ $p=0.0009$) and episodic memory scores ($F(2,66)=6.21$ $p=0.003$).

Concerning executive functions, *post-hoc* comparisons showed that complaint^{AUD+KS} patients were comparable to HC ($p=0.20$), contrary to no-complaint^{AUD+KS} patients who presented lower executive performance compared to both HC ($p = 0.0001$) and complaint^{AUD+KS} patients ($p = 0.008$; Fig 2A).

For episodic memory, graded effects were observed with no-complaint^{AUD+KS} patients showing lower performance than complaint^{AUD+KS} patients, these latter showing also reduced performance compared to HC (all p values <0.01; Fig 2A).

3.2.2. HC vs complaint^{AUD} patients vs no-complaint^{AUD} patients vs no-complaint^{KS} patients

The ANCOVAs revealed a significant effect of group for executive ($F(3,64)=5.31$ $p=0.002$) and episodic memory scores ($F(3,62)=20.31$ $p<0.0001$).

Concerning executive functions, *post-hoc* comparisons showed that complaint^{AUD} patients presented similar performance as HC ($p=0.51$) and no-complaint^{AUD} patients ($p=0.23$). No-complaint^{AUD} patients and no-complaint^{KS} patients had significantly lower executive performance than HC ($p=0.02$ and $p=0.001$ respectively), but did not differ from each other ($p=0.94$; Fig 2B).

Regarding episodic memory, *post-hoc* comparisons showed that no-complaint^{AUD} patients and complaint^{AUD} patients presented similar performance as HC ($p=0.47$ and $p=0.05$ respectively) and did not differ from each other ($p=0.92$). No-complaint^{KS} patients performed significantly lower than the three other groups ($p=0.0001$ for all comparisons; Fig 2B).

- Insert Figure 2 –

3.3. Pattern of brain alterations according to sleep quality.

3.3.1. Gray-matter volume

Compared to HC, no-complaint^{AUD+KS} patients had significantly lower GM volume in frontal and prefrontal areas, insula, lateral and medial temporal cortices (including the hippocampus and parahippocampal gyrus), cingulate and occipital cortices, but also in subcortical regions including the thalamus, putamen and caudate nuclei, and in the cerebellum ($p<0.001$, uncorrected, $k=60$). These results remained significant after correction for multiple comparisons but with smaller cluster size (Family Wise Error (FWE), $p<0.05$; Fig 3A).

Compared to HC, complaint^{AUD+KS} patients had lower GM volume in frontal and prefrontal areas, insula, lateral and medial cortices (including the hippocampus and parahippocampus gyrus), cingulate and occipital cortices, but also in subcortical regions including the thalamus, putamen and caudate

nuclei, and in the cerebellum ($p < 0.001$, uncorrected, $k=60$). After correction for multiple comparisons, only the bilateral precentral gyrus (clusters encompass the postcentral gyrus), the right insula, the bilateral lingual gyrus, the bilateral cuneus and the left thalamus remained significant (FWE, $p<0.05$; Fig 3B).

- Insert Figure 3 -

As shown in Figure 4A, compared to complaint^{AUD+KS} patients, no-complaint^{AUD+KS} patients had significantly lower GM volume in frontal and prefrontal areas (including the right middle frontal gyrus, the median frontal gyrus, bilateral precentral gyrus, bilateral inferior frontal gyrus, left superior frontal gyrus), middle cingulate gyrus, bilateral precuneus, the temporal pole, the occipital gyrus and the left thalamus ($p<0.001$ uncorrected, $k=60$). These results did not remain significant after correction for multiple comparisons. The reverse comparison did not reveal any significant difference.

From this comparison (complaint^{AUD+KS} patients > no-complaint^{AUD+KS} patients), signal values within each cluster were extracted and compared between the different subgroups (HC, complaint^{AUD} patients, no-complaint^{AUD} patients and no-complaint^{KS} patients).

Compared to HC, no-complaint^{AUD} patients and no-complaint^{KS} patients showed significantly lower values for all extracted clusters ($p<0.001$). Compared to HC, complaint^{AUD} patients presented significantly lower GM volume in all clusters except in the medial prefrontal cortex ($p=0.06$). Compared to complaint^{AUD} patients, no-complaint^{AUD} patients exhibited lower values only for the middle frontal gyrus ($p=0.002$), the inferior frontal gyrus ($p=0.02$), the superior frontal gyrus ($p=0.03$), the temporal pole ($p=0.02$) and the occipital cortex ($p=0.003$). Compared to complaint^{AUD} patients, no-complaint^{KS} patients exhibited significant GM atrophy for all extracted clusters (all p values <0.05). No difference was observed between no-complaint^{AUD} patients and no-complaint^{KS} ($p>0.05$; Fig 4B).

Partial Pearson's correlations adjusted for age, sex and BMI were conducted in the two groups of patients pooled together (no-complaint^{AUD+KS} patients vs complaint^{AUD+KS} patients) between regional volumes in all extracted clusters on the one hand and neuropsychological performance on the other hand. We found significant relationships only between the thalamus ($r=0.61$, $p=0.005$), the temporal pole ($r=0.52$, $p=0.02$), the lingual gyrus ($r=0.47$, $p=0.04$) and episodic memory results as well as

between the volume in the middle frontal and precentral gyri and the executive performance (r=0.60, p=0.006; r=0.50, p=0.02 respectively) in no-complaint^{AUD+KS} patients. There was no significant correlation in the complaint^{AUD+KS} patients between cerebral volume and cognitive functions.

- Insert Figure 4 -

3.3.2. White-Matter integrity

Compared to HC, no-complaint^{AUD+KS} patients had significantly lower FA values, indicating an alteration of WM, in a large set of fibers including the corpus callosum, the anterior corona radiata, the anterior limb of the internal capsule, the cingulum, the middle cerebellar peduncle and the fornix. These results remained significant after correction for multiple comparisons but with smaller cluster size (FWE, $p<0.05$; Fig 3C).

The same pattern of white matter abnormalities was observed in complaint^{AUD+KS} patients compared with HC. These results did not remain significant after correction for multiple comparisons (Fig 3D).

As shown in Figure 5A, compared to complaint^{AUD+KS} patients, no-complaint^{AUD+KS} patients had significantly lower FA values in the anterior and superior parts of the corana radiata, the bilateral cingulum, the inferior and superior parts of the longitudinal fasciculus, the right fornix (encompassing the cerebral peduncle and the internal capsule), the bilateral external capsule, the left anterior thalamic radiation, and the white matter within the post-central gyrus, the angular gyrus, the superior frontal gyrus and the precuneus ($p<0.001$, uncorrected, $k=60$). These results did not remain significant after correction for multiple comparisons. The reverse comparison did not reveal any significant difference.

From this comparison (complaint^{AUD+KS} patients > no-complaint^{AUD+KS} patients), signal values were extracted within each significant cluster and compared between subgroups (HC, complaint^{AUD} patients, no-complaint^{AUD} patients and no-complaint^{KS} patients). Compared to HC, i) complaint^{AUD} patients presented lower FA values in the anterior thalamic radiation ($p=0.008$); ii) no-complaint^{AUD} patients exhibited lower FA values in all extracted clusters $p<0.01$, except for the white matter in the post-central gyrus ($p=0.74$) and the superior longitudinal fasciculus ($p=0.07$); and iii) no-complaint^{KS} patients showed lower FA values in all clusters ($p<0.001$). Compared to complaint^{AUD} patients, no-complaint^{AUD} patients presented lower FA values in all extracted clusters except in the left anterior

thalamic radiation (p=0.08), the external capsule (p=0.22) and the white matter of the supramarginal gyrus (p=0.06), the precuneus (p=0.06) and the postcentral gyrus (p=0.39). No difference was found between no-complaint^{AUD} patients and no-complaint^{KS} patients (Fig 5B).

Partial Pearson's correlations adjusted for age, sex and BMI were conducted in the two groups of patients pooled together (no-complaint^{AUD+KS} patients vs complaint^{AUD+KS} patients) between regional FA values in all extracted clusters on the one hand and neuropsychological performance on the other hand.

In complaint^{AUD+KS} patients, we found significant relationships between FA values of the WM part of the angular gyrus and episodic memory performance (r=0.69, p=0.02). In no-complaint^{AUD+KS} patients, we found significant relationships between the anterior thalamic radiation (r=0.62, p=0.008), the external capsule (r=0.60, p=0.01), the inferior longitudinal fasciculus (r=0,50, p=0.04), the bilateral cingulum (r=0.72, p=0.001), the anterior corona radiata (r=0.61, p=0.009) and executive functions. We also showed significant relationships between the bilateral cingulum (r=0.60, p=0.01), the superior longitudinal fasciculus (r=0.52, p=0.03) and episodic memory.

- Insert Figure 5 -

4. DISCUSSION

The aim of the present study was to investigate, in recently detoxified AUD and KS patients, whether self-estimated sleep quality is related to cognitive functioning and brain integrity.

First, in agreement with previous studies, we observed a high prevalence of sleep complaint in recently detoxified AUD patients (Angarita et al., 2016; Chakravorty et al., 2016). We showed that, compared to HC, AUD patients with sleep complaint present a pattern of macrostructural brain damage in frontal and temporal cortices, as well as cingulate gyrus and thalamus, known to be affected by heavy and chronic alcohol consumption (Zahr, 2014). Interestingly, all these regions are involved in the generation and maintenance of both NREM and REM sleep rhythms (Maquet et al., 1996; Massimini et al., 2004; Murphy et al., 2009; Schabus et al., 2007). Moreover, reduced GM volume in the frontal cortex have been related to higher sleep complaint (Sexton et al., 2014). AUD patients with sleep complaint also had lower FA values in the anterior thalamic radiation, in accordance with a recent study showing that altered WM tracts were associated with higher sleep complaint in older adults (Sexton et al., 2017). Thus, in this group of patients who complain about their sleep, poor self-rated sleep quality may be related to the objective sleep alterations expected given their pattern of brain dysfunction (Chakravorty et al., 2016).

Our study showed that most of the KS patients (14 out of 17) reported sleeping as well as healthy controls. To the best of our knowledge, our study is the first to investigate, in KS patients, sleep complaint using a validated and widely used sleep questionnaire (Buysse et al., 1989) in KS patients. Our findings are not in accordance with polysomnography studies showing objective sleep alterations in KS patients (Martin et al., 1986), highlighting the frequent discrepancies between self-perception and objective sleep measurements reported in AUD (Angarita et al., 2016), as also frequently reported in aging (Nguyen-Michel et al., 2015; Van Den Berg et al., 2008) and neurodegenerative diseases (Hita-Yañez et al., 2013; Most et al., 2012). The rarity of sleep complaint in KS patients is in agreement with their "without complaints appearance" (Walvoort et al., 2016) and may be explained by their cognitive deficits and/or impaired insight that affect their ability to recognize and report problems in self-evaluation questionnaires (Arts et al., 2017; Walvoort et al., 2016). Anosognosia is indeed a specific clinical feature of KS and reflects the most severe form of impaired self-awareness,

defined as the inability to accurately estimate one's functional capacity (Prigatano, 2009). It is frequently observed in amnesic patients with associated executive dysfunction (Arts et al., 2017; Shimamura and Squire, 1986).

Some of the recently detoxified AUD patients presented a profile of executive dysfunction as well as macrostructural and microstructural brain abnormalities similar to those observed in KS patients. These patients with severe brain dysfunction, sometimes considered at risk of developing KS (Pitel et al., 2012, 2007; Segobin et al., 2015), did not complain about their sleep. Compared to AUD patients with sleep complaint, these patients presented more severe alterations in fronto-temporal regions and specific damage in the frontal-subcortical tracts. Besides, executive impairments were not found in AUD patients with sleep complaint. These findings suggest a key role of the fronto-temporal network and executive functions in subjective assessment of sleep quality. The evaluation of sleep quality using the PSQI is a complex cognitive task that requires a self-interpretation of internal and physical states, which in turn implies having efficient executive functions to judge both sleep quantity (includes evaluating parameters like total sleep time, sleep latency, number of awakenings, among others) and subjective aspects of sleep quality such as feeling tired or daytime sleepiness (Buysse et al., 1989). Executive impairments result in self-awareness deficits (Goldstein et al., 2009) related to damage within the frontal cortex, especially the dorsolateral (Schmitz, Kawahara-Baccus, & Johnson, 2004; Shany-Ur et al., 2014) and medial parts of the prefrontal cortex (Fleming & Dolan, 2012; Schmitz & Johnson, 2007). Previous studies have reported altered self-awareness in AUD patients, who tend to underestimate their daily alcohol consumption (Lincoln et al., 2011) and cognitive deficits (Kornreich, 2002; Le Berre et al., 2010; Walvoort et al., 2016). In the present study, AUD patients with executive dysfunction and lower gray matter volume in the dorsolateral and medial parts of the prefrontal cortex as well as lower WM integrity in fibers connecting fronto-subcortical regions may thus not be cognitively able to accurately estimate their sleep. It is also worth noting that the group of AUD patients without sleep complaint is highly heterogeneous (figure 2B) and potentially consisted of two sub-groups of patients: one that would be similar to HC or complaint AUD regarding brain structure and function while the other would be similar to KS patients (Parsons, 1998; Pitel et al., 2012, 2007;

Segobin et al., 2015). The complaint AUD group is more homogeneous since it mainly includes patients with preserved performance and brain measures.

The thalamus has been shown to play a crucial role in self-awareness (Shany-Ur et al., 2014) and may also be implicated in self-reported sleep quality. This subcortical structure is known to be affected by chronic and excessive alcohol consumption, with graded effects in thalamic volume from AUD to KS patients (Pitel et al., 2012). Interestingly, while AUD patients with sleep complaint have thalamic volumes significantly different from those of KS patients, the thalamic shrinkage in patients without sleep complaint is similar to that of KS patients. The thalamus being a key node of the Papez circuit involved in episodic memory, one would expect AUD patients without sleep complaint to perform on par with KS patients on the episodic memory task. Conversely, in line with the diagnosis, KS patients were impaired in episodic memory compared with both HC and the two subgroups of AUD, who did not differ from each other. Taken together, these findings suggest that the contribution of the thalamus in self-reported sleep quality may not be related to the involvement of episodic memory abilities, contrary to our hypothesis. Rather, several subcortical regions, including the thalamus, "*subserve transforming lower-level interoceptive bodily sensations and representations of self into higher-level self-referential mental representations*" (Shany-Ur et al., 2014). AUD patients with severe thalamic abnormalities may be unable to accurately perceive and update current physical states, resulting in the absence of sleep complaint.

One potential limitation of the present study is the absence of objective sleep measures by polysomnography, generally not available in clinical practice. Even though it was not the objective of the present study, it would allow determining whether patients without sleep complaint do present objective sleep disturbances. Further studies combining both objective and subjective sleep measures as well as neuropsychological and multimodal neuroimaging examinations are under way to confirm the proposed cognitive and brain mechanisms underlying sleep perception in AUD and KS patients.

5. CONCLUSION

Taken together, our data contribute to a better understanding of self-reported sleep quality in recently detoxified AUD patients, by incorporating new insights from neuropsychological and neuroimaging

examinations. Given the high prevalence of sleep complaint in AUD patients (Angarita et al., 2016; Chakravorty et al., 2016), the use of a sleep questionnaire in clinical practice should not be abandoned since it reflects the subjective perception of mental states and feelings on which most alcohol treatments are proposed. However, sleep questionnaires should be employed and interpreted with caution with AUD patients presenting executive dysfunction. A neuropsychological assessment of alcohol-related cognitive deficits is thus a crucial step in the treatment of AUD patients early in abstinence. In patients who are cognitively unable to complain, sleep problems would be neglected under a clinical setting and therefore remain untreated. Such a situation would worsen sleep-related clinical consequences in AUD such as increased mood disturbances (Zhabenko et al., 2012), impair their overall quality of life and likely trigger relapse (Brower, 2003), hence defeating the purpose of their initial treatment.

6. ACKNOWLEDGMENTS

The authors are grateful to the Cyceron MRI staff members for their help with patients and imaging examination acquisition, Claire André, Nicolas Cabé and Angéline Maillard for their helpful comments on the manuscript. We would also like to thank all the participants for their implication in this study.

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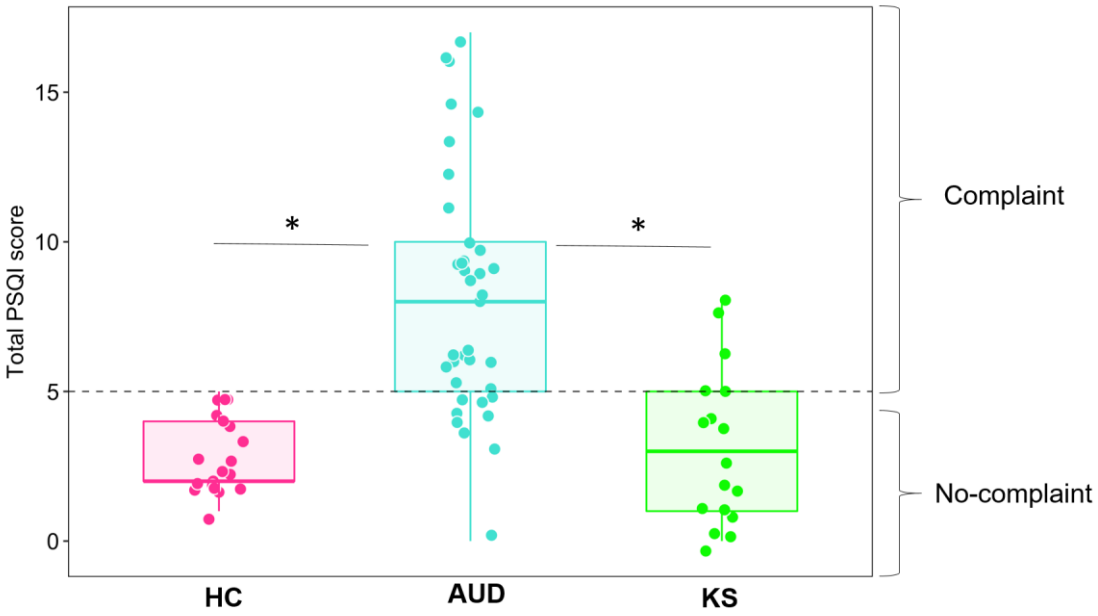
582 *8.* FIGURE LEGENDS:



583

584 **Figure 1: Prevalence of sleep complaint in HC, AUD and KS patients**

585 The dotted line represents the cut-off score (5) of the PSQI, which indicates the presence of a sleep
586 complaint. For each boxplot, the median is represented by the bold line. HC = healthy controls; AUD
587 = patients with Alcohol Use Disorder without Korsakoff's syndrome; KS = patients with Alcohol Use
588 Disorder with Korsakoff 's Syndrome. *:$p<0.05$ (Tukey's tests).

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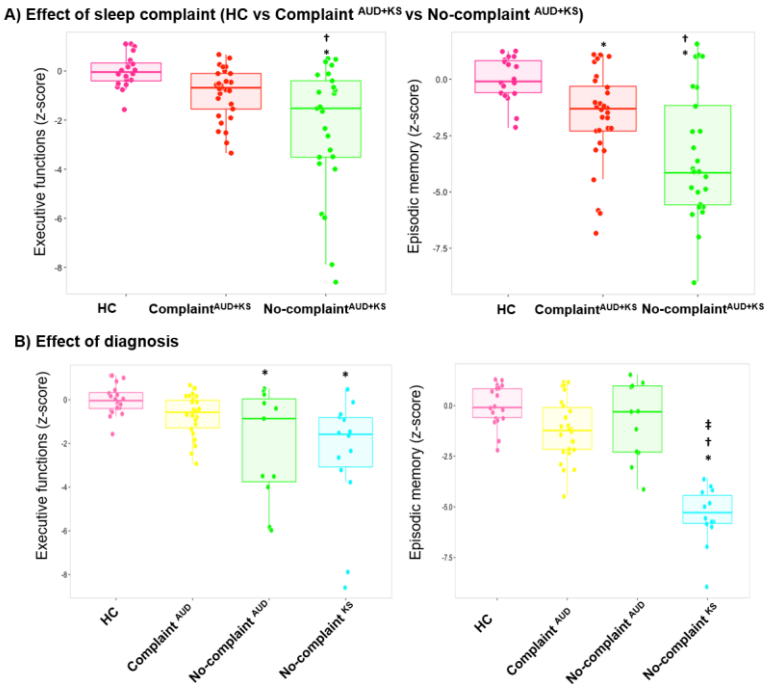

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593 **<u>Figure 2:</u> Executive and episodic memory performance in controls and patients according to the**

594 **sleep complaint (A) and diagnosis (B)**

595 This figure shows executive (left) and memory (right) z-scores. * : significant difference compared to

596 HC ($p<.05$); † : significant difference compared to complaint^{AUD} ($p<.05$); ‡ : significant difference

597 compared to no-complaint^{AUD} ($p<.05$). Tukey's tests.

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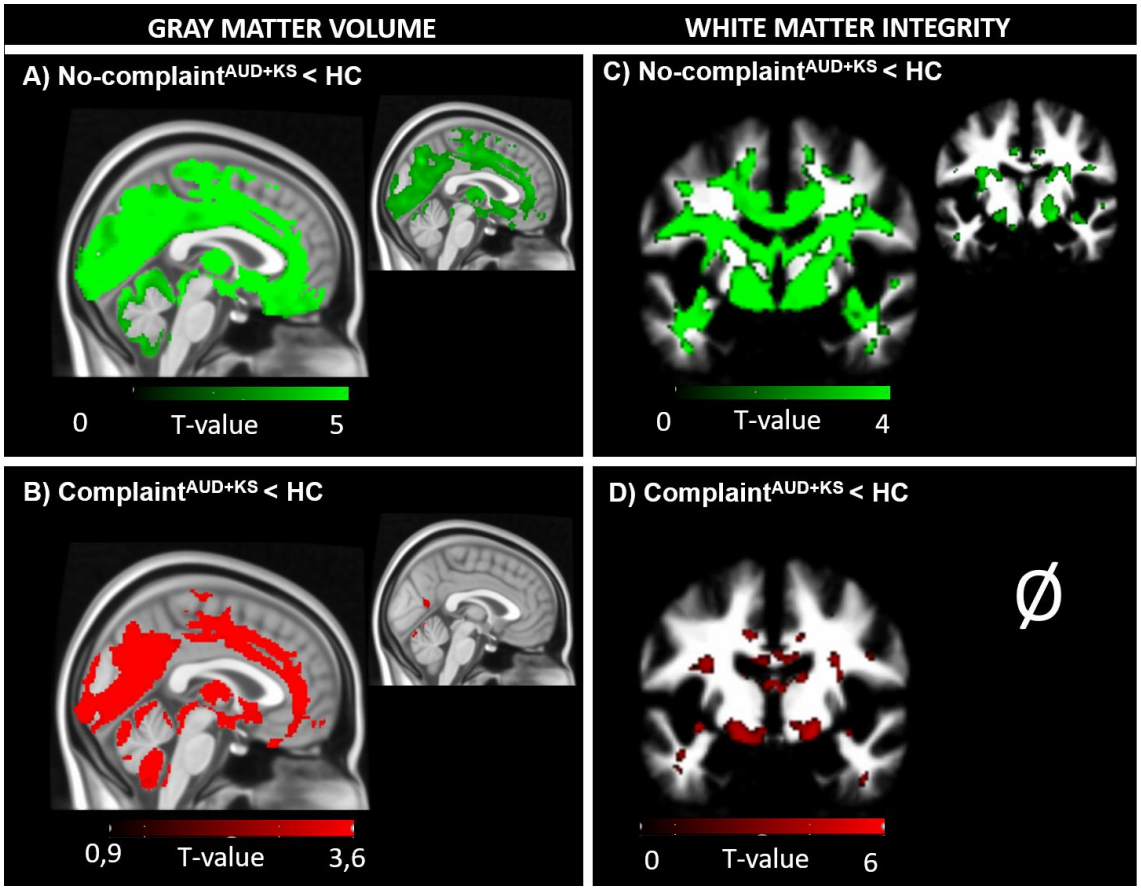
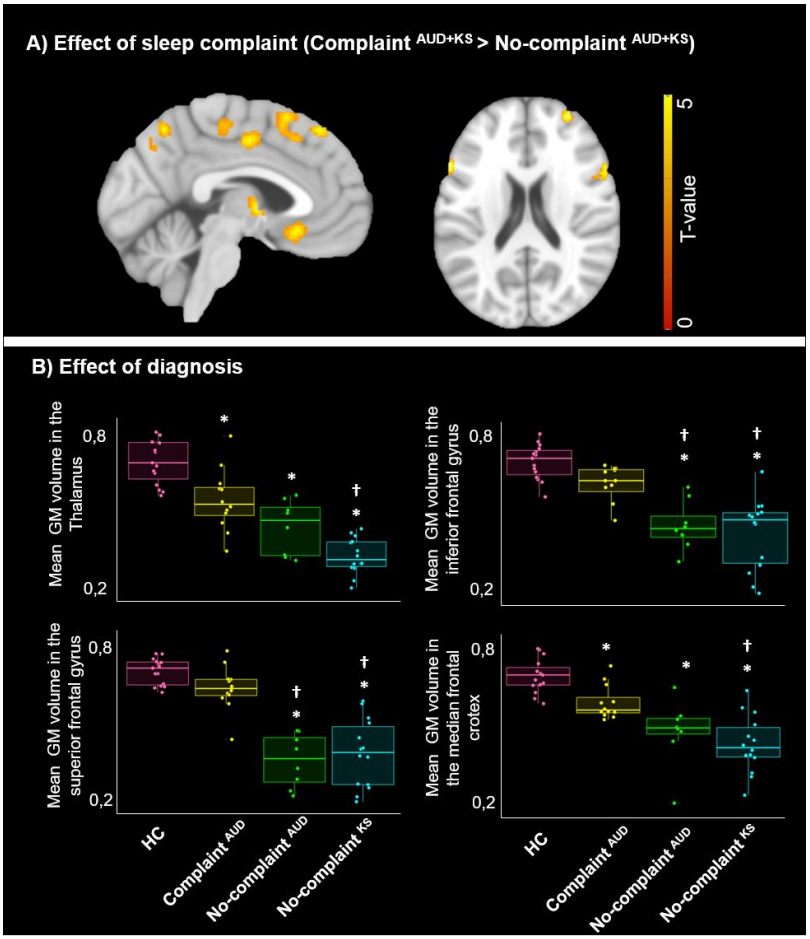


Figure 3: Structural brain abnormalities in patients with and without sleep complaint compared with controls

A: Lower gray matter volumes (left) and altered white matter integrity (right) in no-complaint^{AUD+KS} compared to HC. B: Lower gray matter volumes (left) and altered white matter integrity (right) in complaint^{AUD+KS} compared to HC. We used a p value cutoff of $p<0.001$ uncorrected (larger images) but also display the results using a restrictive $p<0.05$ corrected for family-wise error (smaller images) to highlight the most significant regions. For D) No significant results at $p<0.05$ FWE. Cluster size: >60 voxels.



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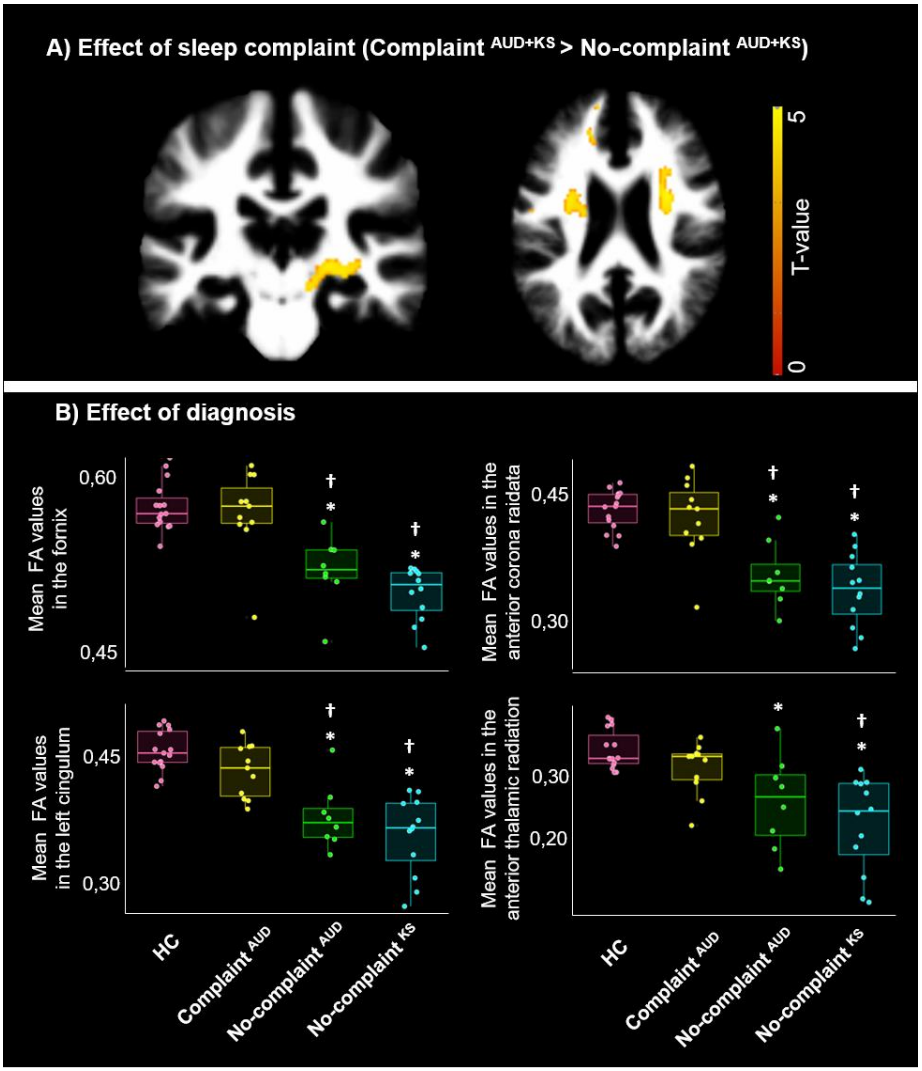
612 **<u>Figure 4:</u> Gray matter volume in controls and patients according to the sleep complaint (A) and**

613 **diagnosis (B)**

614 A: voxel by voxel analysis, p<0.001 uncorrected, k=60. B: example of regions of interest extracted

615 from the previous analysis. * : significant difference compared to HC (p<.05) ; † : significant

616 difference compared to complaint^{AUD} (p<.05) . Tukey's tests.



<u>Figure 5:</u> White matter integrity in controls and patients according to the sleep complaint (A) and diagnosis (B)

A: voxel by voxel analysis, p<0.001 uncorrected, k=60. B. example of regions of interest extracted from the previous analysis. *: significant difference compared to HC (p<.05); †: significant difference compared to complaint^{AUD} (p<.05). Tukey's test

9. TABLES

TABLE 1: DEMOGRAPHICAL AND CLINICAL DESCRIPTION OF THE HEALTHY CONTROLS (HC), ALCOHOL USE DISORDER PATIENTS WITHOUT KORSAKOFF'S SYNDROME (AUD) AND ALCOHOL USE DISORDER PATIENTS WITH KORSAKOFF'S SYNDROME (KS

	HC (N=20)	AUD (N=37)	KS (N=17)	Post-hoc comparisons
Age	42.50±5.94 [31;53]	45.59±9.21 [32;65]	56.41±4.79 [49;67]	(HC = AUD) > KS
Gender. male %	80%	70.3%	41.2%	(HC = AUD) > KS
Education (years of schooling)	12.20±2.01 [9 ;15]	11.43±1.57 [9 ;15]	10.65±2.34 [8 ;15]	HC = AUD ; HC > KS ; AUD = KS
BMI	26.53±6.73 [19.53 ;48.88]	24.23±4.61 [16.02 ;39.84]	23.77±5.45 [15.94 ;35.42]	HC = AUD = KS
BDI	3.25±3.47 [0 ;14]	13.11±7.64 [2 ;28]	7.05±6.33 [0 ;19]	(HC = KS) < AUD
STAI A	26.05±6.68 [20 ;47]	32.32±35 [20 ;61]	35±13.99 [20 ;66]	HC = AUD = KS
STAI B	32.80±7.59 [20 ;50]	44.22±12.47 [28 ;72]	38.67±10.03 [24 ;57]	HC < AUD ; HC = KS ; AUD = KS
AUDIT	2.7±1.92 [0 ;6]	28.92±6.22 [9 ;40]	NA	HC < AUD
Alcohol use (years)	/	15.30±4.06 [7 ;32]	NA	/
Alcohol misuse (number of years)	/	16.54±8.34 [2 ;34]	NA	/
Alcohol dependence (number of years)	/	8.65±7.73 [0 ;34]	NA	/
Daily alcohol consumption (units[a])	/	18.49±8.82 [0-39.4]	NA	/
Number of previous detoxifications	/	2.64±2.21 [0 ;11]	NA	/
Maximum Cushman score	/	5.33±2.42 [0 ;11]	NA	/
Days of sobriety before inclusion	/	10.5±3.99 [4 ;21]	NA	/
Mini Mental State Examination (MMSE) (/30)	29.22±0.73 [28 ;30]	27.17±2.15 [21 ;30]	22.59±3.75 [12 ;27]	HC > AUD > KS
Executive Functions (z-scores)	0±0.68 [-1.57 ;1.10]	-1.14±1.66 [-5.98 ;0.67]	-2.46±2.48 [-8.6 ;0.48]	HC > AUD > KS
Episodic Memory (z-scores)	0±1 [-2.15;1.25]	-0.97±1.57 [-4.43;1.54]	-5.33±0.99 [-6.99;-3.57]	HC > AUD > KS

TABLE 2: DESCRIPTIVE STATISTICS IN THE DIFFERENT SUBGROUPS ACCORDING TO THE SLEEP COMPLAINT

	HC	No-complaint			Complaint		
	n=20	**No-Complaint^{AUD+KS}** ***n=25***	**No-Complaint^{AUD}** ***n=11***	**No-Complaint^{KS}** ***n=13***	**Complaint^{AUD+KS}** ***n=29***	**Complaint^{AUD}** ***n=26***	**Complaint^{KS}** ***n=3***
Age (years)	42.50 ± 5.94 [31-53]	50.68 ± 9.55 [34-67]	42.73 ± 8.16 [34-61]	56.93 ± 4.66 [49-67]	47.55 ± 9.37 [32-65]	46.81 ± 9.51 [32-65]	54 ± 5.57 [49-0]
Gender. male %	80%	60%	81.81%	42.85%	62.06%	65.38%	33.3%
Education (years)	12.20 ± 2.01 [9-15]	11.4 ± 2.08 [8-15]	11.78 ± 1.64 [9-14]	10.93 ± 2.33 [8-15]	11.00 ± 1.66 [8-15]	11.32 ±1 .56 [9-15]	9.33 ± 2.3 [8-12]
BMI	26.53 ± 6.73 [19.53-48.88]	24.16 ± 4.63 [15.94-35.42]	24.07 ± 2.7 [19.23-29.97]	23.89 ± 5.85 [15.94-35.42]	24.161 ± 5.09 [16.02-39.84]	24.30 ± 5.26 [16.02-39.84]	23.24 ± 6.73 [19.53-46.88]
BDI	3.25 ± 3.47 [0-14]	9.4 ± 8.11 [0-27]	14.73 ± 8.17 [4-27]	5.21 ± 5.22 [0-15]	12.75 ± 7.16 [2-28]	12.42 ± 7.46 [2-28]	15.67 ± 3.05 [13-19]
STAI A	26.05 ± 6.68 [20-47]	32 ± 11.99 [20-59]	33.09 ± 13.44 [20-59]	31 ± 11 [20-55]	33.96 ± 12.37 [20-66]	32.00 ± 10.71 [20-61]	51.00 ± 15.00 [36-66]
STAI B	32.80 ± 7.59 [20-50]	39.65 ± 10.65 [24-59]	43.73 ± 11.31 [28-59]	35.92 ± 8.87 [24-50]	44.96 ± 12.64 [28-72]	44.42 ± 13.13 [28-72]	49.67 ± 6.65 [44-57]
AUDIT	2.7 ± 1.92 [0-;6]	/	26.64 ± 8.23 [9-39]	/	/	29.92±4.97 [16-40]	/
Alcohol use (years)	/	NA	14.36 ± 2.61 [10-19]	NA	NA	15.69±4.53 [7-32]	NA
Alcohol misuse (number of years)	/	NA	18.27 ± 7.65 [6-26]	NA	NA	15.81±8.65 [2-34]	NA
Alcohol dependence (number of years)	/	NA	9.72 ± 7.79 [2-26]	NA	NA	8.16±7.82 [0-34]	NA
Daily alcohol consumption (units)	/	NA	19.03 ± 8.69 [0-30]	NA	NA	18.23±9.07 [2-39.40]	NA
Number of previous detoxifications	/	NA	3.81 ± 3.21 [0-11]	NA	NA	2.15±1.43 [0-6]	NA
Maximum Cushman score	/	NA	5.9±1.91 [3-9]	NA	NA	5.11±2.59 [0-11]	NA
Days of sobriety before inclusion	/	NA	13.55±4.15 [7-21]	NA	NA	9.16±3.15 [4-15]	NA

TABLE 3: PREVALENCE, SEVERITY AND NATURE OF THE SLEEP COMPLAINT ON THE PSQI IN HEALTHY CONTROLS (HC), ALCOHOL USE DISORDER PATIENTS WITHOUT KORSAKOFF'S SYNDROME (AUD) AND ALCOHOL USE DISORDER PATIENTS WITH KORSAKOFF'S SYNDROME (KS).

	HC	AUD	KS	Statistics[a]	Post hoc comparisons[b]
Total score (0 to 21)					
Prevalence (PSQI >5)	0%	70% (N=26)	17% (N=3)	$X^2 = 31.19$ p<0.0001	AUD > KS = HC
Severity	3 ± 1.21 [1-5]	8.32 ± 3.97 [0-17]	3.35 ± 2.80 [0-9]	F(2.68)=26.63 p<0.0001	AUD > KS = HC
Subcomponents (0 to 3)					
Subjective sleep quality	0.6 ± 0.5 [0-1]	1.35 ± 0.85 [0-3]	0.52 ± 0.51 [0-1]	F(2.68)=10.98 p<0.0001	HC = KS > AUD
Sleep latency	0.6 ± 0.68 [0-2]	1.32 ± 0.94 [0-3]	0.76 ± 1.03 [0-3]	F(2.68)=5.30 p=0.007	HC = KS ; HC < AUD ; AUD = KS
Sleep duration	0.6 ± 0.82 [0-3]	1.21 ± 1.05 [0-3]	0.11 ± 0.33 [0-1]	F(2.68)=8.75p=0.0004	HC = KS; HC = AUD; KS > AUD
Habitual sleep efficiency	0.05 ± 0.22 [0-1]	0.70 ± 1.10 [0-3]	0.29 ± 0.58 [0-2]	F(2.68)=10.55 p<0.0001	HC = KS ; HC < AUD; AUD= KS
Sleep disturbances	0.85 ± 0.36 [0-1]	1.64 ± 0.78 [0-3]	0.76 ± 0.56 [0-2]	F(2.68)=13.48 p<0.0001	HC = KS > AUD
Use of sleeping medication	0.05 ± 0.22 [0-1]	0.97 ± 1.38 [0-3]	0.52 ± 1.17 [0-3]	F(2.68)=4.36 p=0.01	HC = KS ; HC < AUD; AUD = KS
Daytime dysfunction	0.25 ± 0.44 [0-1]	1.10 ± 0.77 [0-3]	0.35 ± 0.78 [0-3]	F(2.68)=10.99 p<0.0001	HC = KS > AUD
Quantitative data					
Sleep duration (min)	447±49.53 [360-510]	397.02±107.37 [180-660]	499.41±71.10 [420-720]	F(2,68)=7.57 p=0.001	HC = KS; HC = AUD; KS > AUD
Sleep latency (min)	14.75±9.38 [5-30]	26.27±25.88 [0-120]	22.5±15.76 [7.5-60]	F(2,68)=3.76 p=0.03	HC = AUD = KS
Sleep efficiency (%)	94.61±5.33 [82.35-100]	84.24±16.58 [36.36-100]	90.67±7.59 [77.77-100]	F(2,68)=8.22 p=0.0006	HC = KS; HC > AUD; AUD = KS

TABLE LEGENDS

Table 1: Demographical and clinical description of the healthy controls (HC), alcohol use disorder patients without Korsakoff's syndrome (AUD) and alcohol use disorder patients with Korsakoff's syndrome (KS).

Mean ± Standard Deviation and range [minimum; maximum] are reported. BMI= Body Mass Index; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; AUDIT = Alcohol Use Disorders Identification Test. NA: not available ; [a]: an alcohol unit = 10g of pure ethanol

Table 2: Descriptive Statistics in the different subgroups according to the sleep complaint

Mean ± Standard Deviation and range [minimum; maximum] are reported. BMI= Body Mass Index; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; AUDIT = Alcohol Use Disorders Identification Test. NA: not available ; [a]: an alcohol unit = 10g of pure ethanol

Table 3: Prevalence, severity and nature of the sleep complaint on the PSQI in healthy controls (HC), alcohol use disorder patients without Korsakoff's syndrome (AUD) and alcohol use disorder patients with Korsakoff's syndrome (KS).

The prevalence of sleep complaint corresponded to the proportion of participants in each group (HC, AUD, KS) with a PSQI total score > 5 which is a validated cut-off score indicating poor sleep quality. The severity of sleep complaint corresponded to the mean PSQI total score for each group (HC, AUD, KS) which is to the sum of the seven PSQI subcomponents, ranging from 0 (no sleep complaint) to 21 (major sleep disturbances). Each PSQI subcomponent score ranged from 0 (good) to 3 (poor). For PSQI continuous variables, short sleep duration and low sleep efficiency correspond to higher component scores. [a]: Data were analyzed using ANCOVAs adjusted for age, sex and body mass index (BMI), except for the frequency of sleep complaint for which we used a Chi^2 test. [b]: Between-groups comparisons were performed with Tukey's tests corrected for unequal sample size. Mean ± Standard Deviation and range [minimum-maximum] are reported.