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

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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

58 1. INTRODUCTION

59 Alcohol-related neurological disorders exist principally in two clinical forms that can be distinguished
60 based on the severity of brain dysfunction (Zahr, 2014) and cognitive deficits (Oscar-Berman et al.,
61 2014). The more severe clinical form is the Korsakoff's syndrome (KS), which is a neurological
62 complication related to the combination of chronic and excessive alcohol consumption and thiamine
63 deficiency. KS is described as a severe and profound amnesia potentially associated with executive
64 dysfunction. Alcohol Use Disorder without KS (AUD) is also characterized by episodic memory
65 deficits and executive dysfunction, from mild to moderate in most cases up to severe in some patients
66 at risk for KS (Pitel et al., 2008).

67 Chronic and heavy alcohol consumption is not only associated with neuropsychological impairments
68 but also with major sleep disorders. Sleep disturbances are frequently present in recently detoxified
69 AUD patients (Angarita et al., 2016) with a variable sleep complaint reported by 36 to 72% of the
70 population. Such variability can be explained by the AUD patients' clinical features (the criteria used
71 to diagnose AUD or alcohol abuse, the length of sobriety at the time of the sleep assessment), as well
72 as the absence of standard definitions and measurements of sleep complaint (different sleep
73 questionnaires with, for example, different time frames; Brower, 2001; Stein and Friedmann, 2005).
74 While objective sleep quality seems affected in KS patients (Lairie and Pottier, 1979; Martin et al.,
75 1986), only one study considered their subjective sleep perception (Lairie and Pottier, 1979) and
76 suggested that KS patients would report sleeping well. This seemingly absent sleep complaint in KS
77 patients may be related to their characteristic impaired self-awareness (Arts et al., 2017).

78 Even in absence of KS, altered abilities to accurately self-evaluate have been described in AUD
79 patients regarding neuropsychological performance (overall cognitive abilities, episodic memory
80 decoding of facial emotions) and daily recall of alcohol consumption (Kornreich, 2002; Le Berre et al.,
81 2010; Lincoln et al., 2011; Rinn et al., 2002; Walvoort et al., 2016). The variability in the sleep
82 complaint prevalence observed in AUD patients may thus be related to their ability to self-assess their
83 sleep quality. Indeed, an accurate subjective sleep evaluation requires efficient episodic memory
84 abilities to recall recent sleep periods and executive functions to interpret internal and physical states,
85 to quantify sleep duration and to respond to a written sleep questionnaire. AUD patients with episodic

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

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

97

98 2. MATERIALS AND METHODS

99 *2.1. Participants*

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

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

115 KS were recruited as inpatients at Caen University Hospital (n=9) and in a nursing home (Maison
116 Vauban, Roubaix, France; n=8). All KS patients were diagnosed with reference to the clinical DSM-
117 IV criteria of ''amnesia due to substance abuse'' and "major neurocognitive disorders, confabulatory
118 type, persistent" according to the DSM-5. All KS patients had a history of heavy drinking, but it was
119 difficult to obtain accurate information about their alcohol intake due to their amnesia. The case of
120 each patient was examined by a multidisciplinary team made up of specialists in cognitive
121 neuropsychology and behavioural neurology. A detailed neuropsychological examination enabled the
122 diagnosis of all KS patients presenting disproportionately severe episodic memory disorders compared
123 to other cognitive functions (Table 1). Clinical and neuroimaging investigations ruled out other
124 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).

233 *3.* RESULTS

234 *3.1. Prevalence of sleep complaint in AUD and KS patients.*

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

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

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

249 *- Insert Figure 1 and Table 3 –*

250 *3.2. Pattern of cognitive alterations according to sleep quality.*

251 *3.2.1. HC vs no-complaint^{AUD+KS} patients vs complaint^{AUD+KS} patients*

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

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

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

260 *3.2.2. HC vs complaint^{AUD} patients vs no-complaint^{AUD} patients vs no-complaint^{KS} patients*

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

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

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

271 *- Insert Figure 2 –*

272 *3.3. Pattern of brain alterations according to sleep quality.*

273 *3.3.1. Gray-matter volume*

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

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

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

287 *- Insert Figure 3 -*

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

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

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

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

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

313 *- Insert Figure 4 -*

314 *3.3.2. White-Matter integrity*

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

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

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

329 From this comparison (complaint^{AUD+KS} patients > no-complaint^{AUD+KS} patients), signal values were
330 extracted within each significant cluster and compared between subgroups (HC, complaint^{AUD} patients,
331 no-complaint^{AUD} patients and no-complaint^{KS} patients). Compared to HC, i) complaint^{AUD} patients
332 presented lower FA values in the anterior thalamic radiation (p=0.008); ii) no-complaint^{AUD} patients
333 exhibited lower FA values in all extracted clusters p<0.01, except for the white matter in the post-
334 central gyrus (p=0.74) and the superior longitudinal fasciculus (p=0.07); and iii) no-complaint^{KS}
335 patients showed lower FA values in all clusters (p<0.001). Compared to complaint^{AUD} patients, no-
336 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 -

353 *4.* DISCUSSION

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

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

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

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

384 Some of the recently detoxified AUD patients presented a profile of executive dysfunction as well as
385 macrostructural and microstructural brain abnormalities similar to those observed in KS patients.
386 These patients with severe brain dysfunction, sometimes considered at risk of developing KS (Pitel et
387 al., 2012, 2007; Segobin et al., 2015), did not complain about their sleep. Compared to AUD patients
388 with sleep complaint, these patients presented more severe alterations in fronto-temporal regions and
389 specific damage in the frontal-subcortical tracts. Besides, executive impairments were not found in
390 AUD patients with sleep complaint. These findings suggest a key role of the fronto-temporal network
391 and executive functions in subjective assessment of sleep quality. The evaluation of sleep quality
392 using the PSQI is a complex cognitive task that requires a self-interpretation of internal and physical
393 states, which in turn implies having efficient executive functions to judge both sleep quantity (includes
394 evaluating parameters like total sleep time, sleep latency, number of awakenings, among others) and
395 subjective aspects of sleep quality such as feeling tired or daytime sleepiness (Buysse et al., 1989).
396 Executive impairments result in self-awareness deficits (Goldstein et al., 2009) related to damage
397 within the frontal cortex, especially the dorsolateral (Schmitz, Kawahara-Baccus, & Johnson, 2004;
398 Shany-Ur et al., 2014) and medial parts of the prefrontal cortex (Fleming & Dolan, 2012; Schmitz &
399 Johnson, 2007). Previous studies have reported altered self-awareness in AUD patients, who tend to
400 underestimate their daily alcohol consumption (Lincoln et al., 2011) and cognitive deficits (Kornreich,
401 2002; Le Berre et al., 2010; Walvoort et al., 2016). In the present study, AUD patients with executive
402 dysfunction and lower gray matter volume in the dorsolateral and medial parts of the prefrontal cortex
403 as well as lower WM integrity in fibers connecting fronto-subcortical regions may thus not be
404 cognitively able to accurately estimate their sleep. It is also worth noting that the group of AUD
405 patients without sleep complaint is highly heterogeneous (figure 2B) and potentially consisted of two
406 sub-groups of patients: one that would be similar to HC or complaint AUD regarding brain structure
407 and function while the other would be similar to KS patients (Parsons, 1998; Pitel et al., 2012, 2007;

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

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

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

432 *5.* CONCLUSION

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

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

446

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452

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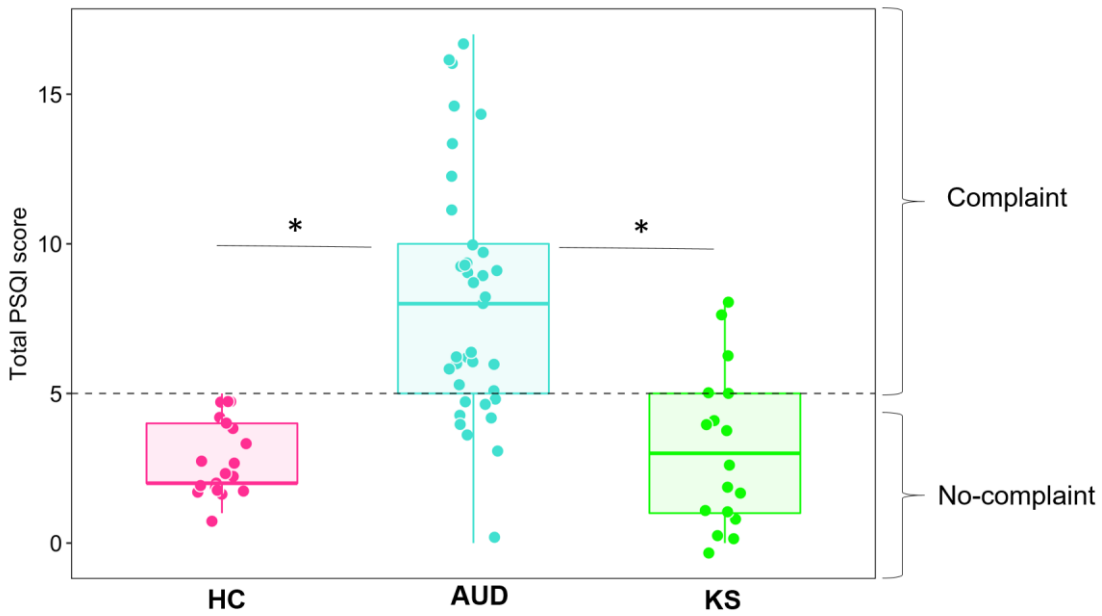
582 *8.* FIGURE LEGENDS:



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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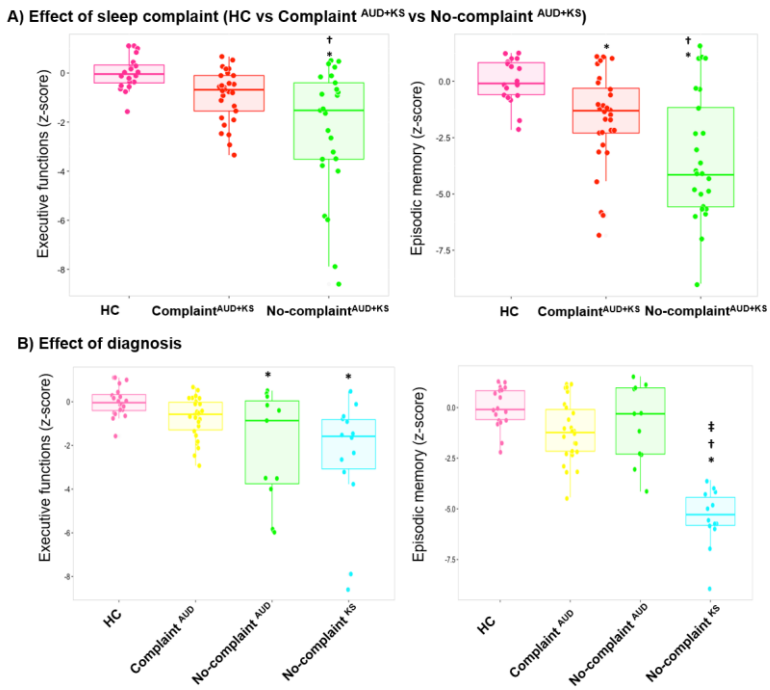

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592

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.

598

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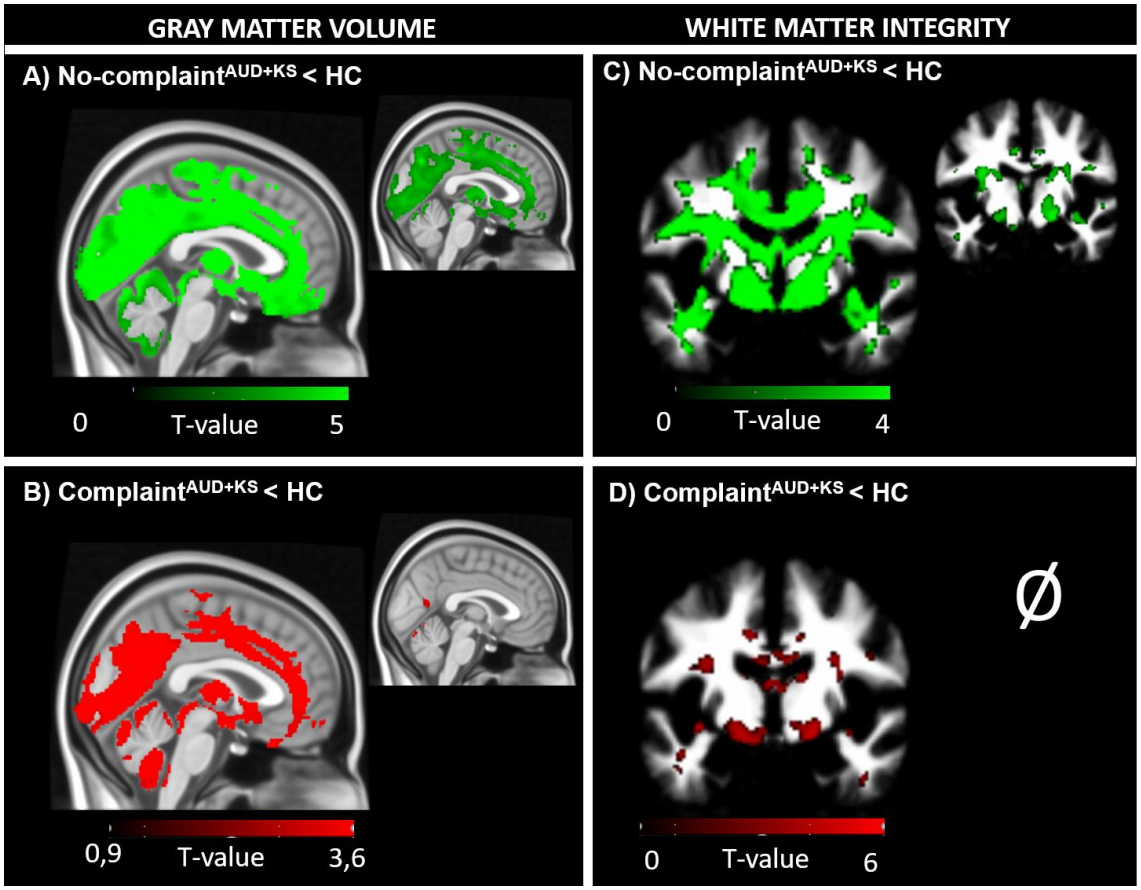
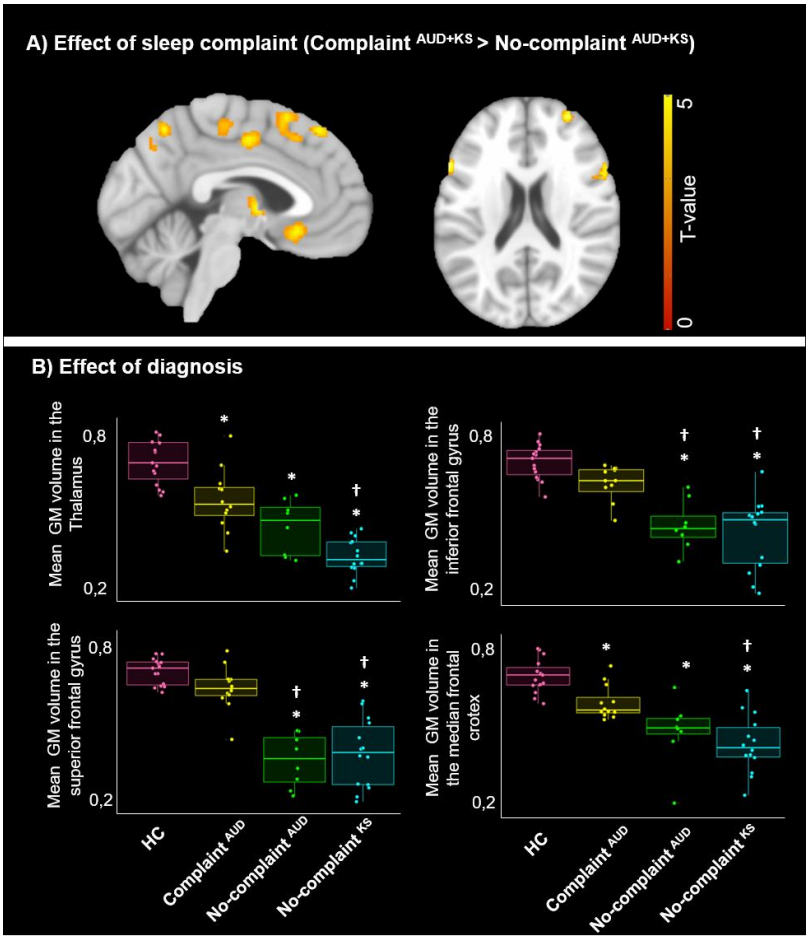


<u>Figure 3</u>: Structural brain abnormalities in patients with and without sleep complaint compared with controls

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.



<u>Figure 4:</u> Gray matter volume 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 tests.

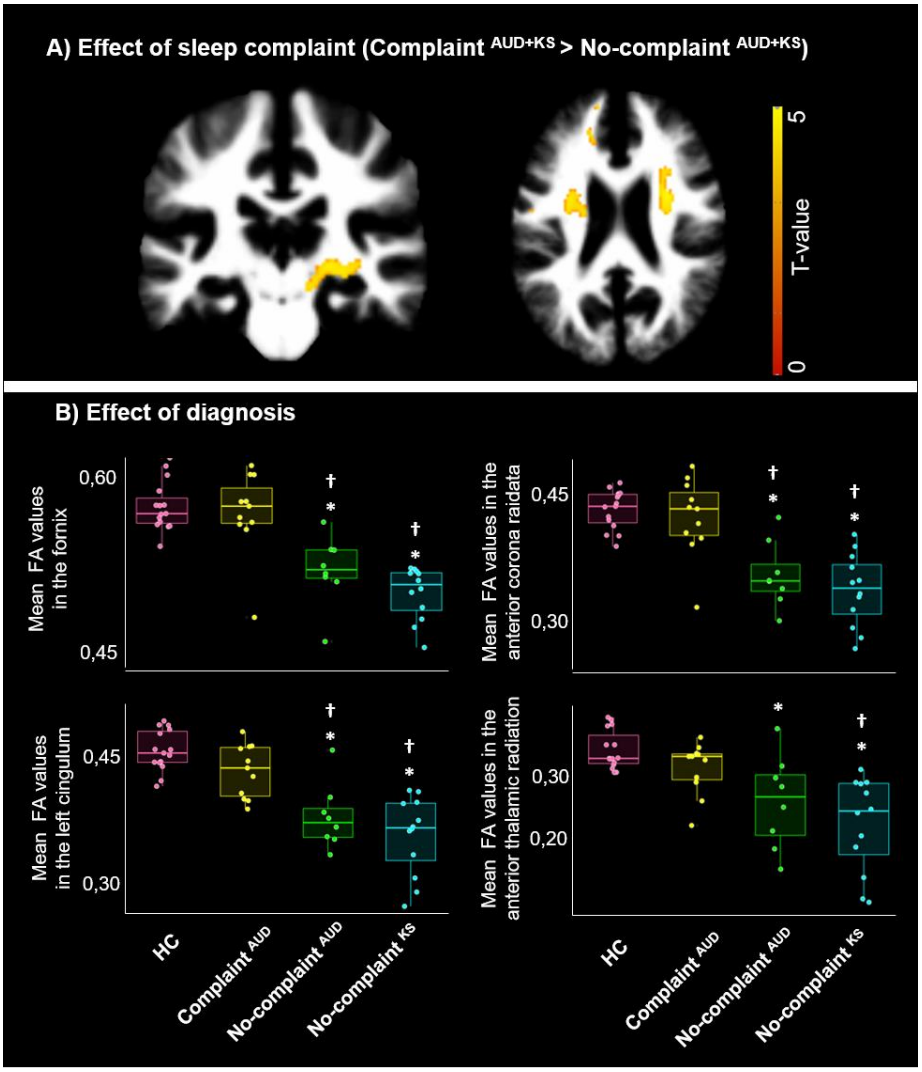


Figure 5: **White matter integrity in controls and patients according to the sleep complaint (A) and diagnosis (B)**

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.