The effect of Alcohol Withdrawal Syndrome severity on sleep, brain and cognition Running title: The harmful effects of drinking cessation

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Title: The effect of Alcohol Withdrawal Syndrome severity on sleep, brain and cognition

Running title: The harmful effects of drinking cessation

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Abstract:

Background: In Alcohol Use Disorder (AUD), drinking cessation is frequently associated with an alcohol withdrawal syndrome (AWS). Early in abstinence (within the first two months after drinking cessation), when patients do not exhibit physical signs of AWS anymore (such as nausea, tremor or anxiety), studies report various brain, sleep and cognitive alterations, highly heterogeneous from one patient to another. While the acute neurotoxicity of AWS is well known, the contribution of AWS severity to structural brain alterations, sleep disturbances and neuropsychological deficits observed early in abstinence has never been investigated.

Objective: This study aimed at elucidating the association between AWS severity and brain volume, sleep and cognitive functioning in recently detoxified AUD patients.

Methods: We included 54 AUD patients early in abstinence (from 4 to 21 days of sobriety) and 50 healthy controls (HC) matched for age, sex and education. When acute physical signs of AWS were no more present, patients performed a detailed neuropsychological assessment, a T_1-weighted MRI, and a polysomnography for a subgroup of patients. According to the severity of the clinical symptoms collected during the acute withdrawal period, patients were subsequently classified as Mild-AWS patients (Cushman score $\leq$ 4, no benzodiazepine prescription, N=17) or Moderate-AWS patients (Cushman score > 4, benzodiazepine prescription, N=37). Patients with severe withdrawal complications (delirium tremens or seizures) were not included.

Results: Mild-AWS patients presented similar gray matter (GM) volume and sleep quality as HC, but lower processing speed and episodic memory performance. Compared to HC, moderate-AWS patients presented Non-Rapid Eye Movement (NREM) sleep alterations, widespread GM shrinkage and lower performance for all the cognitive domains assessed (processing speed, short-term memory, executive functions and episodic memory). Moderate-AWS patients presented a lower percentage of slow wave sleep, GM atrophy in fronto-insular and thalamus/hypothalamus regions, and lower short-term memory and executive performance than mild-AWS patients. Mediation analyses revealed both direct and fronto-insular and thalamus/hypothalamus atrophy-mediated relationships between poor sleep quality and cognitive performance.

Conclusion: AWS severity, which reflects neurotoxic hyperglutamatergic activity, should be considered as a critical factor for the development of NREM sleep alterations, fronto-insular atrophy and executive impairments in recently detoxified AUD patients. The glutamatergic activity is involved in sleep-wake circuits and may thus contribute to molecular mechanisms underlying alcohol-related brain damage, resulting in cognitive deficits. AWS severity and sleep quality deserve special attention for a better understanding and treatment of brain and cognitive alterations observed early in abstinence, and ultimately for more efficient relapse prevention strategies.

Keywords: Alcohol Use Disorder; Alcohol Withdrawal Syndrome; Sleep; Brain Structure; Cognition; Executive Functions.

Abbreviated summary

Even in absence of severe alcohol withdrawal syndrome (AWS), moderate-AWS was associated with lower percentage of slow-wave sleep, which related to cognitive deficits both directly and indirectly via gray matter shrinkage. AWS severity seems to contribute to the pathophysiology of brain, sleep and cognitive damage in Alcohol Use Disorder patients.

Abbreviations:

AHI: Apnea-Hypopnea Index

AUD: Alcohol Use Disorder

AUDIT: Alcohol Use Disorder Identification Test

AWS: Alcohol Withdrawal Syndrome

BDI: Beck Depression Inventory

ESS: Epworth Sleepiness Scale

FWE: Family wise error

GM: Gray Matter

HC: Healthy Controls

MNI: Montreal Neurological Institute

NREM: Non Rapid Eye Movement

PSG: polysomnography

PSQI: Pittsburg Sleep Quality Index

REM: Rapid Eye Movement

SE: sleep efficiency

SPM: Statistical Parametric Mapping,

TST: Total sleep time

1. Background

In Alcohol Use Disorder (AUD) patients, cessation of alcohol consumption is frequently associated with several clinical symptoms (tremor, nausea, anxiety, insomnia, etc.) that constitutes the alcohol withdrawal syndrome (AWS; American Psychiatric Association, 2013). The severity of AWS is variable in AUD patients, ranging from a mild clinical form to severe neurological complications such as seizures and *delirium tremens*, potentially leading to death (Jesse *et al.*, 2017). From a neurobiological perspective, AWS results from a brain hyperexcitability due to increased glutamate transmission combined with decreased GABA transmission (De Witte *et al.*, 2003). This excessive brain glutamate release is neurotoxic and has important consequences on brain functioning, mainly underlying the acute symptomatology of AWS (Tsai and Coyle, 1998; Lukoyanov *et al.*, 1999; Kühn *et al.*, 2014; Frischknecht *et al.*, 2017).

This cerebral hyperexcitability is also known to be related to sleep abnormalities, which can persist several months after alcohol cessation and increase the risk of relapse (Begleiter and Porjesz, 1979; Chakravorty *et al.*, 2016). Early in abstinence (from 2 to 8 weeks after detoxification, when acute physical symptoms of alcohol withdrawal are no more present), sleep abnormalities can be observed and consist of increased sleep latency and fragmentation, decreased sleep duration and sleep efficiency (defined as the ratio between time spent asleep and time in bed) as well as a decreased percentage of stage 3 (N3) of Non Rapid Eye Movement (NREM) sleep, also named slow-wave sleep (Heilig *et al.*, 2010; Angarita *et al.*, 2016). The potential alteration of Rapid Eye Movement (REM) sleep is still debated (Gillin *et al.*, 1990; Chakravorty *et al.*, 2016).

Structural brain alterations and cognitive deficits have been well-described (Zahr *et al.*, 2017) in recently sober AUD patients. Neuroimaging studies reported gray matter (GM) alterations mainly affecting two brain networks: the fronto-cerebellar (Kelly and Strick, 2003) and Papez circuits (Aggleton, 2012), which are involved in motor and executive abilities, and episodic memory respectively. As a result, a large number of recently detoxified AUD patients present neuropsychological deficits including executive, working memory and episodic memory impairments (Stavro *et al.*, 2013; Le Berre *et al.*, 2017). The extent of these cognitive alterations is extremely variable. Some patients have preserved abilities, others exhibit mild-to-moderate deficits and others present severe impairments. This heterogeneity observed in the severity of AUD-related brain and cognitive deficits could be explained by several factors, such as demographical variables (Bates *et al.*, 2002; Nolen-Hoeksema, 2004;

Oscar-Berman *et al.*, 2004), alcohol-related history (Zahr and Sullivan, 2008; Ritz *et al.*, 2016), malnutrition and thiamine deficiency (Zahr and Sullivan, 2008; Pitel *et al.*, 2011), liver disease (Junghanns *et al.*, 2004; Ritz *et al.*, 2016), and repeated alcohol withdrawals (Kouimtsidis *et al.*, 2019).

Several studies reported that AUD patients who experienced multiple detoxifications (two or more) have more severe executive and decision making deficits (Duka *et al.*, 2003, 2011; Loeber *et al.*, 2009), emotional impairments (Townshend and Duka, 2003; O'Daly *et al.*, 2012), increased craving and anxiety-levels (Loeber *et al.*, 2010), brain functional connectivity abnormalities (O'Daly *et al.*, 2012) and altered cognitive recovery (Loeber *et al.*, 2010) compared to patients with none or only one previous withdrawal. Beyond the frequency of alcohol-withdrawal experiences, AWS severity may contribute to the heterogeneity of altered brain structure and function observed in AUD patients. To date, studies mainly focused on the identification of clinical predictors to prevent the development of severe AWS (Goodson *et al.*, 2014; Kim *et al.*, 2015; Silczuk and Habrat, 2020). These investigations highlighted the role of the alcohol consumption level and the number of previous detoxifications (Duka *et al.*, 2004) in the development of seizures and/or *delirium tremens*. To our knowledge, little is known regarding the effect of mild to moderate AWS on cognitive performance, GM volume and sleep quality in recently detoxified AUD patients.

The aim of the present study was thus to explore whether, even in absence of *delirium tremens* and/or seizures, AWS severity contributes to the heterogeneity of cognitive deficits, brain alterations and sleep changes observed in recently detoxified AUD patients.

2. Materials & Methods

2.1. Participants

One hundred and four participants were included in this study: fifty-four AUD inpatients and fifty healthy controls (HC). None of them had a history of neurological, endocrinal, infectious diseases, depression (assessed using both the Beck Depression Inventory (BDI (Beck *et al.*, 1961) and a psychiatric assessment) 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. The study was conducted in France from 2016 to 2019.

AUD patients were recruited by clinicians while they were receiving withdrawal treatment as inpatients at Caen University Hospital. AUD patients met "alcohol dependence" criteria according to the DSM-IV-TR (American Psychiatric Association (APA), 2000) or "severe AUD" criteria according to the DSM-5 (Harper, 2014) for at least 5 years. HC were recruited to match the demographics (age, sex and education) of the AUD patients. They were interviewed with the Alcohol Use Disorder Identification Test (AUDIT; (Gache *et al.*, 2005) to ensure that they did not meet the criteria for alcohol abuse (AUDIT < 7 for men and <6 for women). None of the controls had a BDI (Gache *et al.*, 2005) score > 29 and a Mini-Mental State Examination (Folstein *et al.*, 1975) score < 26. Demographical data are presented in **Table 1.**

2.2.Experimental design

Assessment of alcohol withdrawal syndrome (AWS)

All AUD inpatients included in this study underwent a symptom-triggered approach to the treatment of alcohol withdrawal, which requires to provide medication only when patients present alcohol-withdrawal symptoms (Saitz *et al.*, 1994; Daeppen *et al.*, 2002). The Cushman score was used to monitor the severity of AWS (Cushman *et al.*, 1985), as recommended by the French Addiction Medicine Society and recognized by the European Federation of Addiction Societies (Société Française D'Alcoologie, 2017). This score takes the following clinical variables into account: hearth rate, systolic blood pressure, respiratory rate, tremor, sweating, agitation, and sensorial disorders. Each variable is scored from 0 to 3 according to the severity of the symptom. The Cushman score refers to the sum of these subscores.

Alcohol withdrawal symptoms were systematically assessed every four hours by the nursing staff supervised by a physician specialized in addiction medicine. When the Cushman score was, for the first time, superior or equal to 4, it was assessed a second time 30 minutes later to avoid false positive (caused by anxiety for example). When the Cushman score was higher than 4 twice in a row and/or when a history of severe alcohol withdrawal complications (seizure, *delirium tremens*) was known, a long-acting benzodiazepine with active metabolites (e.g. diazepam) was orally administered in order to alleviate AWS and prevent the development of a more severe AWS (Daeppen *et al.*, 2002). In patients with hepatocellular or respiratory insufficiency, oxazepam was preferred to avoid over sedation or respiratory depression. A decrease in the benzodiazepine dosage was decided when the

Cushman score was lower or equal to 2 for at least 24 hours, at a rate of 15 to 30% of the total dose every 24 to 48 hours.

AUD patients were classified into two groups according to the severity of AWS:

- *mild-AWS:* a maximum Cushman score ≤ 4 and no benzodiazepine treatment required during the acute alcohol withdrawal period according to the symptom-triggered approach.
- *moderate-AWS:* a maximum Cushman score > 4 and/or the presence of a history of severe alcohol withdrawal complications resulting in a benzodiazepine administration during the acute alcohol withdrawal period.

None of the patients had undergone severe AWS defined by neurological complications such as *delirium tremens* or seizures during the acute withdrawal period examined in the course of the present study.

For all AUD patients, the maximum Cushman score and the number of previous detoxifications were collected. For patients whom benzodiazepines were prescribed, we also recorded the number of days and the total amount of benzodiazepines received during alcohol withdrawal. Alcohol-related variables and withdrawal history are summarized in **Table 1.**

Neuropsychological assessment

All participants underwent a detailed neuropsychological examination focusing on processing speed, short-term memory, executive functioning, and episodic memory. Processing speed was measured with a composite score including the part A (time in seconds) of the Trail Making Test (Reitan and Wolfson, 1985) and the denomination condition (time in seconds) of the Stroop Test (Stroop, 1935). Short-term memory was assessed using verbal spans of the WAIS-III (Wechsler, 1997). For executive functions, a composite score was computed including performance on 3 tests assessing manipulation of information (verbal backward spans of the WAIS-III; Wechsler, 1997), inhibition (Stroop Test; Stroop, 1935) with the 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) with the number of perseverative errors. Two patients had missing data for one

measure; their composite score assessing executive functions was therefore computed using remaining scores. Episodic memory was examined through the sum of the 3 free recalls of the French version of the Free and Cued Selective Reminding Test (Van der Linden *et al.*, 2004). Neuropsychological data were transformed into z-scores using the mean and standard deviation obtained from the HC. The sign of all variables for which high scores were in the impaired direction (such as completion time or number of errors) was reversed so that all the z-scores had the same direction: higher z-scores reflecting better performance.

Magnetic Resonance Imaging Data Acquisition and preprocessing

Brain imaging examinations were conducted in 31 HC and 43 AUD patients (13 mild-AWS and 30 moderate-AWS) within the same week as the neuropsychological assessment. HC and the two subgroups of AUD patients were matched for age, sex and education level. All neuroimaging examinations were performed at Cyceron center (Caen, France).

A high-resolution T1-weighted anatomical image was acquired for each subject on a Philips Achieva 3T scanner (Philips Health-care/Philips Medical Systems International B.V., Eindhoven, the Netherlands) using a 3-dimensional fast-field echo sequence (sagittal; repetition time, 20 ms; echo time, 4.6 ms; flip angle 10°; 180 slices; slice thickness: 1 mm; field of view 256 x 256 mm^2; matrix, 256 x 256). The volumetric magnetic resonance imaging (MRI) data were analyzed using the Statistical Parametric Mapping software (SPM12; Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Preprocessing steps included segmentation of the MRI data into gray matter (GM) and spatial normalization to the Montreal Neurological Institute (MNI) template (voxel size = 1.5 mm^3, matrix = 121 x 145 x 121). The normalized GM images were modulated by the Jacobian determinants to correct for nonlinear warping so that the resulting brain volumes were corrected for brain size. The resulting images were smoothed by a Gaussian kernel of 8 mm full width at half maximum (FWHM). A GM mask was obtained taking the unmodulated GM images of HC normalized to the MNI space, averaging them, and thresholding the resultant mean image at 0.5. The resulting GM mask was applied to GM data analyses.

Sleep

A subgroup of 21 AUD (8 mild-AWS and 13 moderate-AWS) and 15 HC, matched for age, sex and education, underwent one night of polysomnography (PSG) using a portable recording device (Siesta®, Compumedics, Australia), allowing AUD patients to sleep at the

addiction department and HC at their home. The PSG was conducted within the same week as the neuropsychological and MRI examinations. The PSG acquisition consisted of twenty EEG electrodes (Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, P3, P4, O1, O2, FZ, CZ, PZ, vertex ground and a bi-mastoid reference) placed over the scalp according to the international 10-20 system, with impedances kept below 5 kΩ. We also recorded the electrooculogram (EOG), chin EMG, ECG, respiratory movements using abdominal and thoracic belts, respiratory airflow using nasal and oral thermistor, and oxygen saturation with a finger pulse oximeter. The EEG signal was digitalized at a sampling rate of 256 Hz. High-pass and low-pass filters were applied, respectively at 0.3 Hz and 35 Hz. PSG recordings were scored in 30-s epochs according to the American Association of Sleep Medicine (AASM, 2017) standard criteria. The following parameters were obtained: total sleep time (TST; in minutes), sleep efficiency (SE (%), corresponding to time spent asleep/ time in bed), sleep onset latency (in minutes, referring to the time from lights-off to the first three epochs of any stage of sleep), wake after sleep onset (in minutes), time spent in each sleep stage (N1, N2, N3, and REM sleep, expressed as percentages of TST), arousal index (number of arousals/ TST), stage shifts index (number of sleep stage transitions to N1/TST) and the Apnea-Hypopnea Index (AHI, corresponding to the number of respiratory events per hour of sleep). We also calculated a composite score to assess sleep fragmentation including the micro-arousal index, the arousal index and the number of stage transitions to N1.

All participants underwent a self-assessment of their sleep quality using the Pittsburg Sleep Quality Index (PSQI; Buysse et al., 1989) in its initial version (previous month) for HC and with an adapted version (previous week, to better reflect the different stages of alcohol treatment) for AUD patients. The Epworth Sleepiness Scale (ESS; Johns et al., 1991) was proposed to assess signs of daytime sleepiness in all participants.

2.3.Statistical analysis

To test the differences between HC and the two subgroups of AUD patients (mild-AWS and moderate-AWS), non-parametric Kruskall-Wallis's tests were conducted on demographical variables (age and education) and a Chi² test was performed to compare the sex ratio in each group. Mann-Whitney's tests were performed between mild-AWS and moderate-AWS for alcohol- and withdrawal-related variables. Non-parametric Kruskall-Wallis's tests were conducted on neuropsychological data and sleep measures followed by *post-hoc* comparisons (Mann-Whitney's tests) when appropriate. The statistical threshold was set to $p < 0.05$.

Neuroimaging data were analyzed using SPM12 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). More precisely, we conducted voxel-based ANCOVAs to compare GM volume between HC, mild-AWS and moderate-AWS patients, controlling for the intracranial volume. We corrected for multiple comparisons (family wise error (FWE), $p<0.05$) with a minimal cluster size (k) of 60 voxels (200 mm^3). Then, comparisons between the two-subgroups of AUD patients were reported at $p<0.001$ with a minimal cluster size (k) of 60 voxels (200 mm^3). Only results surviving a cluster-level correction are reported.

Finally, the relationships between GM volume, sleep variables and cognitive performance were examined in the entire group of AUD patients with Spearman's correlations. Only the variables for which we found a significant difference between mild-AWS and moderate-AWS were entered in the analyses. When we observed significant relationships between a sleep variable on the one hand and both a GM volume and a cognitive variable on the other hand, we performed causal mediation analyses to assess the directionality of the relationships. Mediations analyses allow to test whether the causal effect of an independent variable (X) on a dependent variable (Y) is explained by a mediating variable (M). In other words, X exerts its effects on Y because X affects M, which in turn, affects Y (Goldstone *et al.*, 2018). Applied to our study, two models were tested to determine i) whether GM volume mediates the relationships between sleep and cognitive performance or ii) whether sleep mediates the relationships between GM volume and cognition. These analyses were performed using the "mediation" R package (Tingley *et al.*, 2014). We reported the average direct effects (ADE) and average causal mediation effect (ACME) estimated using nonparametric bootstrapping (5000 simulations, $p<.05$) for each model.

2.4.Data availability

All data and materials used within this study will be made available, upon reasonable request, to research groups wishing to reproduce/confirm our results.

3. Results

3.1.Comparisons between HC, mild-AWS and moderate-AWS patients

Demographical variables and anxiety-depression levels: Kruskall-Wallis tests with Group as a between-subject factor (HC, mild, moderate-AWS) did not reveal any significant effect of group for age ($H_{(2,104)} = 2.48$, $p = 0.29$) and education ($H_{(2,104)} = 4.24$, $p = 0.12$). A Chi^2-test

showed that sex ratio was similar between groups (χ^2 = 2.85, p = 0.24). Kruskall-Wallis tests showed a significant effect of group for depression ($H_{(2,103)}$ = 42, p<0.0001), anxiety-state ($H_{(2,102)}$ = 8.55, p=0.01) and anxiety-trait ($H_{(2,102)}$ = 32.83, p<0.0001). Mild-AWS and moderate-AWS were both more depressed than HC (all p-values < 0.0001) but did not differ from each other (p = 0.85). Only moderate-AWS differed from HC on the anxiety-state questionnaire (p = 0.004). Mild-AWS and moderate-AWS exhibited higher levels of anxiety-trait compared to HC (all p-values < 0.0001), but did not differ from each other (p = 0.14). Results are presented in **Table 1.**

Alcohol-related variables: A Kruskall-Wallis test showed a significant effect of group for the AUDIT score ($H_{(2,103)}$ = 76.97, p < 0.0001). *Post-hoc* comparisons revealed, as expected, that mild-AWS and moderate-AWS patients presented higher AUDIT scores than HC (all p-values = 0.0001) but did not differ from each other (p = 0.41). Mann-Whitney U tests did not show any significant difference between mild-AWS and moderate-AWS for the duration of alcohol misuse (U = 279,5, p = 0.73) and dependence (U = 265, p = 0.44), but moderate-AWS reported a higher daily alcohol consumption than mild-AWS patients (U = 191,5, p = 0.05; **Table 1**).

Alcohol withdrawal variables: Mild-AWS and moderate-AWS patients had an equivalent number of previous detoxifications (U = 265,5, p = 0.44). As expected, compared to mild-AWS patients, moderate-AWS patients had experienced a higher maximum Cushman score (U = 35, 5, p < 0.0001), had received more diazepam (U = 0, p < 0.0001) and during a longer period (U = 0, p < 0.0001 ; **Table 1).**

Pattern of cognitive alterations Kruskall-Wallis tests revealed a significant effect of group for processing speed ($H_{(2, 104)}$ = 29.7, p < 0.0001), short-term memory ($H_{(2, 103)}$ = 12.68, p = 0.002), executive functions ($H_{(2, 104)}$ = 23.38, p < 0.0001) and episodic memory ($H_{(2, 104)}$ = 22.32, p < 0.0001). *Post-hoc* comparisons indicated that mild-AWS patients presented lower performance than HC for episodic memory (U = 148, p < 0.0001) and processing speed (U = 177, p = 0.0004), but not for short-term memory (U = 422, p = 0.97) and executive performance (U = 384.5 , p = 0.56). Compared to HC, moderate-AWS patients presented lower performance for all cognitive measures (all p-values < 0.001). Compared to mild-AWS patients, moderate-AWS patients had lower executive (U = 154, p = 0.003) and short-term memory performance (U = 178. 5, p = 0.01), but did not differ for processing speed and

episodic memory (all p values > 0.05; **Table 2** and **Fig. 1**).

Pattern of GM alterations: Mild-AWS patients did not differ from HC regarding GM volume ($p_{(FWE)} < 0.05$; **Fig. 2A**). Compared to HC, moderate-AWS 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, cerebellum, and in subcortical regions including the thalamus, putamen, and caudate nuclei ($p_{(FWE)} < 0.05$; **Fig. 2B**). Compared to mild-AWS patients, moderate-AWS patients had significantly lower GM volume in the right inferior frontal cortex (Broadman area 44), the bilateral insula, a cluster encompassing the anterior cingulate cortex and the medial superior frontal cortex, occipito-parietal regions and limbic structures including the anterior part of the thalamus and the hypothalamus. All regions listed above are significant at $p < 0.001$ (uncorrected) threshold and survived the cluster-level correction $p < 0.05$; **Fig. 2C**). The reverse comparison (mild-AWS patients < moderate-AWS patients) did not reveal any significant result.

Pattern of sleep alterations: Non-parametric Kruskall-Wallis tests revealed a significant effect of group for both percentage of sleep stages N1 ($H_{(2, N=36)} = 11.81$ $p = 0.003$) and N3 ($H_{(2, N=36)} = 15.87$ $p = 0.0004$). *Post-hoc* comparisons (Mann-Whitney U tests) showed that compared to HC, mild-AWS patients had similar percentage of N1 ($p = 0.24$) and N3 sleep ($p = 0.52$). Compared to HC, moderate-AWS patients showed higher percentage of N1 ($p = 0.0006$) and lower percentage of N3 sleep ($p = 0.0002$). Compared to mild-AWS patients, moderate-AWS patients showed lower percentage of N3 sleep ($p = 0.004$; **Table 2 and Fig. 3**).

A significant effect of group was observed for the apnea-hypopnea index (AHI) ($H_{(2, N=36)} = 7.99$ $p = 0.02$). *Post-hoc* comparisons showed that mild-AWS patients and moderate-AWS patients exhibited a higher AHI compared to controls ($p = 0.03$ and $p = 0.01$ respectively) but did not differ from each other ($p > 0.05$). No group differences were observed for sleep latency, duration, efficiency and wake after sleep onset (all p-values > 0.05). Results remained unchanged when controlling for the AHI (data not shown).

A significant effect of group was observed for the PSQI score ($H_{(2, N=30)} = 11.19$, $p = 0.004$). *Post-hoc* comparisons showed that compared to HC, moderate-AWS patients had a higher score ($p = 0.001$). Mild-AWS patients did not differ from HC and moderate-AWS patients (all

p-values > 0.05). No group difference was observed on the ESS score (p-value > 0.05; **Table 2**).

3.2. Relationships between GM volume, sleep and cognitive performance in the entire group of AUD patients.

Signal values within the significant clusters obtained from the comparison mild-AWS > moderate-AWS were extracted. Then, we conducted Spearman's correlations between GM volumes, sleep variables and cognitive performance in the entire group of patients. Only variables for which we found a significant difference between mild-AWS and moderate-AWS patients were entered in these analyses (i.e. short-term memory performance, executive abilities and N3 sleep). Short-term memory performance positively correlated with GM volume in the insula (rho = 0.51, p = 0.01), occipito-parietal cortex (rho = 0.62, p = 0.003), inferior frontal gyrus (rho = 0.45, p = 0.04) and thalamus/hypothalamus (rho = 0.45, p = 0.04), but not in the anterior cingulate cortex (p > 0.05). Executive performance positively correlated with all significant clusters of GM volume (insula: rho = 0.7, p = 0.0004; occipito-parietal cortex: rho = 0.66, p = 0.001; anterior cingulate cortex: rho = 0.57, p = 0.007; inferior frontal gyrus: rho = 0.53, p = 0.01; thalamus/hypothalamus: rho = 0.64, p = 0.002). GM volume in all significant clusters positively correlated with the percentage of N3 sleep (insula: rho = 0.52, p = 0.01; occipito-parietal cortex: rho = 0.55, p = 0.009; anterior cingulate cortex: rho = 0.43, p = 0.05; inferior frontal gyrus: rho = 0.56, p = 0.008; thalamus/hypothalamus: rho = 0.51, p = 0.02). Moreover, the percentage of N3 sleep positively correlated with short-term memory (rho = 0.48, p = 0.03) and executive performance (rho = 0.44, p = 0.04).

To better understand the directionality of the relationships between GM volume, N3 sleep and cognitive performance, we conducted mediation analyses and tested two models for each cluster. In the first one (Model 1), N3 sleep was the independent variable (X) and GM volume in the 5 significant clusters reported in the previous analysis was the mediator (M). In the second model (Model 2), GM volume was the independent variable (X) and N3 sleep was the mediator (M). In both models, cognitive variables (short-term memory or executive scores) were entered as the dependent variable (Y). First, considering short-term memory performance as the dependent variable, mediation analyses referring to both Model 1 and 2 were not significant (p > 0.05; **Supplementary Table 1**). Second, considering executive functions performance as the dependent variable, mediation analyses revealed that the volume

of the bilateral insula (p=0.006), right inferior frontal cortex (p=0.02), occipito-parietal cortex (p=0.01) and the cluster including the anterior thalamus and the hypothalamus (p=0.02) significantly mediated the relationships between the percentage of N3 sleep and executive performance**.** None of the analyses referring to Model 2 was significant. Results of these mediation analyses are detailed in **Table 3 and Fig. 4.**

4. Discussion

The present study aimed at determining whether AWS severity contributes to the heterogeneity of sleep changes, brain alterations and cognitive deficits observed in AUD patients early in abstinence. We showed that AWS severity contributes to the pathophysiology of NREM sleep abnormalities, decrease GM volumes in fronto-insular and thalamus/hypothalamus regions as well as short-term memory and executive deficits in AUD patients early in abstinence. We also found that lower percentage of N3 sleep related to cognitive deficits (short-term memory and executive functions) both directly and indirectly via GM shrinkage in AUD patients.

We showed that 68% of AUD patients exhibited a moderate AWS, which is a higher prevalence than the one reported in a previous study (Mirijello *et al.*, 2015). In the present study, all patients were recruited in a special unit for alcohol detoxification. They were thus potentially at risk for AWS complications. Contrary to a previous study (Duka *et al.*, 2004) in which only patients with severe alcohol withdrawal complications were included, we did not observe any association between multiple detoxifications and the severity of the current AWS. We also found that AUD patients with moderate AWS reported higher alcohol consumption during the month preceding withdrawal than those with mild AWS. This result suggests that during withdrawal, the brain hyperexcitability resulting from increased glutamate transmission combined to decreased GABA transmission may be related to the quantity of recent alcohol drinking (De Witte *et al.*, 2003; Jesse *et al.*, 2017).

Our study first confirms the pattern of sleep alterations observed in recently detoxified AUD patients, consisting of increased light sleep (N1), a lower percentage of N3 sleep (Gillin *et al.*, 1990; Junghanns *et al.*, 2009; de Zambotti *et al.*, 2014, Irwin *et al.*, 2016*a*; Singh *et al.*, 2018) and the presence of a sleep complaint (Laniepce *et al.*, 2019). It also specifies that only

patients with moderate AWS presented these objective sleep alterations, as well as self reported sleep difficulties. The difference observed between moderate- and mild-AWS patients for N3 sleep is in accordance with a previous study showing that the number of alcohol withdrawal symptoms was negatively related to the percentage of N3 sleep (Gillin *et al.*, 1990). Sleep changes may be directly related to AWS severity since N3 sleep has been associated with lower glutamate levels (Dash *et al.*, 2009). Even when the clinical symptoms of AWS have faded, a hyper-glutamate activity may persist and alter brain regions involved in the generation and maintenance of sleep rhythms, resulting in lower percentage of N3 sleep (Dang-Vu, 2012). Sleep abnormalities observed in our group of moderate-AWS patients may thus be interpreted as a persistent subacute alcohol withdrawal symptom (Brower, 2001; Feige *et al.*, 2007).

AWS severity was also related to structural brain alterations in the right inferior frontal cortex, the bilateral insula, the anterior cingulate cortex and the thalamus/hypothalamus, which are brain regions known to be affected in AUD patients (Pitel *et al.*, 2012; Yang *et al.*, 2016). Regarding the effect of AWS severity on the anterior cingulate cortex, studies using magnetic resonance spectroscopy reported increased glutamate levels in this brain region during alcohol withdrawal in both humans and rats (Lee *et al.*, 2007; Hermann *et al.*, 2012). Several studies suggested that the extent of structural brain abnormalities in AUD patients may be partially explained by alcohol withdrawal-related toxicity (De Witte *et al.*, 2003; Duka *et al.*, 2011; O'Daly *et al.*, 2012; Trick *et al.*, 2014; Frischknecht *et al.*, 2017). During alcohol withdrawal, the glutamate-mediated excitotoxicity induces neuronal death, which may explain structural brain alterations observed early in abstinence in AUD patients (Tsai and Coyle, 1998). The frontal lobes being particularly rich in glutamatergic pathways (Kril *et al.*, 1997), they are likely to be especially vulnerable to the severity of AWS. However, we do not exclude that these brain alterations may have been present before alcohol cessation because of the effects of chronic and heavy alcohol consumption or a family history of AUD or comorbidities such as liver disease or thiamine deficiency (Harper, 2009; Chen *et al.*, 2012; Filippi *et al.*, 2019). In this case, altered brain structure would constitute a vulnerability factor for exhibiting more severe AWS. Further studies including longitudinal measures of glutamate levels combined with structural MRI at different stages of the disease (active drinking, withdrawal period and abstinence) are now required.

Regarding cognitive abilities, our findings indicate that AWS severity may have deleterious effects on short-term memory and executive performance. While short-term

memory deficits have previously been reported in AUD patients (Pitel *et al.*, 2007), we suggest here that AWS may contribute to this alteration. Executive dysfunctions are frequent in AUD patients early in abstinence (Stavro *et al.*, 2013) and could notably be influenced by alcohol history (Sullivan *et al.*, 2000; Zinn *et al.*, 2004; Maurage *et al.*, 2014), associated liver disease (Ritz *et al.*, 2016) and multiple detoxifications (Duka *et al.*, 2004; Loeber *et al.*, 2009). The present study suggests that beyond the repetition of alcohol withdrawals, the severity of AWS itself may represent another factor influencing the heterogeneity of executive impairments in AUD patients. By contrast, AWS severity does not appear to modulate processing speed and episodic memory deficits. Indeed, episodic memory was affected to the same extent in the two subgroups of patients. Previous studies suggested that episodic memory abilities may rather be influenced by thiamine metabolism (Pitel *et al.*, 2011; Ritz *et al.*, 2016).

Mediation analyses enabled us to deepen our understanding of the relationships between sleep, brain and cognition considering the severity of AWS. For the first time, we showed that poor restorative sleep (reflected by a lower percentage of N3 sleep) is related to cognitive deficits both directly and indirectly through GM shrinkage. In line with a previous study in sleep-deprived individuals (Chengyang *et al.*, 2017), we demonstrated that poor restorative sleep is associated with short-term memory deficits in AUD patients. This relationship was not mediated by GM alterations, suggesting the potential contribution of other mechanisms such as altered functional activity of hippocampal-cortical circuits (Chengyang *et al.*, 2017). Interestingly, we found that poor restorative sleep contributes to fronto-insular shrinkage that in turn results in executive deficits. Our results suggest a potential role of sleep in the pathophysiological mechanisms of alcohol-related GM alterations in AUD patients. Poor sleep quality may result from alcohol-related brain damage such as increased glutamate levels (Cortese *et al.*, 2010), neuroinflammation (Irwin *et al.*, 2016*b*) and oxidative stress (Villafuerte *et al.*, 2015). These mechanisms may contribute to fronto-insular and thalamic/hypothalamic abnormalities in AUD patients recently detoxified. Fronto-insular regions, such as the right inferior frontal gyrus, have been related to executive deficits, notably during inhibition tasks (Levy and Wagner, 2011; Aron *et al.*, 2014; Wiers *et al.*, 2015). The insula promotes the integration and representation of interoceptive information into conscious feelings and viscerosensory signals leading to decision making (Craig, 2009). The insula being also a neuronal substrate of craving, insular shrinkage may underpin the relationship between sleep alterations and relapse (Brower, 2003). Thus, these analyses seem

to explain, at least partially, the potential associations existing between sleep, brain and cognition in AUD patients, by showing that N3 sleep contributes to GM shrinkage in fronto-insular and thalamus/hypothalamus regions resulting in executive deficits. We do not exclude that, on the contrary, alterations in other brain regions may induce sleep abnormalities that, in turn, underlie cognitive functioning.

The present study has several strengths, including a meticulous collection of information about AWS severity associated with a detailed cognitive assessment, an MRI scan and an objective sleep assessment in AUD patients examined early in abstinence. However, several limitations should be mentioned. First, the results of the present study were obtained in AUD patients without comorbidities nor other forms of substance use disorder (except tobacco). They cannot therefore be generalized to all AUD patients in Addiction departments given the frequency of comorbidities and multiple drug use. Second, all participants performed only one night of PSG-recording, which did not allow to control for "the first-night effect". Third, although none of the AUD patients included in the present study fulfilled diagnostic criteria for current anxiety disorder and/or depression, higher self-report anxiety and depressive levels were reported by AUD patients compared to HC. Psycho-affective factors may influence sleep quality and cognitive performance in AUD patients as these factors are known to have a negative impact on neuropsychological abilities (Gualtieri and Morgan, 2008) and sleep quality (Baglioni *et al.*, 2016). Nevertheless, the two groups of AUD patients did not differ from each other on these variables and results remained unchanged when psycho-affective factors (BDI, STAI-A, STAI-B scores) were added as covariates (data not shown). Finally, the current clinical measure of AWS severity makes it difficult to disentangle the direct effect of pathophysiological mechanisms underlying AWS (hyperglutamatergy) from the potential effect of AWS-related benzodiazepine treatment. AWS severity was treated with benzodiazepines, corresponding to the gold-standard for AWS treatment (Amato *et al.*, 2010). Benzodiazepines are known to alter objective sleep quality and cognitive functions after an acute administration (Huron *et al.*, 2001; Deakin *et al.*, 2004; Roux and Kryger, 2010) and/or after a chronic consumption (Barker, 2004; Doghramji and Jangro, 2016; Fond *et al.*, 2018). In the present study, AUD patients with benzodiazepine dependence prior the hospitalization were not included and patients who needed benzodiazepines during withdrawal were prescribed for only a few days (4-17 days). In addition, patients were included at least 48 hours after the last benzodiazepine prescription (according to the half-life of the benzodiazepine used), after a progressive decrease of the

benzodiazepine dosage starting when the Cushman score was lower or equal to 2 for at least 24 hours, at a rate of 15 to 30% of the total dose every 24 to 48 hours. Since prolonged diazepam intake may increase its terminal elimination time, we conducted supplementary analyses that did not show any correlation between the number of days since the last benzodiazepine prescription and our main results (**Supplementary Table 2**). This absence of relationship suggests that the differences observed between mild- and moderate-AWS patients do not result from the residual effects of benzodiazepines. However, further studies are required to specify the effects of short-term prescription of benzodiazepines on sleep quality, GM volumes and cognition in AUD patients.

Taken together, our results bring new insights on the pathophysiological mechanisms of sleep, structural brain alterations and cognitive deficits observed in recently detoxified AUD patients, showing the contribution of AWS severity. Moreover, we added novel evidence that poor sleep quality may contribute to cognitive deficits directly or indirectly through increased GM shrinkage in AUD patients early in abstinence. Further studies aiming at exploring brain, sleep or cognition in AUD patients should consider AWS severity to limit the heterogeneity of the AUD sample. For clinicians, these results suggest that a careful monitoring of AWS is not only useful to prevent the development of severe AWS complications, but also to predict sleep alterations, brain damage and cognitive deficits associated with a poor treatment outcome.

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Competing interests:

The authors report no competing interests.

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Figures legends:

Figure 1: Neuropsychological performance according to the severity of the alcohol withdrawal syndrome.

Z-scores were computed based of the mean and standard deviation of the HC (mean=0; standard deviation=1).

*: significant difference compared to HC.

†: significant difference compared to mild-AWS patients.

Figure 2: Structural brain abnormalities in AUD patients with mild and moderate alcohol withdrawal syndrome (AWS) compared to controls.

A: Absence of gray matter (GM) atrophy in mild-AWS patients compared to healthy controls (HC). B: Pattern of GM atrophy in moderate-AWS patients compared to HC. Results are presented at $p < 0.05$ corrected for family-wise-error (FWE). C: Brain areas showing lower GM volume in AUD-moderate patients compared to AUD-mild patients. Results are presented at $p<0.001$ (uncorrected) but only results surviving a cluster-level correction are reported. Minimum cluster size: > 60 voxels.

Figure 3: Time spent in each sleep stage expressed as a percentage of total sleep time according to the severity of the alcohol withdrawal syndrome

*: significant difference compared to HC.

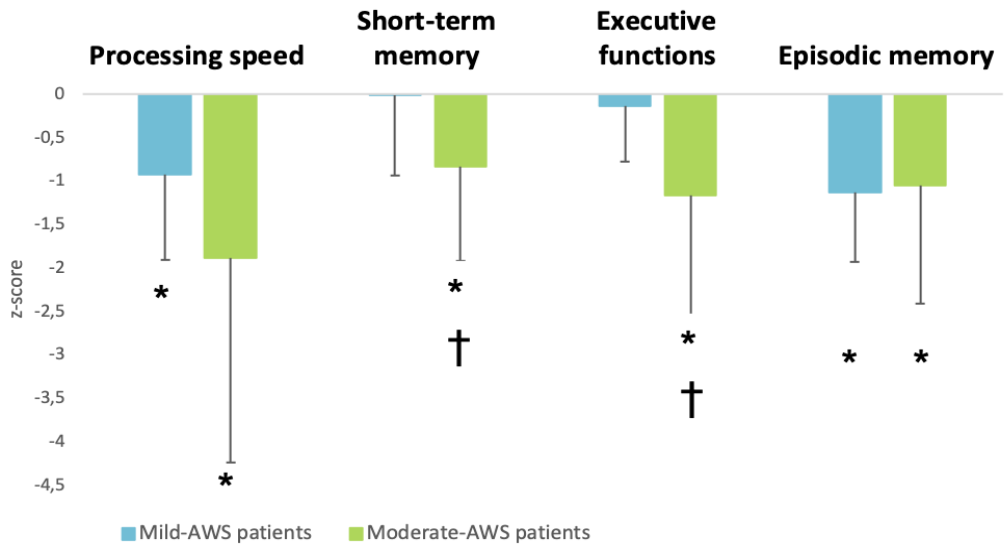
†: significant difference compared to mild-AWS patients.

Figure 4: Results of mediation analyses showing that brain volume mediates the relationships between sleep and executive functions in recently detoxified AUD patients.

Direct effects in filled arrows and indirect effects were represented in dotted arrows (when the effect of brain volume is partially out).

*p<0.05; **p<0.01; ***p<0.001. n.s, non-significant.

Figure 1


Processing speed
Short-term memory
Executive functions
Episodic memory
0
-0,5
-1
-1,5
-2
-2,5
-3
-3,5
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z-score
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Mild-AWS patients
Moderate-AWS patients

Figure 2

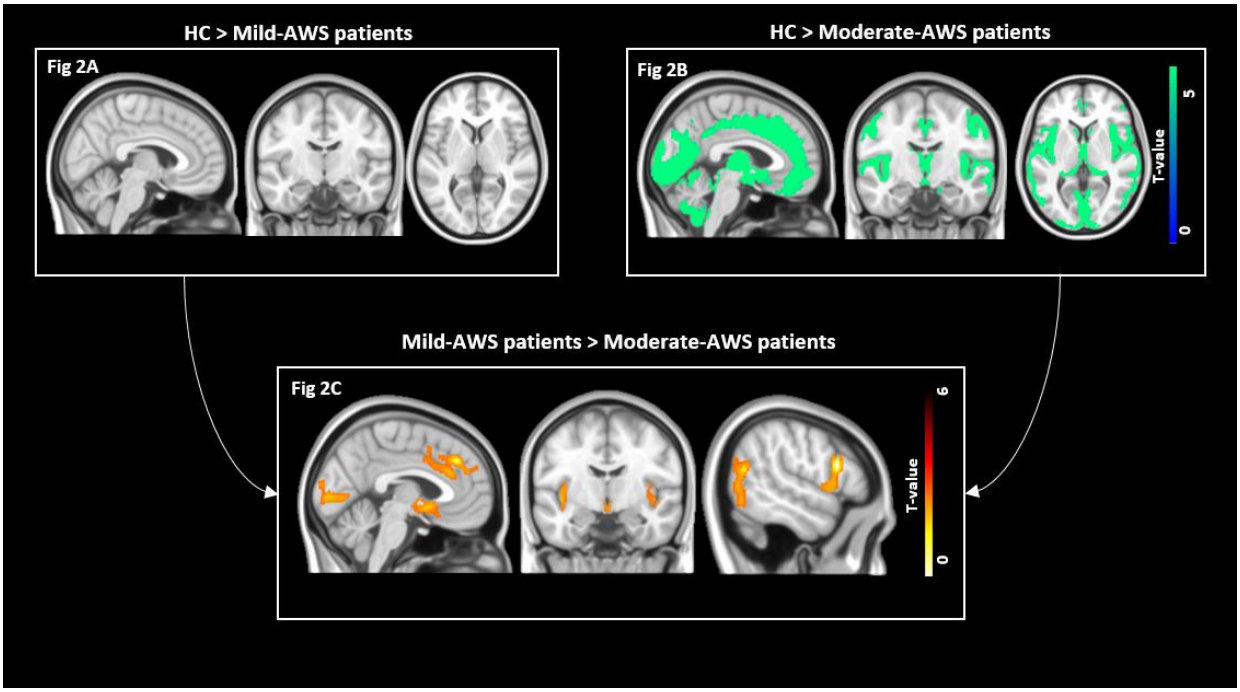

HC > Mild-AWS patients
Fig 2A
HC > Moderate-AWS patients
Fig 2B
T-value
5
0
Mild-AWS patients > Moderate-AWS patients
Fig 2C
T-value
6
0

Figure 3

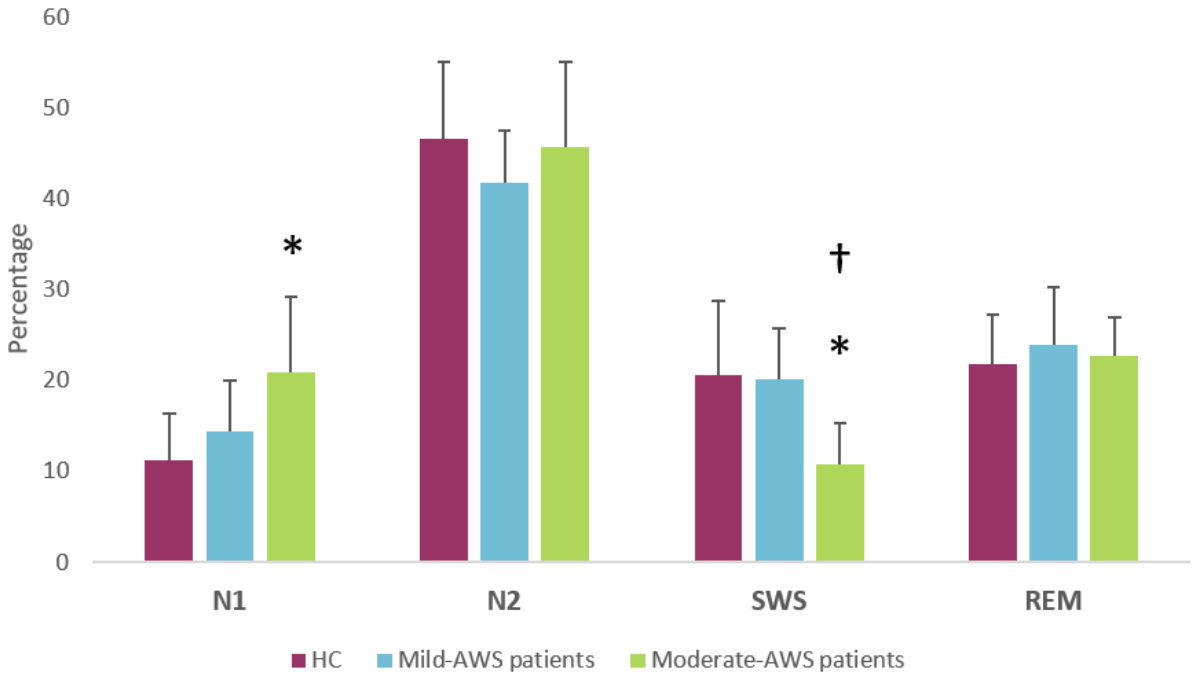
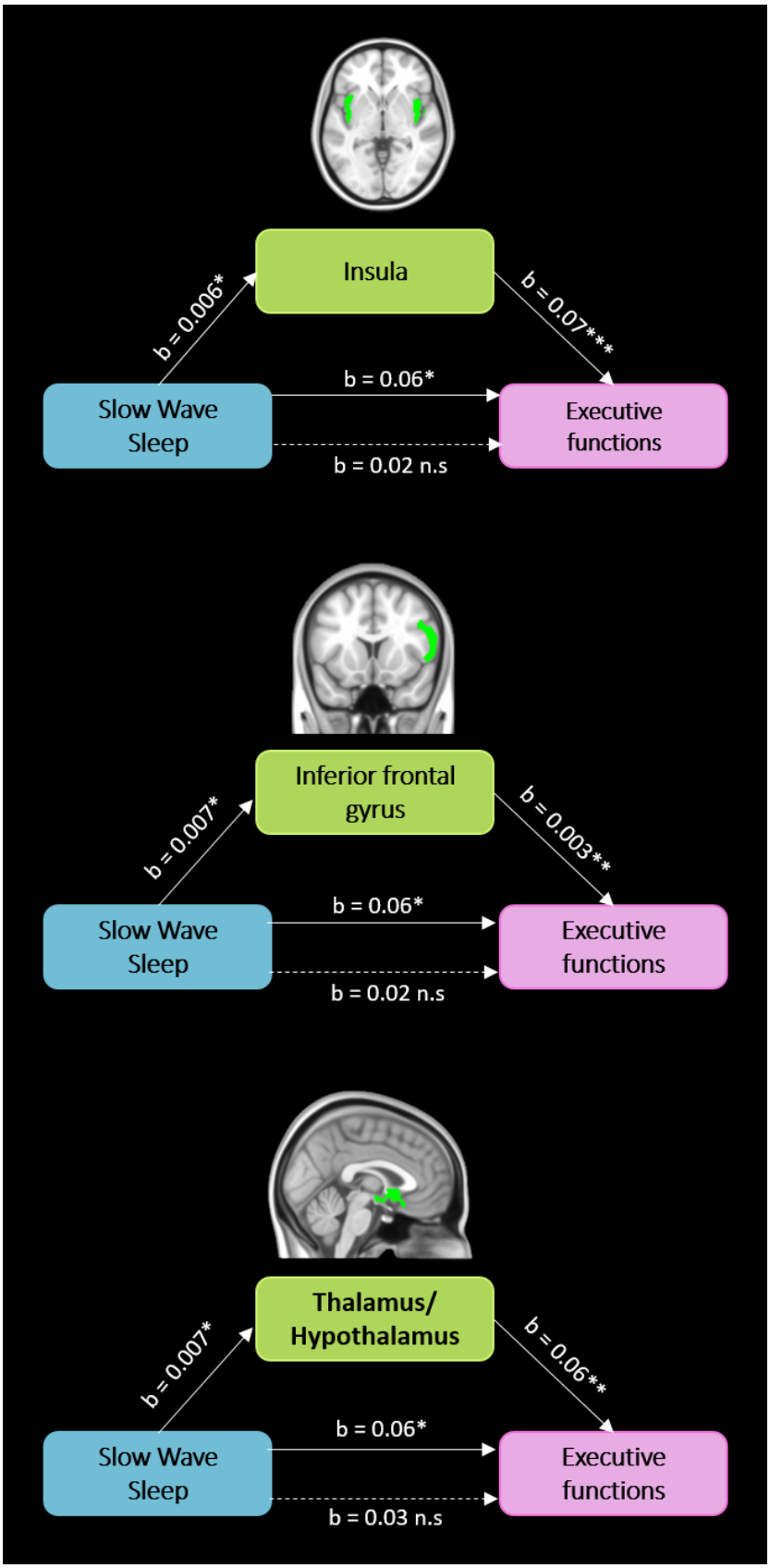

60
50
40
30
20
10
0
Percentage
*
†
*
N1
N2
SWS
REM
HC
Mild-AWS patients
Moderate-AWS patients

Figure 4


Insula
b = 0.006*
b = 0.07***
Slow Wave Sleep
b = 0.06*
b = 0.02 n.s
Executive functions
Inferior frontal gyrus
b = 0.007*
b = 0.003**
Slow Wave Sleep
b = 0.06*
b = 0.02 n.s
Executive functions
Thalamus/ Hypothalamus
b = 0.007*
b = 0.06**
Slow Wave Sleep
b = 0.06*
b = 0.03 n.s
Executive functions

	Healthy controls (HC)	Alcohol Use Disorder patients (AUD)		Between-group comparisons
	HC (N=50)	mild-AWS (n=17)	moderate-AWS (n=37)	
Demographics				
Age (years)	44.02 ± 7.79	45.53 ± 11.36	46.86 ± 8.12	NS
Education (years)	12.30 ± 2.07	11.5 ± 2.18	11.69 ± 2.13	NS
Sex ratio (M/F)	34/16	13/4	31/6	NS
Anxiety and depression factors				
*BDI score**	3.52 ± 3.99	12.29 ± 8.15	13.28 ± 8.96	HC < mild-AWS†††; HC < moderate-AWS††† ; mild-AWS = moderate-AWS
*STAI A (state anxiety)***	26.52 ± 5.72	31.82 ± 11.97	32.05 ± 10.59	HC = mild-AWS; HC < moderate-AWS†† ; mild-AWS = moderate-AWS
*STAI B (trait anxiety)***	32.22 ± 6.84	49.18 ± 12.21	43.59 ± 11.28	HC < mild-AWS†††; HC < moderate-AWS†††; mild-AWS = moderate-AWS
Alcohol history				
*Abstinence before inclusion (days)**	-	8.76 ± 3.73	11.22 ± 3.48	mild-AWS < moderate-AWS†
*AUDIT**	2.60 ± 1.81	28.06 ± 5	28.89 ± 6.24	HC < mild-AWS††† ; HC < moderate-AWS††† ; mild-AWS = moderate-AWS
Daily alcohol consumption (units)	-	15.63 ± 7.67	20.34 ± 8.39	mild-AWS < moderate-AWS$^{\dagger, a}$
Alcohol misuse (years)	-	21.37 ± 10.16	20.62 ± 10.17	NS
Alcohol dependancy (years)	-	13 ± 10.03	11.94 ± 11.47	NS
Alcohol withdrawal history				
Number of days between last benzodiazepines administration and inclusion	-	-	2.78 ± 1.24	-
Number of previous detoxifications	-	1.94 ± 0.82	2.53 ± 1.70	NS
Hightest Cushman score	-	2.88 ± 0.92	5.86 ± 1.81	mild-AWS < moderate-AWS†††
Total amount of benzodiazepine (equivalent diazepam) received (mg)	-	0 ± 0	294.83 ± 221.82	mild-AWS < moderate-AWS†††
Number of days of benzodiazepine prescription	-	0 ± 0	9.05 ± 3.26	mild-AWS < moderate-AWS†††

Table 1: Demographic, clinical and alcohol-related data in healthy controls and AUD patients.

Abbreviations: HC, Healthy Controls; AUD, Alcohol Use Disorder patients; mild-AWS (Cushman ≤ 4), moderate-AWS (Cushman > 4 or the presence of a history of severe alcohol withdrawal history); BDI, Beck Depression scale

Data were analyzed using non-parametric tests for demographic, alcohol- and withdrawal related variables and cognitive functions. Groups effects were tested with Kruskall-Wallis tests and *post-hoc* comparisons were performed using Mann-Whitney U tests. We used a Chi² test to compare the sex ratio in each group.

[a]: correlations between daily alcohol consumption on the one hand, and sleep quality, brain volume, and cognitive abilities on the other hand were not significant neither in the entire group of AUD patients, nor in the two subgroups (data not shown).

*: Missing value for one patient

**: Missing value for two patients

NS: non-significant ; † : $p < 0.05$; †† : $p < 0.01$; ††† : $p < 0.001$

Table 2: Cognitive performance and sleep variables in in healthy controls and AUD patients.

	Healthy controls (HC)	Alcohol Use Disorder patients (AUD)		Between-group comparisons
	HC (N=50)	mild-AWS (n=17)	moderate-AWS (n=37)	
Cognitive functions (z-score)				
Processing speed	0 ± 1	-0.62 ±1.13	-0.97 ± 1.49	HC > mild-AWS†††; HC > moderate-AWS†††; mild-AWS = moderate-AWS
Short term memory	0 ± 1	-0.007 ± 0.93	-0.82 ± 1.09	HC = mild-AWS; HC > moderate-AWS†††; mild-AWS > moderate-AWS††
Executive functions	0 ± 0.64	-0.13 ± 0.62	-1.15 ± 1.40	HC = mild-AWS; HC > moderate-AWS†††; mild-AWS > moderate-AWS†
*Episodic memory**	0 ± 1	-1.12 ± 0.80	-0.95 ±1.25	HC > mild-AWS†††; HC > moderate-AWS†††; mild-AWS = moderate-AWS
Sleep architecture[a]				
Sleep latency (min)	29.07 ± 17.71	14.06 ± 14.18	24.81 ± 15.11	NS
Total sleep time (min)	384.57 ± 53.75	376.87 ± 61.48	381.73 ± 69.30	NS
Sleep efficiency. %	80.95 ± 6.87	88.54 ± 8.72	80.78 ± 7.54	NS
Wake after sleep onset (min)	61.03 ± 31.53	37.19 ± 34.14	64.23 ± 40.65	NS

N1%	11.15 ± 5.22	14.31 ± 5.72	20.91 ± 8.19	HC = mild-AWS ; HC > moderate-AWS††† ; mild-AWS = moderate-AWS
N2%	46.49 ± 8.53	41.7 ± 5.78	45.63 ± 9.39	NS
N3%	20.56 ± 8.15	20.08 ± 5.55	10.71 ± 4.60	HC = mild-AWS; HC > moderate-AWS†††; mild-AWS > moderate-AWS††
REM%	21.79 ± 5.50	23.85 ± 6.41	22.75 ± 4.19	NS
Apnea-hypopnea Index (AHI)	13.59 ± 8.16	24.82 ± 13.57	26.77 ± 16.71	HC < mild-AWS† ; HC < moderate-AWS† ; mild-AWS = moderate-AWS
Composite sleep fragmentation	0 ± 0.85	-0.33 ± 0.96	-0.85 ± 1.18	NS
Subjective sleep assessment[a]				
*PSQI total score***	2.13 ± 1.35	7 ± 4.9	5.9 ± 2.64	HC = mild-AWS ; HC < moderate-AWS†† ; mild-AWS = moderate-AWS
ESS total score	4.78 ± 2	6.37 ± 2.33	3.92 ± 2.56	NS

Abbreviations: see legend of Table 1. PSQI: Pittsburg Sleep Quality Index; ESS: Epworth Severity Scale.

Data were analyzed using non-parametric tests: groups effects were tested with Kruskall-Wallis tests and *post-hoc* comparisons were performed using Mann-Whitney U test.

[a]: For sleep analyses, subgroups consisted of 15 HC, 8 mild-AWS and 13 moderate-AWS patients.

*Missing data for one patient; **Missing data for six AUD patients; NS: non-significant; † : $p < 0.05$; †† : $p < 0.01$; ††† ; $p < 0.001$

Table 3: Mediation analyses between %N3 sleep, GM volumes and executive functioning in AUD patients.

		ADE			ACME		
Brain areas	**Model**	**Estimate**	**CI95%**	**P-value**	**Estimate**	**CI95%**	**P-value**
Bilateral insula	Model 1	0.02	-0.03-0.09	0.47	0.04	0.01-0.09	**0.006***
	Model 2	7.05	3.01-9.91	0.003	0.69	-1.18-3.61	0.46
Right inferior frontal gyrus	Model 1	0.02	-0.05-0.10	0.51	0.04	0.004-010	**0.02***
	Model 2	5.98	0.92-10.95	0.02	0.99	-3.06-4.34	0.56
Cingulate anterior gyrus	Model 1	0.04	-0.02-0.11	0.22	0.02	-0.007-0.07	0.11
	Model 2	3.57	-0.83-7.37	0.08	1.15	-1.01-4.13	0.24
Anterior thalamus/hypothalamus	Model 1	0.02	-0.04-0.10	0.47	0.03	0.004-0.10	**0.02***
	Model 2	5.71	1.56-10.23	0.008	0.90	-2.16-3.23	0.47
Occipito-parietal cortex	Model 1	0.02	-0.04-0.09	0.56	0.05	0.008-0.10	**0.02***
	Model 2	7.77	1.82-12.74	0.02	0.96	-2.95-4.98	0.54

Abbreviations: ADE: average direct effect; ACME: average causal mediation effect; CI: confidence interval.

For the 5 GM clusters, two models were tested. In the first one (Model 1), the percentage of N3 sleep was the independent variable and the GM volume was the mediator. In the second model (Model 2), GM volume was the independent variable and the percentage of N3 sleep was the mediator. In all models, executive functions were entered as the dependent variable. Values in bold accompanied by a "*" indicate the significance of the model.

Supplementary Table 1: Mediation analyses between %N3 sleep, GM volumes and short-term memory in AUD patients.

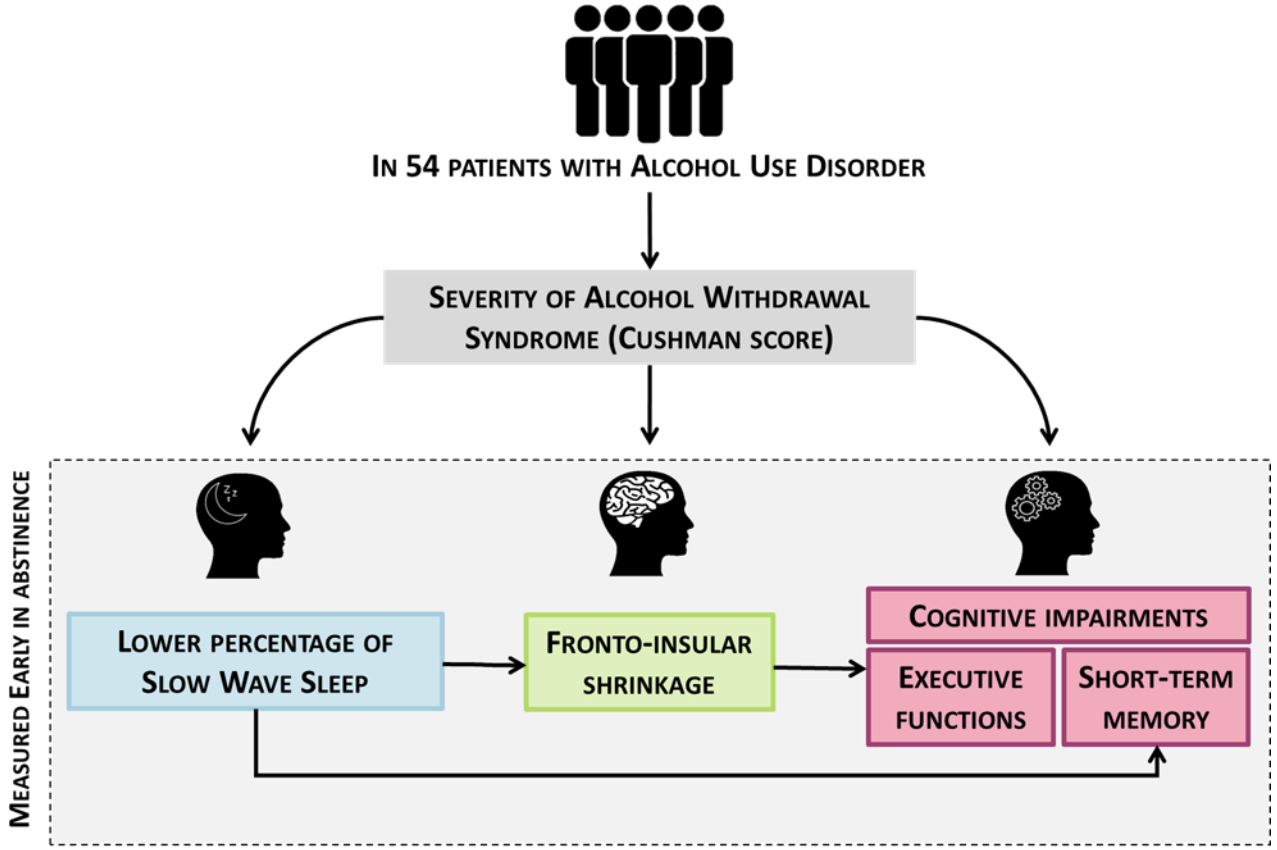
		ADE			ACME		
Brain areas	**Model**	**Estimate**	**CI95%**	**P-value**	**Estimate**	**CI95%**	**P-value**
Bilateral insula	Model 1	0.06	-0.01-0.13	0.11	0.02	-0.01-0.07	0.23
	Model 2	3.09	-2.88-8.76	0.28	1.93	-1.15-5.15	0.2
Right inferior frontal gyrus	Model 1	0.05	-0.02-0.13	0.15	0.02	-0.01-0.07	0. 24
	Model 2	3.01	-1.81-7.97	0.21	1.93	-0.48-5.45	0.13
Cingulate anterior gyrus	Model 1	0.06	-0.03-0.14	0.20	0.02	-0.02-0.08	0.30
	Model 2	3.09	-2.86-8.72	0.08	1.93	-1.13-5.09	0.2
Anterior thalamus/hypothalamus	Model 1	0.06	-0.01-0.12	0.10	0.02	-0.01-0.07	0.25
	Model 2	3.10	-1.79-7.91	0.21	1.92	-0.45-5.43	0.13
Occipito-parietal cortex	Model 1	0.06	-0.02-0.13	0.13	0.02	-0.01-0.07	0.25
	Model 2	3.17	-1.99-8.15	0.19	1.92	-0.17-5.5	0.1

Abbreviations: ADE: average direct effect; ACME: average causal mediation effect; CI: confidence interval.

For the 5 GM clusters, two models were tested. In the first one (Model 1), the percentage of N3 sleep was the independent variable and the GM volume was the mediator. In the second model (Model 2), GM volume was the independent variable and the percentage of N3 sleep was the mediator. In all models, short-term memory performance was entered as the dependent variable. All models were not significant.

<u>Supplementary Table 2 :</u> Relationships between the number of days since the last benzodiazepine prescription and %N3 sleep, GM volumes and cognition.

		Number of days since the last benzodiazepine prescription
Sleep quality	**%N3 sleep**	rho = -0.15 ; p = 0.61
Cognitive functioning	**Short-term memory**	rho = -0.26 ; p = 0.39
	Executive functions	rho = -0.29 ; p = 0.33
GM volumes	**Right inferior frontal**	rho = -0.13 ; p = 0.67
	Bilateral Insula	rho = -0.23 ; p = 0.44
	Anterior cingulate	rho = -0.38 ; p = 0.20
	Occipito-parietal	rho = -0.17 ; p = 0.56
	Thalamus/hypothalamus	rho = -0.42 ; p = 0.15

Spearman's correlations were conducted between the main results of the present study and the number of days since the last benzodiazepine prescription and %N3 sleep, GM volumes and cognition. The number of days since the last benzodiazepine prescription was different between the PSG-recording and the neuropsychological assessment because examinations were not performed during the same day. No correlation was significant.

Graphical abstract