



HAL
open science

Contribution of sleep disturbances to the heterogeneity of cognitive and brain alterations in alcohol use disorder

Alice Laniepce, Najlaa Lahbairi, Nicolas Cabé, Anne-Lise Pitel, Géraldine Rauchs

► To cite this version:

Alice Laniepce, Najlaa Lahbairi, Nicolas Cabé, Anne-Lise Pitel, Géraldine Rauchs. Contribution of sleep disturbances to the heterogeneity of cognitive and brain alterations in alcohol use disorder. *Sleep Medicine Reviews*, 2021, 58, pp.101435. 10.1016/j.smr.2021.101435 . hal-03514130

HAL Id: hal-03514130

<https://hal.science/hal-03514130v1>

Submitted on 13 Feb 2023

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

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



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

CONTRIBUTION OF SLEEP DISTURBANCES TO THE HETEROGENEITY OF COGNITIVE AND BRAIN ALTERATIONS IN ALCOHOL USE DISORDER

Running title: Sleep and alcohol-related brain structure and function

Alice Laniepce^{1*}, Najlaa Lahbairi^{1*}, Nicolas Cabé^{1,2}, Anne-Lise Pitel^{1,3*}, Géraldine Rauchs^{1*}

(1) Normandie Univ, UNICAEN, PSL Université de Paris, EPHE, INSERM, U1077, CHU de Caen, GIP Cyceron, Neuropsychologie et Imagerie de la Mémoire Humaine, 14000 Caen, France

(2) Service d'Addictologie, Centre Hospitalier Universitaire de Caen, 14000 Caen, France

(3) Institut Universitaire de France (IUF)

*: Equally contributed to this work

Corresponding author:

Dr Géraldine Rauchs, PhD

Inserm-EPHE-UNICAEN U1077

GIP Cyceron

Bd Henri Becquerel, BP 5229

14074 CAEN cedex 5

France

geraldine.rauchs@inserm.fr

Number of words: 8293 (without references)

Number of tables: 1

Number of figures: 2 color figures

Number of references: 205

Conflicts of interest: none

Summary

Cognitive and brain alterations are common in alcohol use disorder and vary importantly from one patient to another. Sleep disturbances are also very frequent in these patients and remain largely neglected even though they can persist after drinking cessation. Sleep disturbances may be the consequence of specific brain alterations, resulting in cognitive impairments. But sleep disruption may also exacerbate alcohol-related brain abnormalities and cognitive deficits through common pathophysiological mechanisms. Besides, sleep disturbances seem a vulnerability factor for the development of alcohol use disorder. From a clinical perspective, sleep disturbances are known to affect treatment outcome and to increase the risk of relapse. In this article, we conducted a narrative review to provide a better understanding of the relationships between sleep disturbances, brain and cognition in alcohol use disorder. We suggest that the heterogeneity of brain and cognitive alterations observed in patients with alcohol use disorder could at least partially be explained by associated sleep disturbances. We also believe that sleep disruption could indirectly favor relapse by exacerbating neuropsychological impairments required in psychosocial treatment and for the maintenance of abstinence. Implications for clinical practice as well as perspectives for future research are proposed.

Keywords: Sleep disturbances, alcohol use disorder, cognition, brain, neuroimaging, relapse.

Abbreviations

AUD: alcohol use disorder

AWS: alcohol withdrawal syndrome

CBT: cognitive behavioral therapy

CT: computed tomography

DSM: diagnostic and statistical manual of mental disorders

DTI: diffusion tensor imaging

EEG: electroencephalography

FCC: fronto cerebellar circuit

GABA: gamma aminobutyric acid

GM: gray matter

KS: Korsakoff's syndrome

MRI: magnetic resonance imaging

NREM: non-rapid eye movement

PC: Papez circuit

PLMD: periodic limb movement disorder

PLMs: Periodic limb movements

PSG: polysomnography

PSQI: Pittsburgh sleep quality index

REM: rapid-eye movement

SDB: sleep-disordered breathing

SOL: sleep onset latency

SWS: slow wave sleep

ToM: theory of mind

TST: total sleep time

WASO: wake after sleep onset

WM: white matter

INTRODUCTION

Alcohol is a widely promoted and consumed psychoactive substance that can lead to maladaptive patterns of use such as Alcohol Use Disorder (AUD). AUD is among the most prevalent mental disorders worldwide [1]. The 2018 World Health Organization's global status report on alcohol and health indicated that, in 2016, an estimated 283 million people had AUD (which represents 5.1% of adults aged 15 years and older in the world), with a large variation by countries and gender. Europe shows the highest prevalence (8.8% of the adult population) followed by the US (8.2% of the adult population), and the Western Pacific Region (4.7% of the adult population) and finally the lowest rate was found in the Eastern Mediterranean countries (0.8% of the same age population) [2].

AUD has significant personal, interpersonal, social and economic consequences and is associated with numerous physical and psychiatric comorbidities [3] leading to significant morbidity and mortality [4]. Despite all these considerable negative consequences, very few AUD patients seek treatment (20% of AUD patients in the US [5]) potentially because of social stigma, consequences on personal life and employment of cognitive disabilities leading to lack of insight regarding their situation [6]. Altered perception of these negative consequences may result from the harmful effects of AUD on brain structure and function. Alcohol-related brain abnormalities are associated not only with neuropsychological impairments but also with sleep disturbances that, all together, result in increased risk of relapse.

While there have been other recent reviews on sleep in AUD [7–9], the specific objective of this synthetic narrative review is to address the relationships between sleep disturbances and brain structure and function in AUD. We aim at offering a novel perspective of the pathophysiology of alcohol-related brain damage and cognitive deficits by introducing

sleep disturbances as a key factor. We will first review alcohol-related brain abnormalities, associated neuropsychological deficits and sleep alterations. Then, we will describe the relationships between sleep quality, and cognitive and brain alterations observed in AUD.

ALCOHOL-RELATED NEUROPSYCHOLOGICAL IMPAIRMENTS AND BRAIN ABNORMALITIES

AUD is defined as “a chronic relapsing brain disease characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using”. According to the DSM-5 [10], AUD ranges from mild to severe depending on the number of criteria (out of 11) met by patients. The presence of two or three criteria indicates mild AUD, four to five criteria suggest moderate AUD and more than six criteria defines severe AUD. AUD will be used throughout the article even though this term is relatively recent. Before 2013, “alcoholism” and later “alcohol dependence” or “alcohol abuse” were used as a diagnosis (with specific criteria for each) based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; [11]) or the International Classification of Diseases [12].

Chronic and excessive alcohol consumption affects brain macrostructure and microstructure as well as cognition and motor abilities. These consequences of AUD have been recognized by the DSM-5 as mild or major “alcohol-induced neurocognitive disorders” depending on the severity of the impact on daily life and autonomy. Globally, three brain networks, involved in episodic memory, executive functions and emotion and social cognition, are particularly affected in AUD patients. In the following paragraphs, we will describe how the gray matter (GM) nodes and white matter (WM) connections of these three brain circuits are altered in AUD patients, in absence of alcohol-related neurological complications such as Korsakoff’s syndrome. We will also depict associated neuropsychological deficits observed in 50 to 80% of AUD patients [13].

Episodic memory network

Episodic memory deficits are observed in AUD patients, affecting learning, encoding, and retrieval abilities [14,15]. Moreover, patients had impaired recall of temporal and spatial

context of encoding [14–16] as well as deficits of auto-noetic consciousness, which gives a subject the conscious feeling of travelling in time to relive the original event or to project into the future [14,15]. These episodic memory impairments have been described as genuine as they do not seem to be exclusively explained by executive dysfunction [14,15].

The Papez circuit (PC) [17], involved in episodic memory functioning, includes the hippocampal formation, which connects to the mammillary bodies via the fornix. The thalamus then receives information from the mammillary bodies via the mammillothalamic tract. The anterior limb of the internal capsule connects the thalamus to the cingulate gyrus, which is in turn connected back to the hippocampus through the cingulum bundle.

Shrinkage of the GM nodes of the PC have repeatedly been found in AUD patients, with volume deficits in the hippocampus [18], mammillary bodies [19,20] and cingulate cortex [21]. Structural abnormalities have also been demonstrated in the thalamus of AUD patients [22] and more particularly a disconnection between the hippocampus and the anterior thalamic nuclei [23]. Altered WM fibers were found in the cingulum, fornix and anterior thalamic radiation [24]. Several studies explored brain-function relationships within the PC of AUD patients. Reduced hippocampal volume was reported in AUD patients without episodic memory deficits, suggesting that hippocampal shrinkage itself cannot explain alcohol-related episodic memory impairments [25]. When considering brain microstructure, low episodic memory performance was associated with altered parahippocampal GM [26] and WM integrity in the fornix and cingulum bundle [24].

Executive functions and motor network

Executive dysfunction has been considered as the most frequent cognitive impairment among AUD patients [27], including flexibility, updating, planning, and inhibition deficits [28]. AUD patients also exhibit impaired decision making abilities [28].

Executive deficits have been associated with damage of the fronto-cerebellar circuit (FCC). The FCC consists of two parallel closed loops within the cortico-thalamo-cerebellar circuitry: one executive and one motor [29]. The frontal cortex (dorsolateral prefrontal cortex for the executive loop, motor cortex for the motor loop) is connected to the pons via cortico-pontine tracts and back to the cerebellum (crus I and II for the executive loop, lobules IV–VI of the vermis) through the middle cerebellar peduncle. Then, the superior cerebellar peduncle connects the cerebellum to the thalamus, which is linked to the frontal cortex through the anterior limb of the internal capsule and the anterior corona radiata.

Studies have reached consensus regarding the significant and prominent damage of the frontal cortex and cerebellum in AUD patients [30]. In addition, macrostructural WM alterations have been observed in the pons, cerebellum and midbrain [31,32]. Structural connectivity within the FCC is also affected with altered WM microstructure in the anterior limb of the internal capsule, the anterior corona radiata, middle and superior cerebellar peduncles [24] and fibers connecting the midbrain to the pons [33].

Executive deficits observed in AUD were first related to frontal lobe damage [30]. More recent investigations highlighted that alterations of other nodes of the FCC may be better predictors of executive dysfunction than damage of the prefrontal cortex [31,34]. Executive deficits were related to shrinkage of the pons, thalamus and cerebellum [31,33] as well as to the number of WM fibers between the midbrain and the pons [33]. In a combined MRI-DTI study, Crespi et al. [35] found that executive performance correlated with GM volume and DTI measures of key nodes and fiber tracts of the salience, default-mode and central executive networks

Social cognition network

Social cognition refers to the processes contributing to the perception and understanding of social environments and interactions [36]. It includes several abilities that enable an individual to behave appropriately in a social context or environment: the ability to decode emotions, empathy, and the Theory of Mind (ToM). Empathy refers to the ability to understand and experience what others feel without confusion between oneself and others. ToM refers to the ability to attribute mental (cognitive and affective) states to oneself and others. The social cognition network encompasses three circuits [37]. The cognitive ToM circuit is mediated by the medial and dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, superior temporal sulcus, temporoparietal junction, and temporal poles [38]. The affective ToM (i.e., cognitive empathy) involves the ventromedial prefrontal cortex, temporoparietal junction, and precuneus. Finally, the affective empathy network is mediated by the inferior frontal gyrus, anterior cingulate cortex, amygdala, and insula.

Structural brain alterations in the frontal cortex have been described in the previous section. Temporal cortices are also affected, as well as the amygdala and insula [39,40]. As summarized in a recent narrative review [6], different emotional and social cognition impairments have been described in AUD: altered abilities to express emotions and to decode emotions on faces, in prosody, body postures, and music. Empathy and ToM abilities are also affected [9 for a review].

Very few studies examined the relationship between social cognition and brain structure in AUD. Trick et al. [41] found smaller GM volume in the inferior frontal cortex and insula in AUD patients with low fear recognition performance. Affective empathy was related to cortical thinning in the inferior frontal gyrus [42].

Heterogeneity of brain abnormalities and neuropsychological impairments among AUD patients

AUD is characterized by a marked variability between patients in the nature and extent of brain abnormalities and neuropsychological deficits [27]. Several factors were identified to explain this variability such as parameters related to alcohol history [43–46], or associated malnutrition, thiamine deficiency [47–49] and liver dysfunction [49]. Sleep quality is another factor that could contribute to the heterogeneity of altered brain structure and function in AUD. Indeed, many studies showed that sleep is essential for efficient cognitive abilities [50] and is related to brain integrity [51,52], and there is a considerable evidence that AUD is frequently associated with disturbed sleep.

ALCOHOL-INDUCED SLEEP ABNORMALITIES

Described as alcohol-induced sleep disorder in the DSM-IV and the DSM-5, sleep disturbances can manifest at each stage of AUD, from active alcohol use to sustained abstinence. We will describe, in this section, the nature of sleep complaint and objective sleep disturbances reported during periods of active alcohol use, acute alcohol withdrawal, early abstinence and late abstinence (respectively 1 to 2 weeks, 2 to 8 weeks and more than 8 weeks after drinking cessation; [53]; **Figure 1**).

During active alcohol use

Using the Insomnia Severity Index [54], Chaudhary et al. (2015) reported insomnia symptoms in 74% of AUD patients [55]. Patients actively consuming alcohol complained of difficulties falling asleep (i.e., longer sleep latency; [56] as well as fragmented sleep [57]. Recent studies using the Pittsburgh Sleep Quality index (PSQI [58]) revealed that sleep disturbances are very frequent at this stage of AUD (> 70% of AUD patients [57,59]), independently of age, sex and duration of alcohol dependency [59]. All the dimensions of

sleep explored in the PSQI (subjective sleep quality, sleep latency and duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, daytime dysfunction) are affected [57]. The PSQI score during active drinking predicted sleep disturbances after two weeks of detoxification [59]. Mello and Mendelson reported that active alcohol use induces sleep fragmentation, which is not associated with a decrease in TST. In addition, patients also experience daytime sleepiness combined with occasional naps [60]. Sleepiness would concern about one-third of AUD patients [57].

Polysomnography (PSG) studies conducted at this stage of AUD are scarce but revealed substantial changes in sleep architecture. Thus, sleep onset latency (SOL) and REM sleep latency are increased. Total sleep time (TST) is generally decreased (but see [61] for different results). The amount of slow wave sleep (SWS) increases while time spent in REM sleep is reduced [62–64].

During acute alcohol withdrawal

Drinking cessation is associated in about 50% of AUD patients with clinical symptoms that constitute the alcohol withdrawal syndrome (AWS [65]). The severity of AWS is variable, ranging from a mild clinical form to a more severe one with seizures or *delirium tremens* potentially leading to death [66]. AWS results from a brain hyperexcitability due to increased glutamate transmission combined with decreased GABA transmission [66]. Sleep disturbances are mainly reported during the first week of drinking cessation, in more than 90% of AUD patients assessed with the PSQI [67,68].

These subjective sleep disturbances have been confirmed by actigraphy and PSG recordings. More precisely, studies revealed the persistence of decreased TST [69] and sleep efficiency [57], and increased SOL. The amount of SWS decreases [70], associated with higher sleep fragmentation [57,69,70]. Of note, the proportion of REM sleep, which was

reduced during active alcohol consumption, increases during the withdrawal phase. This phenomenon, called REM sleep rebound [60,70–72], results from an increase in the number of REM episodes and shorter intervals in between. The severity of sleep disturbances during this phase varies importantly across patients, depending on the severity of AWS [69], the history of previous severe neurological complications related to withdrawal (such as *delirium tremens*; [73–75]) or even the global health and nutritional status of the patient [76].

Early in abstinence

Once the acute signs of withdrawal have disappeared and benzodiazepines prescribed during withdrawal no longer affect brain and cognition, AUD patients are generally referred as “early in abstinence” until about 8 weeks of abstinence [9]. Numerous studies have been conducted during this phase and indicate that patients still complain about their sleep [59,67,68,77–89]. They mainly complain of difficulties falling asleep, numerous nocturnal awakenings, decreased TST and daytime sleepiness [9]. Insomnia symptoms are very common in patients, being reported in 36 to 72% of them [53]. This variability can be explained by methodological issues such as different AUD diagnosis criteria, duration of abstinence, sleep measures or contexts in which the assessment was done (in a clinical setting or at home) [72].

Even if it is a little bit out of the scope of this review, it is important to mention that cognitive deficits are not prominent in non AUD insomnia patients. The studies have provided inconsistent findings that can be explained by methodological differences, the definition of the insomnia group and the tasks used that may not be sufficiently sensitive to reveal subtle deficits [90]. A meta-analysis showed that individuals with insomnia exhibit deficits in manipulation and retention in working memory, episodic memory and problem solving, these impairments being of small to moderate magnitude [91]. In another meta-analysis focusing on

executive functions, insomnia patients were impaired on reaction time-based tasks assessing inhibitory control and mental flexibility [92]. Insomnia-related cognitive deficits appear to be observed in tasks relying to some extent on the integrity of the prefrontal cortex. In the case of AUD, we can surmise that insomnia symptoms do not induce major cognitive impairments, but rather exacerbate alcohol-related deficits.

Despite an improvement in sleep quality during the first month of abstinence (in particular, decreased SOL and increased TST), PSG studies revealed that AUD patients early in abstinence still exhibit longer SOL and poorer sleep efficiency than controls after drinking cessation [77,88,93–99]. In addition, such sleep changes are not systematically reported. SOL and SE did not differ from controls in the following studies [78,87,100], while Brower et al. found that only SOL was in the normal range[101].. Sleep is also more fragmented, due to nocturnal awakenings, increased time spent awake and numerous stage shifts [7]. Most of the studies reported significant changes in NREM sleep [7], including a decrease in time spent in N2 and N3 sleep [96,99–101], contrasting with an increase in lighter N1 sleep [77,78,87,88,93–96,98,100]. Compared to controls, EEG analyses showed lower delta activity in N1-N2 [98] and N3 sleep [96,98], supported by visual observation of lower amplitude of K-complexes (evoked delta waves) [85,102]. Changes in REM sleep appear less consistent. Indeed, some studies reported an increase of about 10% in REM sleep proportion related to shorter REM latency [7,70,78,93,96,100,103], an increase in the number of REM sleep episodes and a shorter interval in between [77,88,93,96,101]. An increase in beta activity during REM sleep was also reported [98]. On the contrary, other studies did not observe any change in REM sleep [87,97,99]. These heterogeneous findings could be explained by the presence of psychiatric comorbidities such as depressive symptoms [78,104].

Late in abstinence

Sleep disturbances may persist for a considerable period of time after drinking cessation. The perception of sleep quality remains significantly poorer compared to healthy controls after 3 months [67,79,89], 6 months [77,81] or even one year of abstinence [86]. The significant improvement of insomnia symptoms during the first six months is explained by drinking cessation (55% of the variance explained ; [81]) but is also observed with a reduction of alcohol consumption [105].

Longitudinal PSG studies confirmed the persistence of all sleep disturbances listed above. Increased SOL, decreased TST as well as SWS and REM sleep stages abnormalities are still observed in late abstinence. Lower slow wave activity was reported in NREM sleep, especially over frontal derivations [85]. Difficulties falling asleep (reflected by longer SOL) tend to disappear 5 to 9 months after drinking cessation, while sleep fragmentation seems to persist during 21 months, and TST to normalize within 2 years [93,103]. SWS progressively reaches normal amounts by 2 years of sobriety [93,103]. Regarding REM sleep, here again findings diverge across studies. Drummond et al. reported that, after 27 months of abstinence, most of sleep measures recovered within the normal range, except the proportion of REM sleep which was still higher and REM sleep latency which remained shorter in AUD patients compared to controls [93]. By contrast, other data indicate that after only 3 months of abstinence, REM sleep returns to normal values, and others did not find any significant differences in REM sleep when comparing patients to healthy controls [103,106,107]. These inconsistencies in the dynamic of sleep recovery may be explained by differences in patients' characteristics and the duration of sobriety.

Other sleep disturbances in AUD

Besides changes in sleep quality and architecture, AUD patients also frequently suffer from sleep-disordered breathing (SDB) and periodic limb movement disorder (PLMD) that can both contribute to alter sleep quality. We will also briefly describe alterations in circadian rhythms.

A recent meta-analysis showed that alcohol consumption is a risk factor for the development or worsening of SDB [108]. Few investigations have been conducted on SDB in recently detoxified AUD patients. In a study carried out in 188 AUD patients, a moderate SDB (defined as 10 or more apneas-hypopneas per hour of sleep) was observed in 23,5% of patients aged 40 or over and 50% of patients aged 60 or over [109]. Respiratory events are both central [110] and obstructive [97,109,110]. Several hypotheses have been proposed to explain the high prevalence of SDB in AUD patients. First, alcohol consumption reduces genioglossal muscle tone, favoring upper airway collapse [109]. Second, excessive alcohol consumption represents an important caloric intake, that may lead on the long-term to overweight or obesity, which are known as risk factors for SDB [111]. Finally, alcohol has neurotoxic effects on the brain stem and vagus nerve that are involved in respiratory functions [107].

PLMD is diagnosed when a patient meets the criterion of 15 repetitive limb movements per hour of sleep. The prevalence of PLMD in the general population is 3.9% [112]. Alcohol use has been shown to increase the frequency of periodic limb movements (PLMs; [113]) but, to the best of our knowledge, there is no prevalence estimation in AUD patients. Two studies observed more PLMs in AUD patients compared to controls [106,114] but this result was not consistently reported [97]. In a study conducted in 139 AUD patients, Brower & Hall [115] showed that AUD patients, and especially those aged over 55, had more

PLMs than younger ones and healthy individuals. This higher PLMs-index in AUD patients may be explained by a decrease in dopaminergic neurotransmission [114].

Finally, alterations of circadian rhythms are also common in AUD (see [116] for a recent review). Briefly, acute alcohol intake induces dose-dependent changes in biological rhythms (e.g., core body temperature, melatonin and cortisol secretions) but these changes normalize within 24 hours. In AUD patients, because of chronic alcohol use, those changes are more severe and persist over time. During acute alcohol withdrawal, the desynchronization of circadian rhythms correlates with the severity of AWS and is associated with neurological complications. With abstinence, alterations of circadian rhythms generally recover within one month, except for melatonin secretion whose disruption can last several months [116].

IMPACT OF SLEEP DISTURBANCES ON COGNITIVE IMPAIRMENTS IN AUD

The role of sleep in cognitive and emotional functioning has been well described in healthy individuals [117,118] and accumulating evidence suggests that sleep disturbances are associated with cognitive deficits in ageing [119], Alzheimer's disease [120] and in psychiatric diseases such as schizophrenia [121]. However, the impact of sleep disturbances on cognitive deficits in AUD remains unclear. In this section, we will focus on episodic memory, executive functions, emotion and social cognition, which are known to be frequently impaired in AUD patients as previously mentioned (**Table 1**).

Sleep and episodic memory

One of the essential functions of sleep is to favor the consolidation of recently acquired information into long-term stores [122,123]. For episodic memories, this process mainly operates during NREM sleep [122], but some studies also reported a beneficial effect of REM sleep [124], especially for emotionally-laden memories [125].

To our knowledge, only one study investigated sleep-dependent memory consolidation in AUD patients [79]. The authors proposed a face-name association task to two groups of patients with different lengths of abstinence (short-term (2-4 weeks) and long-term (10-22 weeks) abstinence). In both groups of patients, daily alcohol consumption before drinking cessation negatively correlated with memory performance, and the duration of alcohol dependence negatively correlated with the amount of NREM sleep. The two groups did not differ from each other with respect to sleep parameters and presented similar overnight decline in recall performance. In the group of long-term abstainers, the duration of abstinence positively correlated with the amount of SWS. The authors concluded that chronic and excessive alcohol consumption negatively affects NREM sleep, which in turn impairs sleep-dependent memory consolidation. In this study, patients also performed a mirror tracing task to assess procedural memory consolidation. Both groups improved significantly their

performance with practice. The overnight improvement in mirror tracing performance negatively correlated with SOL and positively correlated with the amount of REM sleep. Compared to normative data, AUD patients showed higher amount of REM sleep [79], but this may not be pathological, as increases in REM sleep were observed after procedural learning [126]. Overall, sleep-dependent memory consolidation has been seldom investigated in recently sober AUD patients. Even though the available data suggest a dissociation between episodic and procedural memory consolidation, the former being impaired and the latter one rather preserved, further studies are needed to confirm these results.

Beyond its contribution to overnight memory consolidation, poor sleep before learning has a negative impact on new learning. Yoo et al. [127] showed that one single night of sleep deprivation reduces hippocampal activity during encoding and modifies functional connectivity in alertness networks, compromising successful encoding of new experiences. A similar phenomenon was also described after multiple nights of partial sleep restriction [128] and in individuals reporting short sleep duration [50]. No study has been conducted in AUD patients, but these results suggest that poor sleep may also have an impact on patients' encoding abilities.

Sleep and executive functions

Executive functions are particularly vulnerable to poor sleep quality [129], total sleep deprivation and chronic sleep restriction [50] in young and middle-aged individuals. Sleep deprivation impairs flexibility [130], inhibition (by increasing perseverations, errors, omissions and the sensibility to interference [50]) and working memory [131]. Sleep duration has an inverse U shaped relationship with executive functions: short and very long sleep durations are associated with lower working memory and mental flexibility performance in young individuals [132,133]. Beyond sleep quantity, impaired sleep continuity (reflected by increased time spent awake after sleep onset) and lower proportion of SWS also have a

negative impact on working memory performance [131,132]. In addition, sleep is essential for decision making, which requires the integration of complex cognitive and emotional information. Sleep deprivation impairs decision making [134], favors risk taking [134], and increases impulsivity [135]. Indeed, total sleep deprivation may alter the functioning of brain areas involved in the reward network, which in turn may favor unrealistic expectations of gains and underestimation of the consequences of losses [136]. Concerning the impact of sleep restriction, results are less clear. Although some studies showed that sleep restriction impairs decision making abilities [137,138], a meta-analysis concluded that evidence in favor of a negative impact of chronic sleep restriction on risk taking is insufficient [50]. Finally, Seeley et al. [139] proposed trials of the Iowa Gambling Tasks prior and after a period of sleep and showed that post-learning sleep, especially theta activity during REM sleep, enhanced decision-making performance.

The impact of sleep disturbances on the executive deficits frequently observed in AUD was explored in only one study reporting that the amount of REM sleep positively correlated with performance on a backward span task, suggesting a relationship between REM sleep and the ability to manipulate information in working memory [140]. Two hypotheses were proposed to explain these results. First, chronic and excessive alcohol consumption alters REM sleep, which in turn impairs the processes underlying the central executive of working memory. Second, chronic and excessive alcohol consumption disrupts common neurobiological mechanisms involved in both sleep and working memory.

A recent study combined an assessment of subjective sleep quality using the PSQI, with cognitive testing and a neuroimaging examination in a sample of AUD patients with and without Korsakoff's Syndrome (KS). The authors found that only the AUD patients who did not complain about their sleep presented executive deficits, similar to those of KS patients who did not complain either [141]. These results suggest that certain cognitive deficits,

especially executive dysfunction, may alter the ability to self-evaluate sleep quality. From a clinical perspective, sleep problems could be neglected in AUD patients who are not cognitively able to complain and would therefore remain untreated. Such a situation would worsen sleep-related consequences in AUD patients, and affect the treatment outcome.

Sleep, emotion and social cognition

In healthy individuals, chronic sleep restriction and total sleep deprivation impair the ability to decode emotional expressions, especially anger [142], happiness [142,143] and sadness [143,144]. In addition, total sleep deprivation [145], lower subjective sleep quality [146], and shorter sleep duration [146] alter the ability to infer the emotional state of other individuals (affective ToM). Sleep deprivation has also been related to more stereotyping and implicit bias toward minority groups, influencing social decision made about individual's trustworthiness based on facial features [147,148]. Finally, poor sleepers are more susceptible to social rejection and conflicting relationships, contributing to social withdrawal and loneliness.

Overall, these studies highlight the links between poor sleep and impaired social cognition abilities, which could accentuate social issues and interpersonal difficulties frequently observed in AUD patients [6]. Complaining about sleep is associated with more severe subjective reports of alcohol-related psychosocial problems in AUD [55,149]. However, no study has investigated the potential moderation effect of sleep disturbances on the relationships between AUD and impaired emotional and social cognition. Finally, social difficulties (loneliness, interpersonal conflicts, perceived social rejection) also have an impact on both subjective and objective sleep quality, suggesting a potential bidirectional relationships between sleep disturbances and interpersonal problems [150].

To sum up, only a few studies have explored the links between sleep alterations and cognitive and emotional impairments in AUD patients. First, these studies show that sleep-dependent episodic memory consolidation is impaired and associated with the amount of SWS. In contrast, consolidation in procedural memory appears as preserved [79]. Second, executive deficits are related to low amounts of REM sleep [140] and an altered ability to self-evaluate sleep quality leading to rare or mild sleep complaint in those patients [141]. Finally, greater self-reported psychosocial problems are associated with major sleep complaints [55,149]. Further studies are now required to deepen our understanding regarding the role of the different sleep components/parameters on cognitive and emotional deficits and to determine whether these associations last with sustained abstinence.

RELATIONSHIPS BETWEEN SLEEP DISTURBANCES AND BRAIN ALTERATIONS IN AUD

Considering the relationships between sleep disturbances and cognitive impairments, it is relevant to investigate how sleep is related to structural (including GM and WM volume) and functional brain alterations in AUD patients.

Structural brain imaging

Cross-sectional studies conducted in middle-aged individuals revealed that poor self-reported sleep quality [51], early morning awakening [151] and daytime sleepiness [152] are associated with lower GM volume in frontal areas. In addition, short sleep duration was related to global atrophy [153], to lower thalamic volume [154] and to altered white matter microstructure in frontal areas, superior corona radiata and the inferior longitudinal fasciculus [155]. In addition, the presence of subjective sleep disturbances correlated with reduced white matter integrity in frontal, anterior cingulate and limbic regions as well as in the insula [155] but see [156] for different results).

Three studies investigated the association between sleep abnormalities and structural brain alterations in abstinent AUD patients. Using a descriptive analysis of 9 AUD patients, Ishibadi et al. [157] showed that with prolonged abstinence, a recovery of structural damage measured with computerized tomography (CT) scans was observed in 5 patients, four of them also presenting an increase in the amount of SWS. The authors concluded that early in abstinence, low amounts of SWS may result from cortical atrophy. In a more recent study, Colrain et al. [158] showed that lower regional GM volumes (in frontal, temporal, sensorimotor, parietal and occipital cortices) contributed to the changes in the amplitude of K-complexes observed in long-term abstinent AUD patients. Regarding subjective sleep quality, a relationship was found between subjective sleep disturbances and brain structure: only the AUD patients who did not complain about their sleep presented brain shrinkage and altered white matter integrity in fronto-temporal regions and in the thalamus. These brain alterations were as severe as those observed in KS patients who did not complain either [141]. Such findings reinforce the idea that preserved brain integrity is required to be able to efficiently self-evaluate sleep quality.

Functional brain imaging

Sleep disturbances are also associated with changes in brain metabolism and functional connectivity in healthy individuals. In young to middle-aged adults, a decrease of the metabolic activity in the frontal cortex, anterior cingulate gyrus, thalamus, basal ganglia and cerebellum has been described following sleep deprivation [159]. Moreover, several brain regions constituting the default mode network, the limbic, salience and executive networks are functionally altered following sleep deprivation [160]. Changes in functional connectivity have been commonly reported after sleep deprivation, notably between the thalamus and middle temporal regions, superior and medial frontal areas, and anterior cingulate cortex

[161]. In particular, functional changes in frontal and anterior cingulate areas induced by sleep deprivation have been related to executive deficits [162]. When exposed to emotional faces, sleep-deprived subjects exhibited higher amygdala activation and lower activity in the prefrontal cortex compared to individuals who slept normally, resulting in a prefrontal-amygdala disconnection [163]. Moreover, sleep-deprived individuals exhibited lower activity in the ToM network (including the temporo-parietal junction, the precuneus and the medial prefrontal cortex) associated with higher subjective rating of loneliness [164].

Poor sleep quality may thus contribute to the changes in brain metabolism and functional connectivity reported in AUD patients. However, studies conducted on that topic are scarce. Only a recent investigation showed that the severity of AUD was associated with poor subjective sleep quality, this association being mediated by the strength of the functional connectivity between the thalamus and the medial prefrontal cortex in AUD patients [165]. However, patients were asked to stop drinking for at least 48 hours before inclusion, which may have directly altered sleep and modified functional brain connectivity through potential AWS.

To sum up, sleep disturbances appear to be associated with structural and functional brain alterations in abstinent AUD patients. While the number of studies is too limited to draw definite conclusions, integrity of fronto-temporal regions and thalamus may be related to sleep quality in this disease [141,165]. Previous studies differ in terms of inclusion criteria, sleep parameters analyzed and neuroimaging approaches used. Further studies are thus needed to specify the brain regions that are particularly vulnerable to poor sleep quality in AUD using multimodal neuroimaging (brain structure, metabolism and functional connectivity), and to determine whether recovery occurs with sustained abstinence.

DISCUSSION

Overall, very few studies have explored the relationships between sleep quality, brain alterations and cognitive deficits in AUD patients. Regarding sleep complaint, subjective sleep quality was associated with both structural [141] and functional brain alterations [165], notably in fronto-temporal regions and the thalamus. Subjective sleep disturbances were also related to poor executive abilities [141] and more severe interpersonal difficulties [55,149]. Regarding objective sleep quality, the decrease in SWS was associated with structural brain alterations [157] and impaired episodic memory consolidation [79]. In contrast, low amounts of REM sleep were rather related to executive deficits [140]. While further studies are required to confirm these relationships, these data suggest that both subjective and objective sleep quality correlate with alcohol-related brain damage and cognitive deficits in AUD patients. Below, we discuss the directionality of these relationships and their time course, as well as their potential role in alcohol relapse (**Figure 2**).

- **Sleep disturbances and alcohol-related brain damage: bidirectional relationships?**

A crucial question concerns the directionality of the relationships between sleep disturbances, and alcohol-related brain abnormalities and dysfunction in AUD. We propose that two complementary hypotheses may explain these bidirectional relationships (**1, Figure 2**). First, sleep disturbances may be a consequence of alcohol-related brain damage. Both chronic and excessive alcohol consumption, as well as alcohol withdrawal, induce brain damage in sleep-promoting regions. Structural and/or functional abnormalities in frontal temporal and parietal cortices, as well as in the thalamus and the insula [166–168] may contribute to sleep disturbances, which may in turn result in cognitive deficits in AUD patients. Second, poor sleep quality may contribute to the development of alcohol-related

brain damage. Alcohol-related sleep disturbances and brain damage may co-occur since resulting from common mechanisms such as impaired neurogenesis [169], increased glutamate levels [170,171], neuroinflammation [172] and oxidative stress [173]. Brain abnormalities and cognitive deficits would thus be exacerbated in AUD patients with poor sleep quality. These two hypotheses seem difficult to disentangle in clinical studies and require preclinical investigations to be put to the test. However, exploration of sleep quality in the course of the disease may provide some first insights.

- **Contribution of sleep disturbances at all stages of AUD**

Sleep disturbances are present at all stages of AUD i.e. during acute alcohol intoxication, the acute alcohol withdrawal phase, as well as early and late in abstinence (2, **Figure 2**). Several studies indicated that sleep disruption may even precede the development of AUD. Retrospective investigations showed that some AUD patients report sleep disruption before the onset of the disease [86]. Moreover, studies conducted in adolescents [174,175] and young adults [176,177] suggest that difficulties in initiating and maintaining sleep may favour excessive alcohol consumption and binge drinking. Finally, the disruption of circadian rhythms may also be a factor contributing to the development of addictive behaviors [116]. In particular, the evening chronotype has been associated with a higher risk of developing AUD [116]. These results first suggest that sleep disturbances may be considered as an early vulnerability factor for substance abuse [178] and notably AUD. In addition, alcohol-related brain abnormalities and cognitive deficits tend to recover [179], at least partially, with sustained abstinence while sleep quality remains poor even in long-term abstainers. It will be relevant, in future studies, to understand how sleep could modulate cerebral and cognitive recovery, and whether poor sleep quality could explain, at least partly, the persistence of some

cognitive deficits despite sobriety. Long-lasting sleep difficulties may thus contribute to persisting functional and structural brain abnormalities in AUD.

- **Direct and indirect role of sleep disturbances in relapse**

Previous studies demonstrated that sleep disturbances constitute a poor prognostic for treatment outcomes in AUD patients, by directly increasing the risk of alcohol relapse [180]. An association was observed between relapse and sleep disruption assessed using both questionnaires (global sleep complaint and difficulty to fall asleep) and objective measures (longer SOL, number of awakenings, increased REM sleep pressure, higher beta activity during REM sleep and decreased amount of NREM sleep; increased PLMs-arousal index) [77,83,88,93,104,114,181,182]. More recently, some authors proposed that sleep disturbances may indirectly contribute to relapse notably by increasing psycho-affective symptoms [94] and alcohol craving [84,183]. Psycho-affective symptoms, such as anxiety and depression, often co-occur in AUD [184,185] and increase the risk of relapse [186]. In AUD, sleep disturbances, and more particularly REM sleep abnormalities have been associated with more severe depressive symptoms [78,104] and relapse [77,83]. We can thus hypothesize an association between sleep disturbances, psycho-affective symptoms and relapse.

Craving, defined as the persistent urge or desire to use a substance [10], is experienced by 54-72% of AUD patients [84]. Some studies reported that a higher alcohol craving score (assessed using the Penn Alcohol Craving Scale, [187]) was related to difficulties falling asleep in recently detoxified AUD patients [84,183] but also after 3 months of abstinence [183]. Different hypotheses have been proposed to explain this relationship. At first, during the acute alcohol intoxication, many AUD patients use alcohol as a coping strategy to treat

their sleep problems [80,188,189]. With prolonged alcohol consumption, the initially helpful effect of alcohol to fall sleep is reduced, due to a progressive tolerance to this hypnotic effect, leading to increased sleep disturbances, fatigue and/or negative mood state. These alterations, together an ineffective coping response to sleep problems or positive expectancies about the effects of alcohol on sleep, may in turn increase their urge to drink [183]. Other mechanisms have been reported, notably the existence of common neurobiological substrates between sleep-wake regulation [190] and the modulation of alcohol consumption by regions involved in the reward system [191]. Further studies are needed to clarify the interactions between sleep, psycho-affective symptoms and craving in the context of alcohol relapse but their co-existence suggests the clinical relevance to manage them simultaneously.

Here, we propose that alcohol-related sleep disturbances may also indirectly increase the risk of alcohol relapse through their contribution to brain alterations and cognitive deficits **(3, Figure 2)**. In this review, we highlighted the fact that alcohol-related sleep alterations are associated with structural and functional abnormalities mainly in fronto-temporal regions and their connections, as well as in the thalamus. These brain regions, involved in several brain networks underlying episodic memory, executive functions, emotion and social cognition, are commonly damaged in recently detoxified AUD patients and such cognitive deficits are consequently frequently observed. Altered episodic memory abilities, executive function or social cognition could have negative consequences on patients' capacity to benefit fully from treatment [192] or to maintain abstinence or reduce alcohol consumption. Indeed, psychosocial treatments, including cognitive-behavioral therapies or motivational interview, require these cognitive abilities [28]. When they decide to change drinking behavior, patients must plan new strategies, inhibit old routines and make the right decision in risky situations. From a clinical perspective, improving sleep quality should thus not only be considered as a

therapeutic target to directly reduce alcohol craving and psycho-affective symptoms, but also to improve brain structure and function, which would indirectly favor treatment outcome.

Overall, sleep quality seems 1) to constitute a critical factor for the development of AUD, 2) to be a consequence of alcohol-related brain damage, 3) to contribute to the development of alcohol-related brain damage and cognitive deficits, and 4) to affect alcohol treatment outcome. It is thus crucial to manage sleep disturbances in AUD patients.

MANAGEMENT OF SLEEP DISORDERS IN AUD

Clinical observation and questioning of the patient are fundamental to reveal and characterize sleep difficulties. Identifying the nature of sleep complaint (difficulties falling asleep, early morning awakening, daytime sleepiness...) is essential to propose adapted intervention strategies and to avoid the use of alcohol as self-medication. In addition, it is of utmost importance to interpret sleep complaint in the light of the cognitive deficits of the patients, especially when those patients present severe executive dysfunction that may alter their self-evaluation abilities [141]. Sleep quality should be assessed in a dynamic way, at each step of the patients' management, to determine the origin of sleep disturbances and when they began. Indeed, a particular attention should be provided to AUD patients who used alcohol as a coping strategy for sleep problems because it may be associated with high risk of craving and subsequent relapse [183].

In this way, treatment of sleep disturbances requires therapeutic options that result in both rapid and lasting sleep improvements. The very first strategy to improve sleep quality must systematically be to favor alcohol drinking cessation [81]. Non-pharmacological sleep interventions can be used from the acute withdrawal period to long-term sobriety. Psychoeducation on sleep hygiene, aiming notably at identifying and correcting the false beliefs about sleep and about the effect of alcohol on sleep, is generally a good starting point but is not sufficient *per se*. Cognitive behavioral therapies can be conducted in case of

persistent insomnia (CBT-I; [193]). This kind of therapy has been successfully used in AUD patients [9]. CBT programs require experienced staff, potentially limiting their application in clinical settings, and their efficacy is observed after several weeks of therapy. However, studies assessing internet-based [194–196] and app-based [197] versions of CBT-1 revealed similar efficacy to more traditional therapy. Thus, these tools could be a relevant option in the treatment of insomnia. In parallel, a short-term prescription of pharmacological agents could also be proposed to promote a rapid sleep improvement in AUD patients with severe sleep difficulties [198]. For instance, a 12 week treatment by Gabapentin, a widely prescribed generic calcium channel/ γ -aminobutyric acid-modulating medication, has been shown to improve the rate of abstinence and reduced the number of heavy drinking days in AUD patients. The treatment also improved mood, sleep disturbances and craving [199]. However, a recent meta-analysis of 16 studies indicated that the effect on mood and sleep are not consistently observed [200]. Physical activity may also have a beneficial effect on sleep both in the general population and in patients with psychiatric diseases [201,202]. Thus, the development of physical activity programs, adjusted to patients' comorbidities, may be useful to improve sleep, but also cognitive abilities and quality of life, in AUD patients.

A persisting sleep complaint and/or the observation of daytime symptoms such as fatigue or excessive daytime sleepiness, may be signs of sleep disturbances and especially sleep apneas. Complementary examinations should be proposed to those patients to confirm the presence of sleep apneas and treat them (for instance with continuous positive airway pressure). Finally, it is also crucial to take psychiatric and other addictive comorbidities into account for the treatment of sleep disorders. These comorbidities could exacerbate existing sleep difficulties. For example, nicotine substitutes should be proposed in smoking AUD patients to reduce the effects of nicotine withdrawal overnight (i.e., multiple awakenings contributing to sleep fragmentation, [203]).

CONCLUSION AND FUTURE DIRECTIONS

To sum up, alcohol-related sleep disturbances are present at all stages of AUD, can persist several months after drinking cessation and predict relapse. They can also be observed before the onset of AUD, favoring the emergence of substance abuse. In AUD patients early in abstinence, sleep disturbances seem to be related to altered structure and function of brain networks underlying episodic memory, executive functions, emotions and social cognition. Sleep disturbances may rather precede the development of AUD than be a consequence of alcohol-related brain damage, and may thus contribute to the pathophysiology of AUD. The understanding of the interactions between sleep disturbances, cognitive deficits and brain alterations in AUD is still in its infancy. Studies combining sleep assessments, multimodal neuroimaging examinations (structural MRI, brain metabolism and functional connectivity) and fine-grained cognitive measures will undoubtedly improve our knowledge of this disease, favor the development of adapted treatment strategies and limit the risk of relapse.

FIGURES AND TABLES

Figure 1: Objective and subjective sleep disturbances at each stage of AUD.

This figure summarizes objective and subjective sleep disturbances in AUD patients during active alcohol use, acute withdrawal phase, early in abstinence (< 2 months of abstinence) and late in abstinence (> 2 months of abstinence).

↑ : increased compared to controls or baseline in the case of longitudinal studies ; ↓ : decreased compared to controls or baseline in the case of longitudinal studies. The dotted arrows indicate inconsistent results (for more details, see section 2: Alcohol-induced sleep abnormalities).

Figure 2: Contribution of sleep disturbances to alcohol-related brain alterations and cognitive deficits in AUD.

This figure summarizes the potential relationships between sleep disturbances and alcohol related brain damage and cognitive deficits in AUD. First, bidirectional relationships may exist between sleep disturbances and alcohol related brain damage in AUD (represented by the green arrows **1**): sleep disturbances could be a consequence of alcohol-related brain damage, but may also contribute to the pathophysiology of AUD by exacerbating pathophysiological mechanisms underlying alcohol-related brain damage in AUD. Second, these bidirectional relationships may exist from acute alcohol consumption to alcohol recovery, suggesting precocity and persistence of these associations (represented by the purple arrow **2**). Finally, sleep disturbances have direct consequences on alcohol relapse through increased craving notably, but may also indirectly influence alcohol relapse by increasing alcohol-related cognitive deficits (represented by the yellow arrows **3**).

Table 1: Descriptive characteristics and main findings of studies conducted on the relationships between sleep disturbances, brain abnormalities and cognitive impairments in abstinent AUD patients.

Abbreviations: AUD : alcohol use disorder (this term is used here to refer to patients with either “alcohol-dependence” according to the DSM-IV criteria or “alcohol use disorder” according to the DSM-5); HC: Healthy controls; KS: patients with Korsakoff’s Syndrome; PSG : polysomnography; PSQI: Pittsburg sleep quality index [58]; ISI : insomnia severity index [54] ; SIP questionnaire: short index of problems [204]; IDTS questionnaire: inventory of drug-taking situations [205] ; CT: computed tomography; GM: gray matter; WM: white matter; DTI: diffusion tensor imaging; REM: rapid eye movement; SWS: slow wave sleep; NREM: non rapid eye movement; /: not available.

For age, duration of alcohol dependence and abstinence before inclusion, the mean was reported and the standard-deviation when this information was available.

RESEARCH AGENDA

- Research needs to clarify the particular aspects of sleep quality, architecture and microstructure that are related to specific cognitive deficits in alcohol use disorder.
- Future studies are needed to specify the brain regions that are particularly vulnerable to poor sleep in alcohol use disorder.
- Longitudinal designs are required to better understand how sleep can modulate brain and cognitive recovery and to determine whether long-lasting poor sleep can explain, at least partly, the persistence of some cognitive deficits in patients with AUD.
- Studies combining sleep assessments, multimodal neuroimaging and cognitive evaluations are needed to improve our knowledge about sleep disturbances in alcohol use disorder, and adapt treatment strategies to reduce the risk of relapse.

PRACTICE POINTS

- Sleep disturbances are very frequent at all stages of alcohol use disorder (i.e. from active alcohol use to sustained abstinence) and can favor relapse.
- Complex bidirectional relationships seem to exist between sleep and alcohol use disorder: sleep disturbances could be the consequence of alcohol-related brain damage, but may also contribute to brain alterations and cognitive deficits.
- Sleep may contribute to the heterogeneity of brain alterations and cognitive deficits observed in patients with in alcohol use disorder.
- Long-lasting sleep difficulties may contribute to persistent functional and structural brain abnormalities in alcohol use disorder.
- Clinicians in Addiction departments should pay a particular attention to sleep disorders to optimize treatment of AUD patients.

CONFLICTS OF INTEREST: The authors have no conflicts of interest to disclose.

REFERENCE LIST

*: KEY REFERENCES

- [1] Carvalho AF, Heilig M, Perez A, Probst C, Rehm J. Alcohol use disorders. *Lancet* 2019;394:781–92. [https://doi.org/10.1016/S0140-6736\(19\)31775-1](https://doi.org/10.1016/S0140-6736(19)31775-1).
- [2] World Health Organization. Global status report on alcohol and health. 2018.
- [3] Rehm J, Gmel GE, Gmel G, Hasan OSM, Imtiaz S, Popova S, et al. The relationship between different dimensions of alcohol use and the burden of disease—an update. *Addiction* 2017;112:968–1001. <https://doi.org/10.1111/add.13757>.
- [4] Connor JP, Haber PS, Hall WD. Alcohol use disorders. *Lancet* 2016;387:988–98. [https://doi.org/10.1016/S0140-6736\(15\)00122-1](https://doi.org/10.1016/S0140-6736(15)00122-1).
- [5] Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 Alcohol Use Disorder. *JAMA Psychiatry* 2015;72:757. <https://doi.org/10.1001/jamapsychiatry.2015.0584>.
- [6] Le Berre A-P. Emotional processing and social cognition in alcohol use disorder. *Neuropsychology* 2019;33:808–21. <https://doi.org/10.1037/neu0000572>.
- *[7] Koob GF, Colrain IM. Alcohol use disorder and sleep disturbances: a feed-forward allostatic framework. *Neuropsychopharmacology* 2020;45:141–65. <https://doi.org/10.1038/s41386-019-0446-0>.
- [8] Colrain IM, Nicholas CL, Baker FC. Alcohol and the sleeping brain. *Handb. Clin. Neurol.*, vol. 125. 1st ed., Elsevier B.V.; 2014, p. 415–31. <https://doi.org/10.1016/B978-0-444-62619-6.00024-0>.
- [9] Chakravorty S, Chaudhary NS, Brower KJ. Alcohol Dependence and Its Relationship With Insomnia and Other Sleep Disorders. *Alcohol Clin Exp Res* 2016;40:2271–82. <https://doi.org/10.1111/acer.13217>.
- [10] American Psychiatric Association. DSM-5 Diagnostic Classification. *Diagnostic Stat.*

- Man. Ment. Disord., American Psychiatric Association; 2013.
<https://doi.org/10.1176/appi.books.9780890425596.x00DiagnosticClassification>.
- [11] American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). vol. 1. Arlington, VA: American Psychiatric Association; 2000.
<https://doi.org/10.1176/appi.books.9780890423349>.
- [12] World Health Organization. Mental and behavioural disorders due to psychoactive substance use. World Heal Organ 1990:F10–9.
https://www.who.int/substance_abuse/terminology/ICD10ClinicalDiagnosis.pdf?ua=1.
- [13] Oscar-Berman M, Marinković K. Alcohol: Effects on neurobehavioral functions and the brain. *Neuropsychol Rev* 2007;17:239–57. <https://doi.org/10.1007/s11065-007-9038-6>.
- [14] Pitel A-L, Beaunieux H, Witkowski T, Vabret F, Guillery-Girard B, Quinette P, et al. Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. *Alcohol Clin Exp Res* 2007;31:1169–78.
<https://doi.org/10.1111/j.1530-0277.2007.00418.x>.
- [15] Noël X, Van der Linden M, Brevers D, Campanella S, Hanak C, Kornreich C, et al. The contribution of executive functions deficits to impaired episodic memory in individuals with alcoholism. *Psychiatry Res* 2012;198:116–22.
<https://doi.org/10.1016/j.psychres.2011.10.007>.
- [16] Pitel A-L, Beaunieux H, Witkowski T, Vabret F, de la Sayette V, Viader F, et al. Episodic and Working Memory Deficits in Alcoholic Korsakoff Patients: The Continuity Theory Revisited. *Alcohol Clin Exp Res* 2008;32:1229–41.
<https://doi.org/10.1111/j.1530-0277.2008.00677.x>.
- [17] Papez JW. A proposed mechanism of emotion. *Arch Neurol Psychiatry* 1937.

- <https://doi.org/10.1001/archneurpsyc.1937.02260220069003>.
- [18] Wilson S, Bair JL, Thomas KM, Iacono WG. Problematic alcohol use and reduced hippocampal volume: a meta-analytic review. *Psychol Med* 2017;47:2288–301. <https://doi.org/10.1017/S0033291717000721>.
- [19] Sullivan EV, Lane B, Deshmukh A, Rosenbloom MJ, Desmond JE, Lim KO, et al. In vivo mammillary body volume deficits in amnesic and nonamnesic alcoholics. *Alcohol Clin Exp Res* 1999;23:1629–36. <https://doi.org/10.1111/j.1530-0277.1999.tb04054.x>.
- [20] Pitel A-L, Chételat G, Le Berre A-P, Desgranges B, Eustache F, Beaunieux H. Macrostructural abnormalities in Korsakoff syndrome compared with uncomplicated alcoholism. *Neurology* 2012;78:1330–3. <https://doi.org/10.1212/WNL.0b013e318251834e>.
- [21] Klaming R, Harlé KM, Infante MA, Bomyea J, Kim C, Spadoni AD. Shared gray matter reductions across alcohol use disorder and posttraumatic stress disorder in the anterior cingulate cortex: A dual meta-analysis. *Neurobiol Stress* 2019;10:100132. <https://doi.org/10.1016/j.ynstr.2018.09.009>.
- [22] Pitel A-L, Segobin SH, Ritz L, Eustache F, Beaunieux H. Thalamic abnormalities are a cardinal feature of alcohol-related brain dysfunction. *Neurosci Biobehav Rev* 2015;54:38–45. <https://doi.org/10.1016/j.neubiorev.2014.07.023>.
- [23] Segobin S, Laniepe A, Ritz L, Lannuzel C, Boudehent C, Cabé N, et al. Dissociating thalamic alterations in alcohol use disorder defines specificity of Korsakoff's syndrome. *Brain* 2019;142:1458–70. <https://doi.org/10.1093/brain/awz056>.
- [24] Segobin S, Ritz L, Lannuzel C, Boudehent C, Vabret F, Eustache F, et al. Integrity of white matter microstructure in alcoholics with and without Korsakoff's syndrome. *Hum Brain Mapp* 2015;36:2795–808. <https://doi.org/10.1002/hbm.22808>.
- [25] Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A. Anterior Hippocampal

- Volume Deficits in Nonamnesic, Aging Chronic Alcoholics. *Alcohol Clin Exp Res* 1995;19:110–22. <https://doi.org/10.1111/j.1530-0277.1995.tb01478.x>.
- [26] Chanraud S, Leroy C, Martelli C, Kostogianni N, Delain F, Aubin H-J, et al. Episodic Memory in Detoxified Alcoholics: Contribution of Grey Matter Microstructure Alteration. *PLoS One* 2009;4:e6786. <https://doi.org/10.1371/journal.pone.0006786>.
- [27] Ihara H, Berrios GE, London M. Group and case study of the dysexecutive syndrome in alcoholism without amnesia. *J Neurol Neurosurg Psychiatry* 2000;68:731–7. <https://doi.org/10.1136/jnnp.68.6.731>.
- [28] Le Berre A-P, Laniece A, Segobin S, Pitel A-L, Sullivan EV. Alcohol Use Disorder Permanent and Transient Effects on the Brain and Neuropsychological Functions. In: Alosco ML, Stern RA, editors., Oxford University Press; 2019, p. 302–32.
- [29] Kelly RM, Strick PL. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *J Neurosci* 2003;23:8432–44. <https://doi.org/10.1523/JNEUROSCI.23-23-08432.2003>.
- [30] Zahr NM, Pfefferbaum A, Sullivan EV. Perspectives on fronto-fugal circuitry from human imaging of alcohol use disorders. *Neuropharmacology* 2017;122:189–200. <https://doi.org/10.1016/j.neuropharm.2017.01.018>.
- [31] Sullivan EV. Compromised pontocerebellar and cerebellothalamocortical systems: Speculations on their contributions to cognitive and motor impairment in nonamnesic alcoholism. *Alcohol Clin Exp Res* 2003;27:1409–19. <https://doi.org/10.1097/01.ALC.0000085586.91726.46>.
- [32] Chanraud S, Martelli C, Delain F, Kostogianni N, Douaud G, Aubin H-J, et al. Brain Morphometry and Cognitive Performance in Detoxified Alcohol-Dependents with Preserved Psychosocial Functioning. *Neuropsychopharmacology* 2007;32:429–38. <https://doi.org/10.1038/sj.npp.1301219>.

- [33] Chanraud S, Reynaud M, Wessa M, Penttilä J, Kostogianni N, Cachia A, et al. Diffusion Tensor Tractography in Mesencephalic Bundles: Relation to Mental Flexibility in Detoxified Alcohol-Dependent Subjects. *Neuropsychopharmacology* 2009;34:1223–32. <https://doi.org/10.1038/npp.2008.101>.
- [34] Zahr NM, Pitel A-L, Chanraud S, Sullivan EV. Contributions of studies on alcohol use disorders to understanding cerebellar function. *Neuropsychol Rev* 2010;20:280–9. <https://doi.org/10.1007/s11065-010-9141-y>.
- [35] Crespi C, Galandra C, Manera M, Basso G, Poggi P, Canessa N. Executive Impairment in Alcohol Use Disorder Reflects Structural Changes in Large-Scale Brain Networks: A Joint Independent Component Analysis on Gray-Matter and White-Matter Features. *Front Psychol* 2019;10. <https://doi.org/10.3389/fpsyg.2019.02479>.
- [36] Frith CD. Social cognition. *Philos Trans R Soc B Biol Sci* 2008;363:2033–9. <https://doi.org/10.1098/rstb.2008.0005>.
- [37] Abu-Akel A, Shamay-Tsoory S. Neuroanatomical and neurochemical bases of theory of mind. *Neuropsychologia* 2011;49:2971–84. <https://doi.org/10.1016/j.neuropsychologia.2011.07.012>.
- [38] Dvash J, Shamay-Tsoory SG. Theory of Mind and Empathy as Multidimensional Constructs. *Top Lang Disord* 2014;34:282–95. <https://doi.org/10.1097/TLD.0000000000000040>.
- [39] Yang X, Tian F, Zhang H, Zeng J, Chen T, Wang S, et al. Cortical and subcortical gray matter shrinkage in alcohol-use disorders: a voxel-based meta-analysis. *Neurosci Biobehav Rev* 2016;66:92–103. <https://doi.org/10.1016/j.neubiorev.2016.03.034>.
- [40] Mackey S, Allgaier N, Chararani B, Spechler P, Orr C, Bunn J, et al. Mega-analysis of gray matter volume in substance dependence: General and substance-specific regional effects. *Am J Psychiatry* 2019;176:119–28.

<https://doi.org/10.1176/appi.ajp.2018.17040415>.

- [41] Trick L, Kempton MJ, Williams SCR, Duka T. Impaired fear recognition and attentional set-shifting is associated with brain structural changes in alcoholic patients. *Addict Biol* 2014;19:1041–54. <https://doi.org/10.1111/adb.12175>.
- [42] Schmidt T, Roser P, Ze O, Juckel G, Suchan B, Thoma P. Cortical thickness and trait empathy in patients and people at high risk for alcohol use disorders. *Psychopharmacology (Berl)* 2017;234:3521–33. <https://doi.org/10.1007/s00213-017-4741-3>.
- [43] Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcohol Clin Exp Res* 2000;24:611–21.
- [44] Ryback RS. The continuum and specificity of the effects of alcohol on memory. A review. *Q J Stud Alcohol* 1971;32:995–1016.
- [45] Zinn S, Stein R, Swartzwelder HS. Executive functioning early in abstinence from alcohol. *Alcohol Clin Exp Res* 2004;28:1338–46.
- [46] Beatty WW, Tivis R, Stott HD, Nixon SJ, Parsons OA. Neuropsychological Deficits in Sober Alcoholics: Influences of Chronicity and Recent Alcohol Consumption. *Alcohol Clin Exp Res* 2000;24:149–54. <https://doi.org/10.1097/00000374-200002000-00003>.
- [47] Coulbault L, Ritz L, Vabret F, Lannuzel C, Boudehent C, Nowoczyn M, et al. Thiamine and phosphate esters concentrations in whole blood and serum of patients with alcohol use disorder: a relation with cognitive deficits. *Nutr Neurosci* 2019:1–12. <https://doi.org/10.1080/1028415X.2019.1652438>.
- [48] Pitel A-L, Zahr NM, Jackson K, Sassoon SA, Rosenbloom MJ, Pfefferbaum A, et al. Signs of preclinical wernicke’s encephalopathy and thiamine levels as predictors of neuropsychological deficits in alcoholism without korsakoff’s syndrome. *Neuropsychopharmacology* 2011;36:580–8. <https://doi.org/10.1038/npp.2010.189>.

- [49] Ritz L, Coulbault L, Lannuzel C, Boudehent C, Segobin S, Eustache F, et al. Clinical and Biological Risk Factors for Neuropsychological Impairment in Alcohol Use Disorder. *PLoS One* 2016;11:e0159616. <https://doi.org/10.1371/journal.pone.0159616>.
- [50] Lowe CJ, Safati A, Hall PA. The neurocognitive consequences of sleep restriction: A meta-analytic review. *Neurosci Biobehav Rev* 2017;80:586–604. <https://doi.org/10.1016/j.neubiorev.2017.07.010>.
- [51] Sexton CE, Storsve AB, Walhovd KB, Johansen-Berg H, Fjell AM. Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults. *Neurology* 2014;83:967–73. <https://doi.org/10.1212/WNL.0000000000000774>.
- [52] Sexton CE, Zsoldos E, Filippini N, Griffanti L, Winkler A, Mahmood A, et al. Associations between self-reported sleep quality and white matter in community-dwelling older adults: A prospective cohort study. *Hum Brain Mapp* 2017;38:5465–73. <https://doi.org/10.1002/hbm.23739>.
- *[53] Brower KJ. Alcohol's effects on sleep in alcoholics. *Alcohol Res Health* 2001;25:110–25.
- [54] Bastien C, Vallières A, Morin C. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297–307. [https://doi.org/10.1016/S1389-9457\(00\)00065-4](https://doi.org/10.1016/S1389-9457(00)00065-4).
- [55] Chaudhary NS, Kampman KM, Kranzler HR, Grandner MA, Debbarna S, Chakravorty S. Insomnia in alcohol dependent subjects is associated with greater psychosocial problem severity. *Addict Behav* 2015;50:165–72. <https://doi.org/10.1016/j.addbeh.2015.06.021>.
- [56] Skoloda T, Alterman A, Gottheil E. Sleep quality reported by drinking and non-drinking alcoholics. *Addict Res Treat Converg Trends Proc First Annu Coatesville-Jefferson Conf Addict Pergamom Press Elmsford, NY* 1979:102–112.

- [57] Hodges CJ, Ogeil RP, Lubman DI. The effects of acute alcohol withdrawal on sleep. *Hum Psychopharmacol Clin Exp* 2018;33:e2657. <https://doi.org/10.1002/hup.2657>.
- [58] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- [59] Neu P, Sofin Y, Danker-Hopfe H. The Effect of Detoxification on Sleep: How Does Sleep Quality Change during Qualified Detoxification Treatment? *J Addict* 2018;2018:1–7. <https://doi.org/10.1155/2018/9492453>.
- [60] Mello NK, Mendelson JH. Behavioral studies of sleep patterns in alcoholics during intoxication and withdrawal. *J Pharmacol Exp Ther* 1970;175:94–112.
- [61] Allen RP, Wagman AMI, Funderburk FR, Wells DT. Slow wave sleep: A predictor of individual differences in response to drinking? *Biol Psychiatry* 1980;15:345-8.
- [62] Gross MM, Goodenough DR, Hastey J, Lewis E. Experimental study of sleep in chronic alcoholics before, during, and after four days of heavy drinking with a nondrinking comparison. *Ann N Y Acad Sci* 1973;215:254–65. <https://doi.org/10.1111/j.1749-6632.1973.tb28281.x>.
- [63] Gross MM, Hastey JM. The relation between baseline slow wave sleep and the slow wave sleep response to alcohol in alcoholics. *Adv Exp Med Biol* 1975;59:467–75. https://doi.org/10.1007/978-1-4757-0632-1_33.
- [64] Wagman AM, Allen RP. Effects of alcohol ingestion and abstinence on slow wave sleep of alcoholics. *Adv Exp Med Biol* 1975;59:453–66. https://doi.org/10.1007/978-1-4757-0632-1_32.
- [65] Schuckit MA. Alcohol-use disorders. *Lancet* 2009;373:492–501. [https://doi.org/10.1016/S0140-6736\(09\)60009-X](https://doi.org/10.1016/S0140-6736(09)60009-X).
- [66] Wood E, Albarqouni L, Tkachuk S, Green CJ, Ahamad K, Nolan S, et al. Will This

- Hospitalized Patient Develop Severe Alcohol Withdrawal Syndrome? *JAMA* 2018;320:825. <https://doi.org/10.1001/jama.2018.10574>.
- [67] Cohn TJ, Foster JH, Peters TJ. Sequential studies of sleep disturbance and quality of life in abstaining alcoholics. *Addict Biol* 2003;8:455–62. <https://doi.org/10.1080/13556210310001646439>.
- [68] Steinig J, Foraita R, Happe S, Heinze M. Perception of sleep and dreams in alcohol-dependent patients during detoxication and abstinence. *Alcohol Alcohol* 2011;46:143–7. <https://doi.org/10.1093/alcalc/agq087>.
- [69] Lahti T, Methuen T, Roine R, Seppa K-L, Sinclair D, Partinen M, et al. The impacts of nitrous oxide gas on sleep quality during alcohol withdrawal. *BMC Res Notes* 2011;4:108. <https://doi.org/10.1186/1756-0500-4-108>.
- [70] Johnson LC, Burdick JA, Smith J. Sleep During Alcohol Intake and Withdrawal in the Chronic Alcoholic. *Arch Gen Psychiatry* 1970;22:406–18. <https://doi.org/10.1001/archpsyc.1970.01740290022004>.
- [71] Allen RP, Faillace LA, Wagman A. Recovery time for alcoholics after prolonged alcohol intoxication. *Johns Hopkins Med J* 1971;128:158–64.
- [72] Stein MD, Friedmann PD. Disturbed sleep and its relationship to alcohol use. *Subst Abus* 2005;26:1–13.
- [73] Greenberg R, Pearlman C. Delirium tremens and dreaming. *Am J Psychiatry* 1967;124:133–42. <https://doi.org/10.1176/ajp.124.2.133>.
- [74] Kotorii T, Nakazawa Y, Yokoyama T, Ohkawa T, Sakurada H, Nonaka K, et al. Terminal sleep following delirium tremens in chronic alcoholics - polysomnographic and behavioral study. *Drug Alcohol Depend* 1982;10:125–34. [https://doi.org/10.1016/0376-8716\(82\)90003-5](https://doi.org/10.1016/0376-8716(82)90003-5).
- [75] Nakazawa Y, Yokoyama T, Koga Y, Kotorii T, Ohkawa T, Sakurada H, et al.

- Polysomnographic study of terminal sleep following delirium tremens. *Drug Alcohol Depend* 1981;8:111–7. [https://doi.org/10.1016/0376-8716\(81\)90106-X](https://doi.org/10.1016/0376-8716(81)90106-X).
- [76] Landolt HP, Gillin JC. Sleep abnormalities during abstinence in alcohol-dependent patients. Aetiology and management. *CNS Drugs* 2001;15:413–25. <https://doi.org/10.2165/00023210-200115050-00006>.
- [77] Gann H, Feige B, Hohagen F, van Calker D, Geiss D, Dieter R. Sleep and the cholinergic rapid eye movement sleep induction test in patients with primary alcohol dependence. *Biol Psychiatry* 2001;50:383–90. [https://doi.org/10.1016/S0006-3223\(01\)01172-6](https://doi.org/10.1016/S0006-3223(01)01172-6).
- [78] Irwin MR, Bjurstrom MF, Olmstead R. Polysomnographic measures of sleep in cocaine dependence and alcohol dependence: Implications for age-related loss of slow wave, stage 3 sleep. *Addiction* 2016;111:1084–92. <https://doi.org/10.1111/add.13300>.
- [79] Junghanns K, Horbach R, Ehrental D, Blank S, Backhaus J. Chronic and high alcohol consumption has a negative impact on sleep and sleep-associated consolidation of declarative memory. *Alcohol Clin Exp Res* 2009;33:893–7. <https://doi.org/10.1111/j.1530-0277.2009.00909.x>.
- *[80] Kolla BP, Schneekloth T, Biernacka J, Mansukhani M, Geske J, Karpyak V, et al. The course of sleep disturbances in early alcohol recovery: An observational cohort study. *Am J Addict* 2014;23:21–6. <https://doi.org/10.1111/j.1521-0391.2013.12056.x>.
- [81] Perney P, Lehert P. Insomnia in Alcohol-Dependent Patients: Prevalence, Risk Factors and Acamprosate Effect: An Individual Patient Data Meta-Analysis. *Alcohol Alcohol* 2018;53:611–8. <https://doi.org/10.1093/alcalc/agy013>.
- [82] Wallen GR, Brooks AT, Whiting B, Clark R, Krumlauf MC, Yang L, et al. The Prevalence of Sleep Disturbance in Alcoholics Admitted for Treatment. *Fam Community Health* 2014;37:288–97. <https://doi.org/10.1097/FCH.0000000000000040>.

- [83] Brower KJ, Aldrich MS, Hall JM. Polysomnographic and subjective sleep predictors of alcoholic relapse. *Alcohol Clin Exp Res* 1998;22:1864–71. <https://doi.org/10.1111/j.1530-0277.1998.tb03995.x>.
- [84] Chakravorty S, Kuna ST, Zaharakis N, O'Brien CP, Kampman KM, Oslin D. Covariates of Craving in Actively Drinking Alcoholics. *Am J Addict* 2010;19:450–7. <https://doi.org/10.1111/j.1521-0391.2010.00067.x>.
- [85] Colrain IM, Crowley KE, Nicholas CL, Padilla M, Baker FC. The Impact of Alcoholism on Sleep Evoked Δ Frequency Responses. *Biol Psychiatry* 2009;66:177–84. <https://doi.org/10.1016/j.biopsych.2008.10.010>.
- [86] Currie SR, Clark S, Rimac S, Malhotra S. Comprehensive assessment of insomnia in recovering alcoholics using daily sleep diaries and ambulatory monitoring. *Alcohol Clin Exp Res* 2003;27:1262–9. <https://doi.org/10.1097/01.ALC.0000081622.03973.57>.
- [87] de Zambotti M, Baker FC, Sugarbaker DS, Nicholas CL, Trinder J, Colrain IM. Poor autonomic nervous system functioning during sleep in recently detoxified alcohol-dependent men and women. *Alcohol Clin Exp Res* 2014;38:1373–80. <https://doi.org/10.1111/acer.12384>.
- [88] Feige B, Scaal S, Hornyak M, Gann H, Riemann D. Sleep Electroencephalographic Spectral Power After Withdrawal from Alcohol in Alcohol-Dependent Patients. *Alcohol Clin Exp Res* 2007;31:19–27. <https://doi.org/10.1111/j.1530-0277.2006.00260.x>.
- [89] Foster JH, Peters TJ. Impaired sleep in alcohol misusers and dependent alcoholics and the impact upon outcome. *Alcohol Clin Exp Res* 1999;23:1044–51. <https://doi.org/10.1111/j.1530-0277.1999.tb04223.x>.
- [90] Brownlow JA, Miller KE, Gehrman PR. Insomnia and Cognitive Performance. *Sleep Med Clin* 2020;15:71–6. <https://doi.org/10.1016/j.jsmc.2019.10.002>.

- [91] Fortier-Brochu É, Beaulieu-Bonneau S, Ivers H, Morin CM. Insomnia and daytime cognitive performance: A meta-analysis. *Sleep Med Rev* 2012;16:83–94. <https://doi.org/10.1016/j.smr.2011.03.008>.
- [92] Ballesio A, Aquino MRJV, Kyle SD, Ferlazzo F, Lombardo C. Executive Functions in Insomnia Disorder: A Systematic Review and Exploratory Meta-Analysis. *Front Psychol* 2019;10:101. <https://doi.org/10.3389/fpsyg.2019.00101>.
- [93] Drummond SPA, Gillin JC, Smith TL, DeModena A. The Sleep of Abstinent Pure Primary Alcoholic Patients: Natural Course and Relationship to Relapse. *Alcohol Clin Exp Res* 1998;22:1796–802. <https://doi.org/10.1111/j.1530-0277.1998.tb03983.x>.
- [94] Gann H, van Calker D, Feige B, Clout O, Brück R, Berger M, et al. Polysomnographic comparison between patients with primary alcohol dependency during subacute withdrawal and patients with a major depression. *Eur Arch Psychiatry Clin Neurosci* 2004;254:263–71. <https://doi.org/10.1007/s00406-004-0494-1>.
- [95] Gillin JC, Smith TL, Irwin M, Kripke DF, Schuckit M. EEG sleep studies in “pure” primary alcoholism during subacute withdrawal: Relationships to normal controls, age, and other clinical variables. *Biol Psychiatry* 1990;27:477–88. [https://doi.org/10.1016/0006-3223\(90\)90439-9](https://doi.org/10.1016/0006-3223(90)90439-9).
- [96] Irwin M, Miller C, Gillin JC, Demodena A, Ehlers CL. Polysomnographic and Spectral Sleep EEG in Primary Alcoholics: An Interaction Between Alcohol Dependence and African-American Ethnicity. *Alcohol Clin Exp Res* 2000;24:1376–84. <https://doi.org/10.1111/j.1530-0277.2000.tb02106.x>.
- [97] Le Bon O, Verbanck P, Hoffmann G, Murphy JR, Staner L, De Groote D, et al. Sleep in detoxified alcoholics: impairment of most standard sleep parameters and increased risk for sleep apnea, but not for myoclonias--a controlled study. *J Stud Alcohol* 1997;58:30–6. <https://doi.org/10.15288/jsa.1997.58.30>.

- [98] Singh LK, Nizamie SH, Tikka SK. Sleep architecture and EEG power spectra in recently detoxified alcohol dependent patients. *Asian J Psychiatr* 2018;32:126–36. <https://doi.org/10.1016/j.ajp.2017.12.005>.
- [99] Snyder S, Karacan I. Sleep patterns of sober chronic alcoholics. *Neuropsychobiology* 1985;13:97–100. <https://doi.org/10.1159/000118169>.
- [100] Irwin M, Gillin JC, Dang J, Weissman J, Phillips E, Ehlers CL. Sleep deprivation as a probe of homeostatic sleep regulation in primary alcoholics. *Biol Psychiatry* 2002;51:632–41. [https://doi.org/10.1016/S0006-3223\(01\)01304-X](https://doi.org/10.1016/S0006-3223(01)01304-X).
- [101] Brower KJ, Hoffmann R, Conroy DA, Arnedt JT, Armitage R. Sleep homeostasis in alcohol-dependent, depressed and healthy control men. *Eur Arch Psychiatry Clin Neurosci* 2011;261:559–66. <https://doi.org/10.1007/s00406-011-0195-5>.
- [102] Willoughby AR, de Zambotti M, Baker FC, Colrain IM. Partial K-Complex Recovery Following Short-Term Abstinence in Individuals with Alcohol Use Disorder. *Alcohol Clin Exp Res* 2015;39:1417–24. <https://doi.org/10.1111/acer.12769>.
- [103] Williams HL, Rundell OH. Altered Sleep Physiology in Chronic Alcoholics: Reversal with Abstinence. *Alcohol Clin Exp Res* 1981;5:318–25. <https://doi.org/10.1111/j.1530-0277.1981.tb04905.x>.
- [104] Gillin JC. Increased Pressure for Rapid Eye Movement Sleep at Time of Hospital Admission Predicts Relapse in Nondepressed Patients With Primary Alcoholism at 3-Month Follow-up. *Arch Gen Psychiatry* 1994;51:189. <https://doi.org/10.1001/archpsyc.1994.03950030025003>.
- [105] Brower KJ, Krentzman A, Robinson EA. Persistent Insomnia, Abstinence, and Moderate Drinking in Alcohol-Dependent Individuals. *Am J Addict* 2011;20:435–40. <https://doi.org/10.1111/j.1521-0391.2011.00152.x>.
- [106] Schiavi RC, Stimmel BB, Mandeli J, White D. Chronic alcoholism and male sexual

- function. *Am J Psychiatry* 1995;152:1045–51. <https://doi.org/10.1176/ajp.152.7.1045>.
- *[107] Vitiello MV. Sleep, alcohol and alcohol abuse. *Addict Biol* 1997;2:151–8. <https://doi.org/10.1080/13556219772697>.
- [108] Kolla BP, Foroughi M, Saeidifard F, Chakravorty S, Wang Z, Mansukhani MP. The impact of alcohol on breathing parameters during sleep: A systematic review and meta-analysis. *Sleep Med Rev* 2018;42:59–67. <https://doi.org/10.1016/j.smr.2018.05.007>.
- [109] Aldrich MS, Brower KJ, Hall JM. Sleep-disordered breathing in alcoholics. *Alcohol Clin Exp Res* 1999;23:134–40.
- [110] Tan ETH, Lambie DG, Johnson RH, Robinson BJ, Whiteside EA. Sleep apnoea in alcoholic patients after withdrawal. *Clin Sci* 1985;69:655–61. <https://doi.org/10.1042/cs0690655>.
- [111] Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5:136–43. <https://doi.org/10.1513/pats.200709-155MG>.
- [112] Ohayon M-M, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res* 2002;53:547–54. [https://doi.org/10.1016/S0022-3999\(02\)00443-9](https://doi.org/10.1016/S0022-3999(02)00443-9).
- [113] Aldrich MS, Shipley JE, Tandon R, Kroll PD, Brower KJ. Sleep-disordered breathing in alcoholics: association with age. *Alcohol Clin Exp Res* 1993;17:1179–83.
- [114] Gann H, Feige B, Fasihi S, Van Calker D, Voderholzer U, Riemann D. Periodic limb movements during sleep in alcohol dependent patients. *Eur Arch Psychiatry Clin Neurosci* 2002. <https://doi.org/10.1007/s00406-002-0371-8>.
- [115] Brower KJ, Hall JM. Effects of age and alcoholism on sleep: a controlled study. *J Stud Alcohol* 2001;62:335–43. <https://doi.org/10.15288/jsa.2001.62.335>.
- [116] Meyrel M, Rolland B, Geoffroy PA. Alterations in circadian rhythms following alcohol use: A systematic review. *Prog Neuro-Psychopharmacology Biol Psychiatry* 2020.

<https://doi.org/10.1016/j.pnpbp.2019.109831>.

- *[117] Rauchs G, Desgranges B, Foret J, Eustache F. The relationships between memory systems and sleep stages. *J Sleep Res* 2005;14:123–40. <https://doi.org/10.1111/j.1365-2869.2005.00450.x>.
- [118] Walker MP, van der Helm E. Overnight therapy? The role of sleep in emotional brain processing. *Psychol Bull* 2009;135:731–48. <https://doi.org/10.1037/a0016570>.
- [119] Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol* 2014;13:1017–28. [https://doi.org/10.1016/S1474-4422\(14\)70172-3](https://doi.org/10.1016/S1474-4422(14)70172-3).
- [120] Peter-Derex L, Yammine P, Bastuji H, Croisile B. Sleep and Alzheimer’s disease. *Sleep Med Rev* 2015;19:29–38. <https://doi.org/10.1016/j.smrv.2014.03.007>.
- [121] Winsky-Sommerer R, de Oliveira P, Loomis S, Wafford K, Dijk D-J, Gilmour G. Disturbances of sleep quality, timing and structure and their relationship with other neuropsychiatric symptoms in Alzheimer’s disease and schizophrenia: Insights from studies in patient populations and animal models. *Neurosci Biobehav Rev* 2019;97:112–37. <https://doi.org/10.1016/j.neubiorev.2018.09.027>.
- [122] Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci* 2010;11:114–26. <https://doi.org/10.1038/nrn2762>.
- [123] Harand C, Bertran F, Doidy F, Guénolé F, Desgranges B, Eustache F, et al. How Aging Affects Sleep-Dependent Memory Consolidation? *Front Neurol* 2012;3. <https://doi.org/10.3389/fneur.2012.00008>.
- [124] Rauchs G, Bertran F, Guillery-Girard B, Desgranges B, Kerrouche N, Denise P, et al. Consolidation of Strictly Episodic Memories Mainly Requires Rapid Eye Movement Sleep. *Sleep* 2004;27:395–401. <https://doi.org/10.1093/sleep/27.3.395>.
- [125] Wagner U, Gais S, Born J. Emotional Memory Formation Is Enhanced across Sleep

- Intervals with High Amounts of Rapid Eye Movement Sleep. *Learn Mem* 2001;8:112–9. <https://doi.org/10.1101/lm.36801>.
- [126] Smith CT, Nixon MR, Nader RS. Posttraining increases in REM sleep intensity implicate REM sleep in memory processing and provide a biological marker of learning potential. *Learn Mem* 2004;11:714–9. <https://doi.org/10.1101/lm.74904>.
- [127] Yoo SS, Hu PT, Gujar N, Jolesz FA, Walker MP. A deficit in the ability to form new human memories without sleep. *Nat Neurosci* 2007;10:385–92. <https://doi.org/10.1038/nn1851>.
- [128] Cousins JN, Sasmita K, Chee MWL. Memory encoding is impaired after multiple nights of partial sleep restriction. *J Sleep Res* 2018;27:138–45. <https://doi.org/10.1111/jsr.12578>.
- [129] Benitez A, Gunstad J. Poor sleep quality diminishes cognitive functioning independent of depression and anxiety in healthy young adults. *Clin Neuropsychol* 2012;26:214–23. <https://doi.org/10.1080/13854046.2012.658439>.
- [130] Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol Bull* 2010;136:375–89. <https://doi.org/10.1037/a0018883>.
- [131] Ferrarelli F, Kaskie R, Laxminarayan S, Ramakrishnan S, Reifman J, Germain A. An increase in sleep slow waves predicts better working memory performance in healthy individuals. *Neuroimage* 2019;191:1–9. <https://doi.org/10.1016/j.neuroimage.2019.02.020>.
- [132] Wilckens KA, Aizenstein HJ, Nofzinger EA, James JA, Hasler BP, Rosario-Rivera BL, et al. The role of non-rapid eye movement slow-wave activity in prefrontal metabolism across young and middle-aged adults. *J Sleep Res* 2016;25:296–306. <https://doi.org/10.1111/jsr.12365>.
- [133] van Oostrom SH, Nooyens ACJ, van Boxtel MPJ, Verschuren WMM. Long sleep

- duration is associated with lower cognitive function among middle-age adults – the Doetinchem Cohort Study. *Sleep Med* 2018;41:78–85. <https://doi.org/10.1016/j.sleep.2017.07.029>.
- [134] Killgore WD, Balkin TJ, Wesensten NJ. Impaired decision making following 49 h of sleep deprivation. *J Sleep Res* 2006;15:7–13. <https://doi.org/10.1111/j.1365-2869.2006.00487.x>.
- [135] Anderson C, Platten CR. Sleep deprivation lowers inhibition and enhances impulsivity to negative stimuli. *Behav Brain Res* 2011. <https://doi.org/10.1016/j.bbr.2010.09.020>.
- [136] Venkatraman V, Chuah YL, Huettel SA, Chee MWL. Sleep Deprivation Elevates Expectation of Gains and Attenuates Response to Losses Following Risky Decisions. *Sleep* 2007;30:603–9. <https://doi.org/10.1093/sleep/30.5.603>.
- [137] Womack SD, Hook JN, Reyna SH, Ramos M. Sleep Loss and Risk-Taking Behavior: A Review of the Literature. *Behav Sleep Med* 2013;11:343–59. <https://doi.org/10.1080/15402002.2012.703628>.
- [138] Maric A, Montvai E, Werth E, Storz M, Leemann J, Weissengruber S, et al. Insufficient sleep: Enhanced risk-seeking relates to low local sleep intensity. *Ann Neurol* 2017;82:409–18. <https://doi.org/10.1002/ana.25023>.
- [139] Seeley CJ, Smith CT, MacDonald KJ, Beninger RJ. Ventromedial prefrontal theta activity during rapid eye movement sleep is associated with improved decision-making on the Iowa Gambling Task. *Behav Neurosci* 2016;130:271–80. <https://doi.org/10.1037/bne0000123>.
- [140] Benson K, Cohen M, Zarcone V. REM sleep time and digit span impairment in alcoholics. *J Stud Alcohol* 1978;39:1488–98. <https://doi.org/10.15288/jsa.1978.39.1488>.
- *[141] Laniepe A, Segobin S, Lannuzel C, Boudehent C, Ritz L, Urso L, et al.

- Neuropsychological and Neuroimaging Examinations of Self-Reported Sleep Quality in Alcohol Use Disorder With and Without Korsakoff's Syndrome. *Alcohol Clin Exp Res* 2019;43:952–64. <https://doi.org/10.1111/acer.13997>.
- [142] van der Helm E, Gujar N, Walker MP. Sleep Deprivation Impairs the Accurate Recognition of Human Emotions. *Sleep* 2010;33:335–42. <https://doi.org/10.1093/sleep/33.3.335>.
- [143] Killgore WD, Balkin TJ, Yarnell AM, Capaldi VF. Sleep deprivation impairs recognition of specific emotions. *Neurobiol Sleep Circadian Rhythm* 2017;3:10–6. <https://doi.org/10.1016/j.nbscr.2017.01.001>.
- [144] Macdonald KJ, Cote KA. Sleep physiology predicts memory retention after reactivation. *J Sleep Res* 2016;25:655–63. <https://doi.org/10.1111/jsr.12423>.
- [145] Guadagni V, Burles F, Ferrara M, Iaria G. The effects of sleep deprivation on emotional empathy. *J Sleep Res* 2014;23:657–63. <https://doi.org/10.1111/jsr.12192>.
- [146] Guadagni V, Burles F, Ferrara M, Iaria G. Sleep quality and its association with the insular cortex in emotional empathy. *Eur J Neurosci* 2018;48:2288–300. <https://doi.org/10.1111/ejn.14124>.
- [147] Alkozei A, Haack M, Skalamera J, Smith R, Satterfield BC, Raikes AC, et al. Chronic sleep restriction affects the association between implicit bias and explicit social decision making. *Sleep Heal* 2018;4:456–62. <https://doi.org/10.1016/j.sleh.2018.07.003>.
- [148] Alkozei A, Killgore WD, Smith R, Dailey NS, Bajaj S, Haack M. Chronic Sleep Restriction Increases Negative Implicit Attitudes Toward Arab Muslims. *Sci Rep* 2017;7:4285. <https://doi.org/10.1038/s41598-017-04585-w>.
- [149] Kolla BP, Mansukhani MP, Biernacka J, Chakravorty S, Karpyak VM. Sleep disturbances in early alcohol recovery: Prevalence and associations with clinical

- characteristics and severity of alcohol consumption. *Drug Alcohol Depend* 2020;206:107655. <https://doi.org/10.1016/j.drugalcdep.2019.107655>.
- [150] Gordon AM, Mendes WB, Prather AA. The Social Side of Sleep: Elucidating the Links Between Sleep and Social Processes. *Curr Dir Psychol Sci* 2017;26:470–5. <https://doi.org/10.1177/0963721417712269>.
- [151] Stoffers D, Moens S, Benjamins J, Van Tol MJ, Penninx BW, Veltman DJ, et al. Orbitofrontal Gray Matter Relates to Early Morning Awakening: A Neural Correlate of Insomnia Complaints? *Front Neurol* 2012;3:1–7. <https://doi.org/10.3389/fneur.2012.00105>.
- [152] Killgore WD, Schwab ZJ, Kipman M, DelDonno SR, Weber M. Voxel-based morphometric gray matter correlates of daytime sleepiness. *Neurosci Lett* 2012;518:10–3. <https://doi.org/10.1016/j.neulet.2012.04.029>.
- [153] Lo JC, Loh KK, Zheng H, Sim SK, Chee MW. Sleep Duration and Age-Related Changes in Brain Structure and Cognitive Performance. *Sleep* 2014;37:821–821. <https://doi.org/10.5665/sleep.3832>.
- [154] Liu C, Kong X, Liu X, Zhou R, Wu B. Long-term total sleep deprivation reduces thalamic gray matter volume in healthy men. *Neuroreport* 2013;1. <https://doi.org/10.1097/WNR.0000000000000091>.
- [155] Khalsa S, Hale JR, Goldstone A, Wilson RS, Mayhew SD, Bagary M, et al. Habitual sleep durations and subjective sleep quality predict white matter differences in the human brain. *Neurobiol Sleep Circadian Rhythm* 2017;3:17–25. <https://doi.org/10.1016/j.nbscr.2017.03.001>.
- [156] Kocevskaja D, Cremers LGM, Lysen TS, Luik AI, Ikram MA, Vernooij MW, et al. Sleep complaints and cerebral white matter: A prospective bidirectional study. *J Psychiatr Res* 2019;112:77–82. <https://doi.org/10.1016/j.jpsychires.2019.02.002>.

- [157] Ishibashi M, Nakazawa Y, Yokoyama T, Koga Y, Miyahara Y, Hayashida N, et al. Cerebral atrophy and slow wave sleep of abstinent chronic alcoholics. *Drug Alcohol Depend* 1987;19:325–32. [https://doi.org/10.1016/0376-8716\(87\)90019-6](https://doi.org/10.1016/0376-8716(87)90019-6).
- *[158] Colrain IM, Sullivan EV, Rohlfing T, Baker FC, Nicholas CL, Padilla ML, et al. Independent Contributions of Cortical Gray Matter, Aging, Sex and Alcoholism to K-Complex Amplitude Evoked During Sleep. *Sleep* 2011;34:787–95. <https://doi.org/10.5665/SLEEP.1050>.
- [159] Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res* 2000;9:335–52. <https://doi.org/10.1046/j.1365-2869.2000.00225.x>.
- [160] Ben Simon E, Maron-Katz A, Lahav N, Shamir R, Hendler T. Tired and misconnected: A breakdown of brain modularity following sleep deprivation. *Hum Brain Mapp* 2017;38:3300–14. <https://doi.org/10.1002/hbm.23596>.
- [161] Krause AJ, Simon EB, Mander BA, Greer SM, Saletin JM, Goldstein-Piekarski AN, et al. The sleep-deprived human brain. *Nat Rev Neurosci* 2017;18:404–18. <https://doi.org/10.1038/nrn.2017.55>.
- [162] Killgore WD. Effects of sleep deprivation on cognition. *Prog Brain Res* 2010;185:105–29. <https://doi.org/10.1016/B978-0-444-53702-7.00007-5>.
- [163] Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep - a prefrontal amygdala disconnect. *Curr Biol* 2007;17. <https://doi.org/10.1016/j.cub.2007.08.007>.
- [164] Ben Simon E, Walker MP. Sleep loss causes social withdrawal and loneliness. *Nat Commun* 2018;9:3146. <https://doi.org/10.1038/s41467-018-05377-0>.
- [165] Liu J, Cai W, Zhao M, Cai W, Sui F, Hou W, et al. Reduced resting-state functional

- connectivity and sleep impairment in abstinent male alcohol-dependent patients. *Hum Brain Mapp* 2019;40:4941–51. <https://doi.org/10.1002/hbm.24749>.
- [166] Dubé J, Lafortune M, Bedetti C, Bouchard M, Franc J, Doyon J, et al. Cortical Thinning Explains Changes in Sleep Slow Waves during Adulthood. *J Neurosci* 2015;35:7795–807. <https://doi.org/10.1523/JNEUROSCI.3956-14.2015>.
- [167] Latreille V, Gaubert M, Dube J, Lina J-M, Gagnon J-F, Carrier J. Age-related cortical signatures of human sleep electroencephalography. *Neurobiol Aging* 2019;76:106–14. <https://doi.org/10.1016/j.neurobiolaging.2018.12.012>.
- [168] Mander BA, Rao V, Lu B, Saletin JM, Lindquist JR, Ancoli-Israel S, et al. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat Neurosci* 2013;16:357–64. <https://doi.org/10.1038/nn.3324>.
- [169] Fernandes C, Rocha NBF, Rocha S, Herrera-Solís A, Salas-Pacheco J, García-García F, et al. Detrimental role of prolonged sleep deprivation on adult neurogenesis. *Front Cell Neurosci* 2015;9:140. <https://doi.org/10.3389/fncel.2015.00140>.
- [170] Cortese BM, Mitchell TR, Galloway MP, Prevost KE, Fang J, Moore GJ, et al. Region-specific alteration in brain glutamate: Possible relationship to risk-taking behavior. *Physiol Behav* 2010;99:445–50. <https://doi.org/10.1016/j.physbeh.2009.12.005>.
- [171] Dash MB, Douglas CL, Vyazovskiy VV, Cirelli C, Tononi G. Long-Term Homeostasis of Extracellular Glutamate in the Rat Cerebral Cortex across Sleep and Waking States. *J Neurosci* 2009;29:620–9. <https://doi.org/10.1523/JNEUROSCI.5486-08.2009>.
- [172] Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry* 2016;80:40–52. <https://doi.org/10.1016/j.biopsych.2015.05.014>.
- [173] Villafuerte G, Miguel-Puga A, Murillo Rodríguez E, Machado S, Manjarrez E, Arias-

- Carrión O. Sleep Deprivation and Oxidative Stress in Animal Models: A Systematic Review. *Oxid Med Cell Longev* 2015;2015:1–15. <https://doi.org/10.1155/2015/234952>.
- [174] Miller MB, DiBello AM, Lust SA, Meisel MK, Carey KB. Impulsive personality traits and alcohol use: Does sleeping help with thinking? *Psychol Addict Behav* 2017;31:46–53. <https://doi.org/10.1037/adb0000241>.
- [175] Hasler BP, Soehner AM, Clark DB. Sleep and circadian contributions to adolescent alcohol use disorder. *Alcohol* 2015;49:377–87. <https://doi.org/10.1016/j.alcohol.2014.06.010>.
- [176] Chung SS, Joung KH. Risk Factors Related to Binge Drinking. *J Sch Nurs* 2019;35:367–77. <https://doi.org/10.1177/1059840518785439>.
- [177] Popovici I, French MT. Binge drinking and sleep problems among young adults. *Drug Alcohol Depend* 2013;132:207–15. <https://doi.org/10.1016/j.drugalcdep.2013.02.001>.
- [178] Hasler BP, Pedersen SL. Sleep and circadian risk factors for alcohol problems: a brief overview and proposed mechanisms. *Curr Opin Psychol* 2020;34:57–62. <https://doi.org/10.1016/j.copsyc.2019.09.005>.
- [179] Perry CJ. Cognitive Decline and Recovery in Alcohol Abuse. *J Mol Neurosci* 2016;60:383–9. <https://doi.org/10.1007/s12031-016-0798-4>.
- *[180] Brower KJ. Insomnia, alcoholism and relapse. *Sleep Med Rev* 2003;7:523–39. [https://doi.org/10.1016/S1087-0792\(03\)90005-0](https://doi.org/10.1016/S1087-0792(03)90005-0).
- [181] Conroy DA, Todd Arnedt J, Brower KJ, Strobbe S, Consens F, Hoffmann R, et al. Perception of sleep in recovering alcohol-dependent patients with insomnia: Relationship with future drinking. *Alcohol Clin Exp Res* 2006;30:1992–9. <https://doi.org/10.1111/j.1530-0277.2006.00245.x>.
- [182] Clark CP, Gillin JC, Golshan S, Demodena A, Smith TL, Danowski S, et al. Increased

- REM Sleep Density at Admission Predicts Relapse by Three Months in Primary Alcoholics with a Lifetime Diagnosis of Secondary Depression. *Biol Psychiatry* 1998;43:601–7. [https://doi.org/10.1016/S0006-3223\(97\)00457-5](https://doi.org/10.1016/S0006-3223(97)00457-5).
- [183] He S, Brooks AT, Kampman KM, Chakravorty S. The Relationship between Alcohol Craving and Insomnia Symptoms in Alcohol-Dependent Individuals. *Alcohol Alcohol* 2019;54:287–94. <https://doi.org/10.1093/alcalc/agz029>.
- [184] McHugh R. Alcohol Use Disorder and Depressive Disorders. *Alcohol Res Curr Rev* 2019;40. <https://doi.org/10.35946/arcr.v40.1.01>.
- [185] Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2004;61:807–16. <https://doi.org/10.1001/archpsyc.61.8.807>.
- [186] Hasin D, Liu X, Nunes E, McCloud S, Samet S, Endicott J. Effects of Major Depression on Remission and Relapse of Substance Dependence. *Arch Gen Psychiatry* 2002;59:375. <https://doi.org/10.1001/archpsyc.59.4.375>.
- [187] Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the Penn Alcohol Craving Scale. *Alcohol Clin Exp Res* 1999;23:1289–95. <https://doi.org/10.1111/j.1530-0277.1999.tb04349.x>.
- [188] Brower KJ, Aldrich MS, Robinson EA, Zucker RA, Greden JF. Insomnia, Self-Medication, and Relapse to Alcoholism. *Am J Psychiatry* 2001;158:399–404. <https://doi.org/10.1176/appi.ajp.158.3.399>.
- [189] Brooks AT, Krumlauf M, Beck KH, Fryer CS, Yang L, Ramchandani VA, et al. A Mixed Methods Examination of Sleep Throughout the Alcohol Recovery Process Grounded in the Social Cognitive Theory: The Role of Self-Efficacy and Craving. *Heal*

- Educ Behav 2019;46:126–36. <https://doi.org/10.1177/1090198118757820>.
- [190] Sutcliffe JG, de Lecea L. The hypocretins: Setting the arousal threshold. *Nat Rev Neurosci* 2002;3:339–49. <https://doi.org/10.1038/nrn808>.
- [191] Valentino RJ, Volkow ND. Drugs, sleep, and the addicted brain. *Neuropsychopharmacology* 2020;45:3–5. <https://doi.org/10.1038/s41386-019-0465-x>.
- [192] Fein G, Bachman L, Fisher S, Davenport L. Cognitive impairments in abstinent alcoholics. *West J Med* 1990;152:531–7.
- [193] Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008;4:487–504.
- [194] Ritterband LM, Thorndike FP, Gonder-Frederick LA, Magee JC, Bailey ET, Saylor DK, et al. Efficacy of an internet-based behavioral intervention for adults with insomnia. *Arch Gen Psychiatry* 2009;66:692–8. <https://doi.org/10.1001/archgenpsychiatry.2009.66>.
- [195] Espie CA, Kyle SD, Williams C, Ong JC, Douglas NJ, Hames P, et al. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep* 2012;35:769–81. <https://doi.org/10.5665/sleep.1872>.
- [196] Zachariae R, Lyby MS, Ritterband LM, O’Toole MS. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia - A systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev* 2016;30:1–10. <https://doi.org/10.1016/j.smr.2015.10.004>.
- [197] Horsch CHG, Lancee J, Griffioen-Both F, Spruit S, Fitrianie S, Neerincx MA, et al. Mobile Phone-Delivered Cognitive Behavioral Therapy for Insomnia: A Randomized Waitlist Controlled Trial. *J Med Internet Res* 2017;19:e70.

<https://doi.org/10.2196/jmir.6524>.

- [198] Geoffroy PA, Lejoyeux M, Rolland B. Management of insomnia in alcohol use disorder. *Expert Opin Pharmacother* 2020;21:297–306. <https://doi.org/10.1080/14656566.2019.1705279>.
- [199] Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence a randomized clinical trial. *JAMA Intern Med* 2014;174:70–7. <https://doi.org/10.1001/jamainternmed.2013.11950>.
- [200] Cheng YC, Huang YC, Huang WL. Gabapentinoids for treatment of alcohol use disorder: A systematic review and meta-analysis. *Hum Psychopharmacol* 2020;Jul 15:e2751. <https://doi.org/10.1002/hup.2751>.
- [201] Kredlow MA, Capozzoli MC, Hearon BA, Calkins AW, Otto MW. The effects of physical activity on sleep: a meta-analytic review. *J Behav Med* 2015;38:427–49. <https://doi.org/10.1007/s10865-015-9617-6>.
- [202] Lederman O, Ward PB, Firth J, Maloney C, Carney R, Vancampfort D, et al. Does exercise improve sleep quality in individuals with mental illness? A systematic review and meta-analysis. *J Psychiatr Res* 2019;109:96–106. <https://doi.org/10.1016/j.jpsychires.2018.11.004>.
- [203] Garcia AN, Salloum IM. Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: A focused review. *Am J Addict* 2015;24:590–8. <https://doi.org/10.1111/ajad.12291>.
- [204] Feinn R, Tennen H, Kranzler HR. Psychometric Properties of the Short Index of Problems as a Measure of Recent Alcohol-Related Problems. *Alcohol Clin Exp Res* 2003;27:1436–41. <https://doi.org/10.1097/01.ALC.0000087582.44674.AF>.
- [205] Turner NE, Annis HM, Sklar SM. Measurement of antecedents to drug and alcohol use: Psychometric properties of the Inventory of Drug-Taking Situations (IDTS).

Behav Res Ther 1997;35:465–83. [https://doi.org/10.1016/S0005-7967\(96\)00119-2](https://doi.org/10.1016/S0005-7967(96)00119-2).



**ACTIVE
ALCOHOL
USE**

**ACUTE WITHDRAWAL
PHASE**

**EARLY IN
ABSTINENCE
(< 2 MONTHS)**

**LATE IN
ABSTINENCE
(> 2 MONTHS)**

OBJECTIVE SLEEP QUALITY

**SLEEP ONSET
LATENCY**

↑

↑

↑

↑

**SLEEP
DURATION**

↓

↓

↓

↓

**SLEEP
FRAGMENTATION**

↑

↑

↑

↑

SWS%

↑

↓

↓

↓

REM SLEEP %

↓

↑

↑

↑

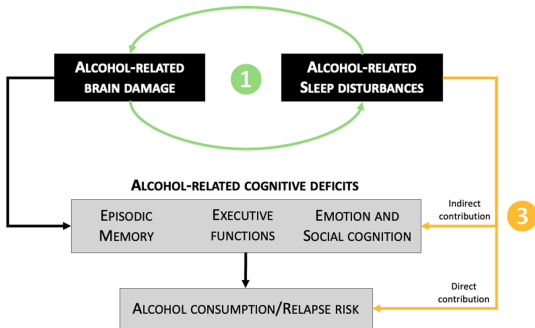
**SUBJECTIVE
SLEEP
ASSESSMENT**

SLEEP COMPLAINT

**EVEN AFTER 1
YEAR OF
ABSTINENCE**

2

FROM ALCOHOL CONSUMPTION TO AUD RECOVERY



Authors, (reference number)	Sample size	Mean age (years)	Duration of alcohol dependence	Abstinence before inclusion	Sleep measure	Neuropsychological assessment	Neuroimaging variables	Main results
Benson et al., 1978 [140]	AUD: 20 No controls	46.9	13.9 years (alcohol misuse)	77.6 days	PSG	Working memory (Digit span task)	/	Significant positive correlation between lower percentage of REM sleep and digit span performance.
Ishibashi et al., 1987 [157]	AUD: 9 No controls	43 ± 7.76	> 10 years	180 days	PSG	/	GM volumes (CT scan)	Significant association between lower percentage of SWS and cortical atrophy.
Junghanns et al., 2009 [79]	AUD: 36 (24 early abstainers (EA) and 12 longer abstainers (LA)) No controls	EA: 40.8 ± 6.2 LA: 40.0 ± 9.0	EA: 116.3 ± 75.6 months LA: 160.7 ± 96.8 months	EA: 21.9 ± 7.6 days LA: 115.7 ± 43.8 days	PSG	Declarative memory (face-name association task) Procedural memory (Mirror-tracing task)	/	Significant association between alcohol-related NREM sleep alteration and decrease in declarative memory performance.
Colrain et al., 2011 [158]	AUD: 40 HC: 40	AUD-M: 50.2 ± 7.5 AUD-W: 49 ± 9.6 HC-M: 51.1 ± 10.3 HC-W: 51.6 ± 10.1	AUD-M: 27.5 ± 8.8 years AUD-W: 22.7 ± 9.4 years	AUD-M: 135.9 ± 147 days AUD-W: 260.2 ± 209.6 days	PSG	/	GM volumes (MRI)	Lower regional GM volumes contributed to the changes in the amplitude of K-complexes.
Chaudhary et al., 2015 [55]	AUD: 123 No controls	44 ± 10.3	/	At least 3 days	ISI	Psychosocial problems (SIP questionnaire)	/	Moderate to severe insomnia was associated with higher psychosocial problems.
Liu et al., 2019 [165]	AUD: 15 HC: 15	AUD: 47.3 ± 5 HC: 47.3 ± 4.9	/	At least 2 days	PSQI	/	Resting state functional connectivity	Functional abnormalities within thalamocortical circuits were associated with drinking behavior and sleep impairments.
Laniepce et al., 2019 [141]	KS: 17 AUD: 37 HC: 20	KS: 56.41 ± 4.79 AUD: 45.59 ± 9.21 HC: 42.50 ± 5.94	AUD: 8.65 ± 7.73 years KS: not available	AUD: 10.5 ± 3.99 days KS: > 10 years	PSQI	Executive functions (composite score) Episodic memory (composite score)	GM volumes (MRI) WM integrity (DTI)	In AUD and KS patients, the absence of sleep complaint reflects the presence of severe executive deficits and fronto-thalamic damage.
Kolla et al., 2020 [149]	AUD: 303 No controls	AUD: 42.22 ± 11.57	/	At least 5 days	PSQI	Self-report alcohol-related psychosocial problems (IDTS questionnaire)	/	Significant positive association between sleep disturbance and the propensity to drink when experiencing unpleasant emotions and conflict.

Table 1: Descriptive characteristics and main findings of studies conducted on the relationships between sleep disturbances, brain abnormalities and cognitive impairments in abstinent AUD patients.