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Conference Report

Proceedings of the 12th Alcohol Hangover Research Group Meeting, in Buenos Aires, Argentina †

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Abstract: The current proceedings summarize the presentations held during the 12th meeting of the Alcohol Hangover Research Group (AHRG) in 2022, in Buenos Aires, Argentina. The aim of the annual AHRG meeting was to discuss advances in research on the causes, consequences, and possible treatment of the alcohol hangover, including methodological issues and the possibilities for future research collaboration.

Keywords: alcohol; hangover; cognition; performance; mood; pathology; treatment; COVID-19

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1. Introduction

In many countries around the world, alcohol is consumed. The mean per capita annual consumption in 2019 surpassed 10 L of pure alcohol in many westernized countries, corresponding to approximately 11 standardized alcoholic drinks per week [1]. Alcohol hangover is a common consequence of excessive alcohol consumption [2] and is defined as "the combination of negative mental and physical symptoms which can be experienced after a single episode of alcohol consumption, starting when blood alcohol concentration (BAC) approaches zero" [3]. Alcohol hangover is associated with economic, physical, and psychological costs [4] that can exacerbate the impact of other stressful experiences, such as those of the COVID-19 pandemic [5–7]. In 2010, the Alcohol Hangover Research Group (AHRG) was founded to promote international research collaboration on alcohol hangover [8]. The proceedings of the 12th Annual Alcohol Hangover Research Group meeting occurring from 4 to 6 August 2022 in Buenos Aires, Argentina, are presented here.

Analia Karadayian (University of Buenos Aires, Argentina) and Joris Verster (Utrecht University, The Netherlands) opened the 12th AHRG meeting. Joris Verster (Utrecht University, The Netherlands) discussed the progress made by the Alcohol Hangover Research Group over the past 12 years. Most notable were the annual AHRG meetings, the consensus papers on research methodology [9,10], and the establishing of a definition for the hangover [4,11].

2. Functional Consequences and Cognition

Jessica Balikji (Utrecht University, the Netherlands) presented data assessing the impact of alcohol hangover on work productivity, absenteeism (not attending work), or presenteeism (attending work while hungover), and estimated costs for the Dutch economy. Previous studies have shown that alcohol hangovers can negatively impact cognitive functioning and daily activities [12], including on-the-job performance [13]. In addition, hangovers may be a cause of absenteeism [14]. Data from an online survey [15], conducted in the Netherlands, investigated work productivity and the number of absenteeism and presenteeism days associated with having a hangover. In this study, Severeijns et al. [16] examined N = 347 Dutch employees for the year 2019, i.e., prior to the 2019 coronavirus disease (COVID)-19 pandemic. Absenteeism was reported by 8.1% of employees (mean = 0.2 days), and 33.4% of the sample reported at least one presenteeism day due to alcohol hangover (mean = 8.3). For presenteeism days, 24.9% productivity loss was reported. The estimated costs for the Dutch economy in 2019 totaled EUR 2.7 billion (absenteeism EUR 234 million and presenteeism EUR 2.4 billion). Although a rough estimate, obtained from a convenience sample, these estimated economic costs underline the significant impact of the alcohol hangover on society.

Lydia Devenney (Atlantic Technological University, Ireland) presented data from a naturalistic study on attention and emotional processing during alcohol hangover. Ecological Momentary Assessment (EMA) was used to monitor alcohol consumption. N = 25 young adults participated in a study comparing a hangover day and a control day (no alcohol consumed). Participants consumed a mean of 12.8 alcoholic drinks on the hangover day. On both test days, participants completed a psychometric test battery, including the Eriksen flanker test, five-choice serial reaction time, psychomotor vigilance, and the attentional blink task. Signal detection analysis revealed significantly longer response times on the attention tasks on the hangover day, compared to the no-alcohol day. However, no significant differences were found in the number of errors between the hangover and control day. Assessments of mood confirmed that on the hangover day, participants reported reduced alertness and increased scores on tranquility. Of interest, the EMA assessments of alcohol consumption recorded a significantly greater number of alcoholic drinks consumed compared to the next-day self-reported number of drinks [17]. This observation warrants further investigation, as it suggests that next-day self-report is less accurate than EMA assessments to accurately record alcohol consumption.

Ann-Kathrin Stock (TU Dresden, Germany) presented and discussed new approaches to detect and quantify white matter brain damage associated with alcohol misuse [18]. Aberrant alcohol consumption results in brain damage, especially to the white matter [19], but it has remained unclear what would be a safe threshold for consumption, or at what levels of drinking functionally relevant brain/white matter damage can be detected. For this reason, whether binge drinking may lead to brain damage and associated cognitive impairments in people not meeting the diagnostic criteria for alcohol use disorder (AUD) has remained a hotly debated matter. The main reason for this lack of knowledge is that commonly used brain imaging techniques allow advanced stages of AUD-related brain damage diagnosis but are not sensitive enough to properly detect early, small changes in otherwise healthy individuals. Single molecule array (SIMOA) analysis is a new way of analyzing blood samples that could help overcome these issues. This methodology allows the detection of neurofilaments that are released into the bloodstream whenever the white matter of the brain is damaged. Given its sensitivity, SIMOA is the first clinical assessment that truly allows investigating even the slightest changes in white matter structural integrity. Stock et al. applied this blood test to investigate whether young healthy men show any signs of brain damage during and after a single night of binge drinking. It was further investigated how this relates to cognitive and behavioral dysfunctions during drinking and during hangover. The analysis revealed that white matter integrity was not compromised during acute alcohol intoxication, but mild detrimental effects could be detected during alcohol hangover. The opposing effects of intoxication and (acute)

tolerance onto glutamatergic signaling may provide the most plausible explanation for this differential finding. Yet, further research is required to substantiate (or refute) this claim. Moreover, neurocognitive impairments were found to be related to subjective hangover severity but not to the assessed increases in serum neurofilament levels. Further research is necessary to evaluate whether there are cumulative effects.

3. Mood

Joris Verster (Utrecht University, the Netherlands) discussed the possible impact of baseline mood, mental resilience, and personality on hangover frequency or severity. Previous studies suggested that guilt about drinking, neuroticism, being angry when drunk, and experiencing negative life events were significant predictors of hangover severity [20,21]. Another study found a significant correlation between mental resilience and hangover severity [22]. However, these studies had significant methodological shortcomings. The findings were not replicated in other studies, which showed no impact on the presence and severity of hangovers of baseline mood and personality (neuroticism [23] or mental resilience [24,25]). Verster discussed the results of an online survey among N = 153 Dutch adults [26]. The participants reported on the hangover they experienced after their heaviest drinking occasion in the period from 15 January to 14 March 2020, i.e., prior to the COVID-19 pandemic. Questions were asked concerning alcohol consumption on their heaviest drinking occasion in this time period, and hangover severity for that day was assessed using a single-item scale ranging from 0 (absent) to 10 (extreme) [27]. Mental resilience was assessed with the Brief Mental Resilience scale [28], personality with the Eysenck Personality Questionnaire—Revised Short Scale [29], and mood via single-item assessments [30]. Partial correlations, corrected for estimated BAC, of mental resilience, personality, and baseline mood, respectively, with hangover severity or frequency were not significant. Regression analysis confirmed that baseline mood, mental resilience, and personality were not relevant predictors of hangover frequency and severity. Thus, while negative mood is a common characteristic of the alcohol state itself, baseline mood, mental resilience, personality, and baseline mood are unlikely to play a relevant role in the pathogenesis of the alcohol hangover.

Kristin Tellez-Monnery (University of Nevada, Reno, USA) presented on psychological aspects of alcohol hangover. While both the scientific and grey literature acknowledge additional anxiety experiences (hangover anxiety) in certain individuals, hangover depression is rarely mentioned. Furthermore, limited research examines factors underlying hangover anxiety and hangover depression. Candidate predictors investigated in the presented research included emotion dysregulation and repetitive negative thinking (RNT). Emotion dysregulation and RNT are transdiagnostic factors underlying many psychopathological symptoms, including general anxiety and depression symptoms and alcohol problems [31,32]. Additionally, emotion dysregulation and RNT may enhance each other [33,34] and, respectively, correlate with problematic alcohol use [31,35].

Undergraduate students from a large public US university reporting current alcohol consumption completed baseline surveys assessing generally occurring anxiety and depression (unrelated to hangover), and emotion dysregulation. At two-week follow-up, students were assessed for RNT, hangover occurrence, and hangover anxiety and depression. Hierarchical linear regression models assessed the predictor impact on hangover depression and hangover anxiety, respectively. For the hangover depression model, baseline depression was the sole predictor in the model's first step, followed by emotion dysregulation, RNT, and emotion dysregulation–RNT interaction, respectively, added in subsequent steps. A similar analysis was conducted for hangover anxiety.

While baseline anxiety significantly predicted hangover anxiety, additional variables added in steps two–four were non-significant, indicating that hangover anxiety may represent baseline anxiety recurrence. However, exploring alternative causational theories is still suggested. Conversely, RNT significantly predicted hangover depression severity beyond the effect of baseline depression and emotion dysregulation [36]. Furthermore, a significant

emotion dysregulation–RNT interaction demonstrated that among those with moderate to high RNT levels, emotion dysregulation also significantly predicted hangover depression, while among those with low RNT levels, emotion dysregulation did not significantly predict higher hangover depression [36].

4. Pathology and Treatment

Joris Verster (Utrecht University, the Netherlands) presented an update on the pathology and treatment of the alcohol hangover. Studies showed that variations in both alcohol metabolism and immune fitness have been found to impact hangover severity [37,38]. In particular, drinkers who metabolize ethanol more quickly [39,40] or have a less pronounced inflammatory response to alcohol intake [41,42] reported less severe hangovers. However, research on alcohol hangover treatments is limited. In addition, the products under investigation often do not aim to prevent or reduce the inflammatory response or enhance ethanol metabolism. Instead, previous studies often focused on the quick removal of acetaldehyde, or incorrectly viewed the hangover as a consequence of dehydration. It is therefore not surprising that no proven effective and safe hangover treatments are currently marketed [43]. The most popular treatment in 2019 in the USA was dihydromyricetin (DHM) [43]. However, a double-blind placebo-controlled clinical trial revealed that DHM had no significant effect on hangover severity [44]. Thus, future research should continue to elucidate the pathology of the hangover to enable the development of effective treatments.

Silvia Lores-Arnaiz and Analia Karadayian (Universidad de Buenos Aires, Argentina) discussed the molecular mechanisms underlying synaptic damage in alcohol hangover. The negative effects of alcohol consumption on the central nervous system are based on the alteration of macromolecules due to the increment in oxidizing species generation, leading to lipid peroxidation, protein carbonylation, and deoxyribonucleic acid (DNA) damage [45]. An experimental animal model of ethanol (3.8 g/kg i.p.) hangover was developed, demonstrating long-lasting motor and affective impairments for at least 14–20 h post hangover onset [46–48]. Based on this model, the after-effects of acute ethanol exposure were associated with an imbalance in free radical and antioxidant production, together with decreases in oxygen consumption, inhibition of respiratory chain complex enzymatic activity, and decreases in mitochondrial membrane potential in the mouse brain cortex and cerebellum [46,49–51].

Mitochondrial function at the synapses can be more deeply studied by the isolation of an enriched fraction of synaptosomes, which are nerve-ending particles formed during homogenization of brain tissues [52]. Synaptosomes can be used to study neurotransmitter synthesis and exocytosis, as well as mitochondrial function parameters including mitochondrial membrane potential, respiratory rates, adenosine triphosphate (ATP) generation, and mitochondrial Ca^{2+} uptake [53]. Therefore, the isolation of synaptosomes represents a useful tool to study bioenergetic function and redox balance in experimental models of aging and neurotoxicity [54,55]. To investigate whether mitochondria present in synaptic terminals could be specifically damaged during ethanol hangover, synaptosomes and non-synaptic mitochondrial fractions were obtained from control and treated mice 6 h after ethanol injection. This experimental approach led to the conclusion that the mitochondria present at brain cortex synaptic terminals were more susceptible to the after-effects of acute ethanol exposure compared to mitochondria from neuronal soma. Specifically, mitochondria at synapses exhibited exacerbated levels of reactive oxygen species, damage to lipids, decreases in enzymatic and non-enzymatic antioxidants, and mitochondrial dysfunction [51,56–58]. The most recent data indicated that ethanol could exert its negative after-effects on nitric oxide (NO) metabolism by reducing the expression of protein complex N-methyl-D-aspartate receptor, postsynaptic density protein-95, and neuronal nitric oxide synthase (NMDAR-PSD-95-nNOS) proteins, decreasing the activity of neuronal nitric oxide synthase (nNOS), and affecting calcium entry at the synapses [59]. Ongoing experiments will be conducted in order to evaluate if mitochondrial dysfunction and oxidative stress could lead to cell death by the activation of mitochondrial apoptotic signaling pathways.

Thus, an integrative process can be proposed by which adverse after-effects of binge alcohol exposure could lead to synaptic pathophysiology (see Figure 1). The understanding of the mechanisms by which neuronal functionality is negatively altered during the residual stage of alcohol misuse could provide new evidence on the persistence of alcohol effects on the central nervous system, even when alcohol is no longer systematically present.

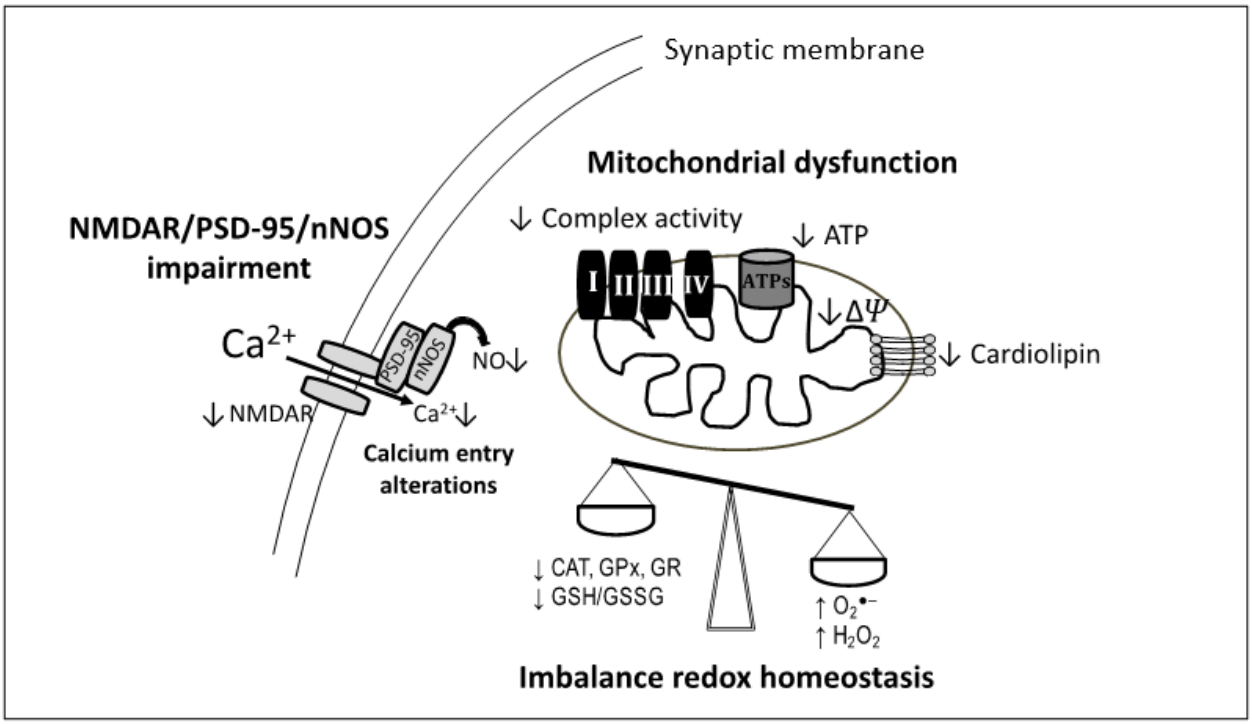

Figure 1. Alcohol after-effects at the synaptic level. At alcohol hangover onset, synaptic terminals exhibited mitochondrial dysfunction, NMDAR/PSD95/nNOS impairments, calcium entry alterations, and an imbalance in redox homeostasis. Abbreviations: ATP = adenosine triphosphate; ATPs = ATP synthase; CAT = catalase; GPx = glutathione peroxidase; GR = glutathione reductase; NMDAR = N-methyl-D-aspartate receptor; NO = nitric oxide; nNOS = neuronal nitric oxide synthase; PSD-95 = postsynaptic density protein 95; ΔΨ = mitochondrial membrane potential.

Pantea Kiani (Utrecht University, the Netherlands) presented data on the genetics of the alcohol hangover. Previous studies found that drinkers possessing the aldehyde dehydrogenase 2 gene (ALDH2*2) allele (e.g., people of Asian descent) typically experience significantly more severe hangovers. [60,61]. Twin studies comparing hangover-sensitive drinkers and hangover-resistant drinkers found that being hangover resistant could be explained up to 55% by genetic variability [62,63].

To increase knowledge on this relatively unexplored area of research, the DNA of N = 30 hangover-sensitive drinkers was compared with the DNA of N = 30 hangover-resistant drinkers (i.e., participants that consumed the same amount of alcohol but claimed never to have had hangovers). Differences between the groups were found in genes related to alcohol metabolism and oxidative stress. In particular, significantly increased exposures of thioredoxin reductase 1 (TXNRD1), thioredoxin reductase 2 (TXNRD2), and cardiolipin synthase 1 (CRLS1) were observed in the hangover-sensitive group. Both TXNRD variants catalyze the oxidative pathway, reducing nicotinamide adenine dinucleotide phosphate (NADPH) into NADP, an essential step in the microsomal ethanol oxidizing system (MEOS). CRLS1 plays a role in maintaining the functional integrity and dynamics of mitochondria under both optimal and stress conditions. In addition, differences between the two groups were found for genes related to the inflammatory response to alcohol, including tyrosine-protein kinase (TXK, involved in the regulation of the adaptive immune response via

differentiation of conventional T cells and non-conventional natural killer T cells), T cell immunoglobulin and mucin domain containing 4 (TIMD4, involved in regulating T-cell proliferation), Hepatitis A virus cellular receptor 2 (HAVCR2, a regulator of the immune response), and zinc finger nuclear transcription factor, X-box binding 1 (ZNFX1, involved in hyperinflammation). These first findings confirm that both alcohol metabolism and the inflammatory response to alcohol are determinants of the presence and severity of alcohol hangover, and justify further research in this area.

5. COVID-19

The COVID-19 pandemic and associated lockdown periods posed significant challenges for scientific research. The limitations of measures to reduce the spread of the SARS-CoV-2 virus such as virtual working environments forced researchers to reconsider study designs [64]. In particular, alcohol research was affected during the COVID-19 pandemic, as naturalistic studies were not possible due to the closure of bars, restaurants, and other drinking venues.

Joris Verster (Utrecht University, the Netherlands) discussed the challenges and accomplishments during the COVID-19 pandemic. For some experimental studies, home testing was used as an alternative for laboratory testing. The possibilities for home testing have increased significantly over the past decades, and validated cognitive test batteries can now be completed on personal phones or computers. In addition, self-report survey data can be gathered online. A large number of these surveys examined the impact of the COVID-19 pandemic on alcohol consumption and hangovers.

Agnese Merlo (Utrecht University, The Netherlands) presented data from a survey that was conducted during the COVID-19 pandemic. The online survey was conducted among Dutch students and investigated alcohol hangover during the COVID-19 pandemic in the Netherlands [6,65]. Compared to no-lockdown periods, a significant reduction in both quantity and frequency of alcohol consumption was found during the first two lockdown periods. Similarly, during the lockdown periods, both the frequency and severity of alcohol hangovers was significantly lower. The transition from face-to-face education to online teaching during the COVID-19 pandemic demonstrated a largely variable impact on academic input (e.g., time invested in the study) and academic output (e.g., grade point average). However, a consistent reduction was reported in the amount of interactions with teachers and other students. Students who reported the highest alcohol consumption levels prior to the COVID-19 pandemic, including a higher severity and frequency of hangovers, benefited most from the lockdown periods. Their reduction in alcohol consumption and hangovers was significantly associated with improved academic performance.

Ann-Kathrin Stock (TU Dresden, Germany) presented selected data collected in an online study investigating COVID-19 lockdown effects on mood, alcohol consumption, academic functioning, and perceived immune fitness in young adults in Germany [7]. Specifically, the presented data compared retrospective assessments of these factors for the year before the start of the pandemic, as well as two following spring/winter/fall lockdown periods and one summer period characterized by reductions in lockdown and social distancing measures. The data presented at the meeting were restricted to university students and employees and limited to the question of alcohol- and hangover-related differences between those time points. The main findings were that the study participants reported a significant reduction in the number of standard drinks per week, drinking days and binge drinking days per month, hangover days per month, and subjective hangover severity of hangover occasions during the first lockdown period, as compared to the time before the first lockdown, as well as the first summer between lockdowns. During the second lockdown, there was again a reduction in the number of standard drinks per week, hangover days per month, and subjective hangover severity of hangover occasions, but no reduction in the number of drinking days or binge drinking days per month, as compared to the time before the first lockdown, as well as the first summer between lockdowns.

Analia Karadayian (University of Buenos Aires, Argentina) reported on alcohol consumption and hangover during the COVID-19 pandemic in Argentina [5,66]. COVID-19 pandemic effects on university students were analyzed in Argentina. A retrospective online survey was conducted among students from the University of Buenos Aires (18–35 years old) between July and November 2021 to investigate and discuss potential changes in alcohol intake, and hangover episodes and severity during the pandemic. Argentina had two extensive lockdown periods during which university education remained virtual. Survey questions covered four periods (before the pandemic, the first and second lockdown periods, and a no-lockdown period). The participants were invited via university email to complete the survey. For the current analysis, only participants who consumed alcohol were included. The main finding from this study was that the COVID-19 first and second lockdowns were associated with reductions in alcohol consumption, hangover severity, and subjective intoxication. The results indicated that the number of alcoholic drinks consumed during the second lockdown was lower than before the pandemic, and moreover, for the heaviest drinking occasions, students presented lower alcohol consumption, drunkenness, and hangover severity during all periods compared to before the pandemic. Related to sex differences, women seemed to consume fewer alcoholic drinks on their heaviest drinking occasion during the second lockdown, which was also accompanied by lower levels of subjective intoxication and next-day hangover severity compared to men. Apart from pandemic effects on alcohol consumption, smoking patterns were evaluated as well. In this sense, the youngest students reduced the number of cigarettes smoked per day during the two lockdown periods, while older students smoked more days per week. Taken together, in line with studies from other countries around the world, Argentinian college students exhibited a decrease in alcohol consumption and hangover severity during the lockdown periods. The closure of drinking venues and lack of social gatherings during the lockdown periods may account for the overall reduction in alcohol consumption.

6. Discussion

The presentation on hangover treatment highlighted that the current market lacks effective, evidence-based treatment. Evidence-based hangover treatments could not only minimize hangover-related personal health and cognitive/emotional consequences but may also help to minimize economic costs. Indeed, as highlighted by the first presentation, hangover-related economic costs are steep. Extrapolating similar costs across countries and continents leads to a staggering conclusion about hangover-associated economic impacts, which are likely also increasing as worldwide alcohol consumption increases.

Other presentations focused on somewhat conflicting mood study results. Specifically, a large cross-sectional study using multiple hangover scales found mood symptoms to be less common and bothersome than physical hangover symptoms, while conversely, a small longitudinal study assessing mood symptom prevalence and severity observed high prevalence and moderate severity scores. This difference may be partially due to the lack of mood symptom representation in the three major multiple-item hangover assessment scales. That is, the Alcohol Hangover Severity Scale (apathy and confusion) and the Hangover Symptoms Scale (depression and anxiety) include only two mood items [67,68], whereas the Acute Hangover Scale includes no mood items [69]. This leads to a lack of proper assessment of mood in many hangover studies. The focus on physical symptoms and limited inclusion of mood symptoms highlights that mood symptoms are a neglected facet of hangover research. Specifically, researchers may not consider mood-related research questions if a scale does not include mood symptoms. Furthermore, no consensus currently exists on how to assess hangover mood symptom severity. The only current methods involve adapting anxiety, depression, and other non-hangover (i.e., general or other contextual) mood scale instructions for participants to exclusively consider hangover experiences when responding. Future research should develop hangover-specific mood scales.

Multiple speakers presented their country-specific results from a multi-national COVID-19 hangover study. All country samples observed decreased drinking behavior, hangovers, and hangover severity. While potentially stress-inducing academic and other stressful experiences persisted and may indeed have increased due to sudden changes in academic delivery, evaluation, and lockdown measures, drinking behavior decreased. This decrease suggests that among the samples, which all consisted of university students and young university employees, drinking motives are more highly linked to social interaction than to internal stressful experiences. This conclusion is further supported by the observation in the Netherlands that the students with the greatest alcohol consumption and hangover frequency prior to the pandemic benefitted the most academically from the alcohol consumption decrease during the pandemic.

Other speakers also presented on underlying hangover mechanisms, discussing data from both humans and mice. In humans, significantly increased expression of a mitochondrial functional integrity and dynamics gene was observed in hangover-sensitive drinkers, suggesting a mitochondrial role in hangover dynamics. Moreover, in mice, brain cortex synaptic mitochondrial damage was detected. As these mitochondria specifically support energy demands related to communication between brain cells, these data further suggest hangover-associated impaired communication between brain cells. Similarly, acute white matter damage in humans, quantified using previously neglected methods, was observed during hangover. As brain white matter plays an important role supporting communication between different cells and parts of the brain, this study further suggests hangover-associated neural communication impairments. Interestingly, these communication impairments may also be observed behaviorally, as longer within-subject attentional task response times were recorded during hangover as compared to a sober period. Cumulatively, these studies help to triangulate hangover-associated neural cellular impairments, highlighting the roles of white matter and cortex synaptic mitochondria. Aside from communication impairments, genetic data also suggest associations between inflammation, alcohol metabolism, and hangover severity. Further investigating the role of alcohol metabolism and inflammation in the pathology of alcohol hangover will help to develop effective hangover treatments in the future.

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