Original Article

# Sex differences in dorsolateral prefrontal cortical and superior colliculus activities support the impact of alcohol use severity and sleep deficiency on two-back memory

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**Background:** Working memory refers to a process of temporary storage and manipulation of information to support planning, decision-making, and action. Frequently comorbid alcohol misuse and sleep deficiency have both been associated with working memory deficits. However, how alcohol misuse and sleep deficiency interact to impact working memory remains unclear. In this study, we aim to investigate the neural processes inter-relating alcohol misuse, sleep deficiency and working memory.

**Methods:** We curated the Human Connectome Project (HCP) dataset and investigated the neural correlation of working memory in link with alcohol use severity and sleep deficiency in 991 young adults (521 women). The two were indexed by the first principal component (PC1) of principal component analysis of all drinking metrics and Pittsburgh Sleep Quality Index (PSQI) score, respectively. We processed the imaging data with published routines and evaluated the results with a corrected threshold. We used path model to characterize the inter-relationship between the clinical, behavioral, and neural measures, and explored sex differences in the findings.

**Results:** In whole-brain regression, we identified $\beta$ estimates of dorsolateral prefrontal cortex response (DLPFC $\beta$) to 2- *vs.* 0-back in correlation with PC1. The DLPFC showed higher activation in positive correlation with PC1 across men and women (r=0.16, P<0.001). Path analyses showed the model PC1 → DLPFC $\beta$ → differences in reaction time (2- minus 0-back; $RT_{2\text{-}0}$) of correct trials → differences in critical success index (2- minus 0-back; $CSI_{2\text{-}0}$) with the best fit. In women alone, in addition to the DLPFC, a cluster in the superior colliculus (SC) showed a significant negative correlation with the PSQI score (r=–0.23, P<0.001), and the path model showed the inter-relationship of PC1, PSQI score, DLPFC and SC β's, and $CSI_{2\text{-}0}$ in women.

**Conclusions:** Alcohol misuse may involve higher DLPFC activation in functional compensation, whereas, in women only, sleep deficiency affects 2-back memory by depressing SC activity. In women only, path model

suggests inter-related impact of drinking severity and sleep deficiency on 2-back memory. These findings suggest potential sex differences in the impact of drinking and sleep problems on working memory that need to be further investigated.

**Keywords:** Working memory; alcohol dependence; alcohol use disorder (AUD); insomnia

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## Introduction

### *The effects of drinking and sleep deficiency on cognitive function*

Alcohol is an organic solvent which in high doses has both direct and indirect harmful influences on the body and the brain (1). Individuals engaged in excessive drinking are at significant risk of cognitive dysfunction (2,3) across multiple domains (4,5). Findings from human adolescents suggest that binge drinking and heavy alcohol use are associated with poorer cognitive functioning on a broad range of neuropsychological assessments, including learning, psychomotor speed, attention, and executive functioning, including impulse control. In addition, these cognitive and neural consequences may persist into adulthood (6). Binge drinking is associated with poorer performance of executive functions subserved by the dorsolateral prefrontal cortex (DLPFC) (7). A recent review associated alcohol use disorder (AUD) with cognitive impairments and highlighted the interaction of AUD and its comorbidities in increasing the risk of cognitive impairment (8).

Sleep is critical to both physical and mental health (9-11). Sleep deficiency compromises general cognitive function (12,13) and accelerates age-related cognitive decline (14,15). For instance, obstructive sleep apnea (OSA) is associated with working memory, episodic memory, and executive control dysfunction and the deficits may be irreversible in untreated cases (16). Importantly, alcohol misuse and sleep deficiency are frequently comorbid and may inter-relate in compounding cognitive dysfunction and perpetuating drinking and sleep problems (17-19). An earlier study showed that the functional connectivities between the left thalamus and medial prefrontal cortex mediated the relationship between the severity of problem drinking and sleep deficiency in individuals with alcohol dependence (20). Many studies have examined the relationship between alcohol use, hangover, and withdrawal severity, sleep disturbance, and cognitive dysfunction (21,22). It is posited that sleep disturbances may reflect a consequence of alcohol-related brain damage. However, research of the interactions between sleep disturbances, cognitive deficits, and brain alterations in AUD is still in its infancy (17). In particular, very little is known about how alcohol misuse and sleep deficiency jointly influence cognitive function in non-clinical populations.

### *The effects of drinking and sleep deficiency on working memory*

Many studies of the effects of alcohol misuse or sleep deficiency on cognition have focused on working memory. Working memory refers to a process of temporary storage and manipulation of information to support planning, decision making, and action (23). A recent resting-state functional magnetic resonance imaging (fMRI) work reported hyperconnectivity between the salience and frontoparietal networks in positive correlation with Pittsburgh Sleep Quality Index (PSQI) score (24). Many behavioral paradigms have been used to investigate the psychological and neural processes of working memory (25,26). Among them, the N-back task is widely used in combination with fMRI or electroencephalography (EEG) to investigate working memory function and dysfunction as a consequence of excessive drinking (27-30) or sleep deficiency (31-33). For instance, both recent consumption and a history of excessive drinking of alcohol led to impaired working memory in a virtual Morris water task (34). Another study showed that the average number of drinks per drinking day mediated the impact of alcohol-induced decline in working memory and other adverse consequences of alcohol use (35). Sleep deprivation (SD) leads to impaired accuracy in spatial working memory (36) and the capacity and filtering efficiency of visual working memory (37). In adolescents, sleep restriction results in

 

greater medial prefrontal cortical activation and weaker precuneus activation during N-back memory (38). Thus, both alcohol misuse and sleep deficiency affect working memory; however, how these frequently comorbid conditions may interact to impact working memory remains to be examined in non-clinical populations.

### *Sex differences in working memory and the impacts of alcohol misuse and sleep deficiency*

Sex differences in brain function, including hippocampus-dependent processes such as working memory, have long been reported in the literature (39,40). Males outperformed females on hippocampus-dependent tasks both in rodents and in humans (41). In a fMRI study of maintenance of visuospatial working memory, men surpassed women in performance and showed stronger bilateral intraparietal activation (42).

A study of cue-elicited alcohol craving found that working memory altered the relationship amongst stress and craving, buffering against stress-induced craving specifically in male adolescents (43). An earlier work showed that binge drinking during adolescence was associated with gender-specific differences in frontal, temporal, and cerebellar brain activation during a spatial working memory task. For female binge drinkers, less activation was associated with poorer sustained attention and working memory performance, whereas for male binge drinkers, greater activation was linked to better spatial performance (44).

A review with meta-analysis discussed sex differences in sleep loss-induced cognitive deficits, with the majority of studies reporting greater impacts of sleep loss on cognitive health in women than in men (45). A more recent study tested sex differences in the association between hippocampal volume and working memory in a national sample of children 9 to 10 years old and reported larger bilateral hippocampal volumes in association with better working memory (46). Further, females *vs.* males showed stronger positive associations between the hippocampal volumes and working memory. However, no studies to our knowledge have examined sex differences in the interactive effects of alcohol misuse and sleep deficiency on working memory.

### *The present study*

We examined the effects of alcohol use severity and sleep deficiency on working memory and the neural bases of these effects. Previous studies have suggested the effects of alcohol misuse and SD on working memory, but no studies have investigated the interactive effects of alcohol misuse and sleep deficiency. To this end, we employed the Human Connectome Project (HCP) data where young adults were evaluated with the PSQI, alcohol use behavior, and fMRI during a 2-back working memory task. We identified the neural correlation of working memory in link with alcohol use severity and PSQI score and used path model to characterize the inter-relationship between the clinical, behavioral, and neural measures. In view of a literature documenting sex differences, we performed the analyses for the entire sample as well as for men and women separately.

## Methods

### *Dataset*

We employed the HCP 1200 Subjects Release (S1200) data in this study. A total of 1,082 young adults completed a N-back task scan and, after exclusion of 91 subjects who had head movements greater than 2 mm in translation or 2 degrees in rotation or for whom the images failed in registration to the template, 991 (521 women) were retained. All subjects were physically healthy with no severe neurodevelopmental, neuropsychiatric or neurological disorders. Individuals may use alcohol to varying extents, which is known to influence brain structure and function (47-49). HCP evaluated alcohol use with multiple questions and, as in our earlier work (50,51), we conducted a principal component analysis of all drinking-related measures and identified the first principal component (PC1, eigenvalue: 7.44 and explaining variance: 49.57%) to evaluate alcohol drinking severity (higher score representing more alcohol use). PSQI (52) was used to evaluate sleep quality (higher score representing worse sleep quality). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Imaging protocol, data preprocessing and N-back task*

The protocol of imaging was designed by HCP (53). We followed the same published preprocessing routines in our earlier studies (54,55).

Participants completed two runs of the N-back task in a fixed order (*Figure 1A*). Images of body part, face, place, tool (*Figure 1B*) were shown in separate blocks. We used the reaction time (RT) of correct responses and critical success

 

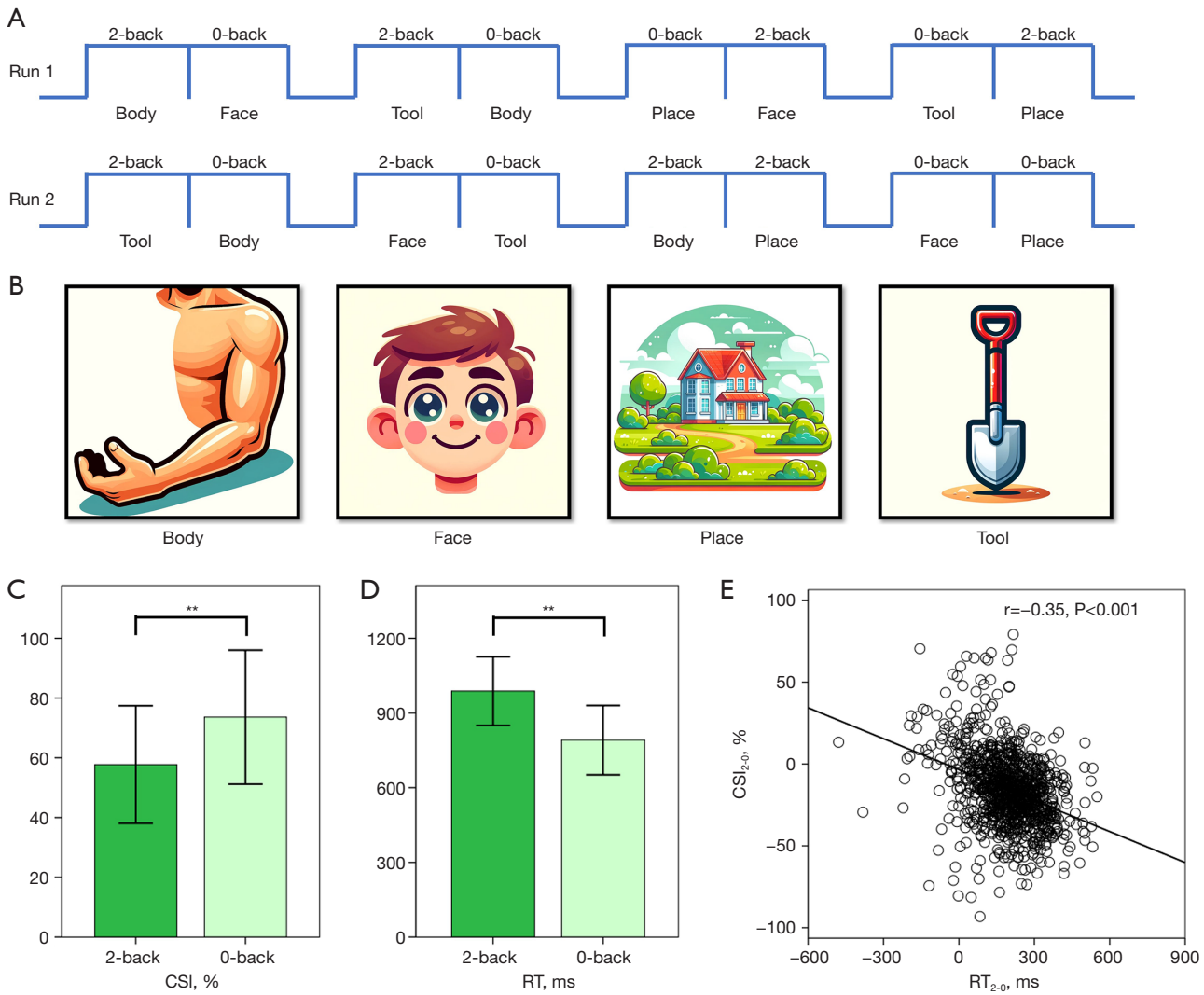


**Figure 1** N-back task and the correlation between $CSI_{2\text{-}0}$ (%) and $RT_{2\text{-}0}$ (ms). (A) Block sequence, (B) stimuli, (C) mean ± standard deviation of CSI and (D) RT of correct trials of the N-back task. (E) The $CSI_{2\text{-}0}$ and in $RT_{2\text{-}0}$ of correct trials showed a significant negative correlation with age, sex and years of education as covariates. Each data point represents one subject. **, P<0.001. CSI, critical success index; RT, reaction time; $CSI_{2\text{-}0}$, difference in CSI between 2- and 0-back; $RT_{2\text{-}0}$, the difference in RT of correct trials between 2- and 0-back.

index (CSI) to evaluate N-back performance.

### *Imaging data modeling and statistics*

Same with our previous work (56), we constructed a contrast "2- minus 0-back" for each individual, and in group analyses, a whole-brain regression of this contrast against drinking severity PC1 (or PSQI score) was conducted in the entire cohort with age, sex, and years of education as covariates. The results were evaluated at voxel P<0.001, uncorrected, in combination with a cluster P<0.05, corrected for family-wise error (FWE) of multiple comparisons. We confirmed sex differences with slope tests.

### *Mediation and path analyses*

Mediation analyses were performed to evaluate the relationships between contrast "2- minus 0-back" markers (DLPFC beta), differences in CSI (2- minus 0-back; $CSI_{2\text{-}0}$) and differences in RT (2- minus 0-back; $RT_{2\text{-}0}$) of correct trials (see Results). Please note the results of mediation analyses did not imply causality but served to clarify the

**Table 1** Demographics and behavioral performances of the participants

| Characteristic | Men (n=470) | Women (n=521) | *t* | P value* |
|---|---|---|---|---|
| Age, years | 28.0±3.6 | 29.6±3.6 | −6.96 | <0.001 |
| Education, years | 14.9±1.7 | 15.0±1.8 | −1.36 | 0.175 |
| Drinking severity PC1 | 0.34±1.04 | −0.31±0.79 | 10.31 | <0.001^ |
| PSQI | 4.53±2.17 | 4.95±3.02 | −2.84 | 0.005^ |
| CSI, 2-back, % | 61.4±19.3 | 54.4±19.5 | 5.17 | <0.001^ |
| CSI, 0-back, % | 75.7±22.3 | 71.7±22.4 | 2.41 | 0.016^ |
| RT, 2-back, ms | 985±142 | 990±134 | −0.02 | 0.981^ |
| RT, 0-back, ms | 787±141 | 795±138 | −0.52 | 0.600^ |
| CSI, 2- minus 0-back | −14.3±23.2 | −17.2±21.8 | 1.96 | 0.050^ |
| RT, 2- minus 0-back | 199±128 | 195±123 | 0.56 | 0.574^ |

Values are mean ± standard deviation. *, two-sample *t*-test (^, with age and years of education as covariates). Drinking severity PC1, the first principal component obtained of principal component analyses of all drinking measures; PSQI, Pittsburgh Sleep Quality Index; CSI, critical success index; RT, reaction time of correct trials.

inter-relationships of multiple, correlating variables. We also employed path analysis to evaluate how PC1, DLPFC beta, $RT_{2-0}$ and $CSI_{2-0}$ (see Results) were inter-related.

## Results

### *Behavioral performance and its relationship to PC1 and PSQI*

Subjects averaged at a CSI of 73.6±22.4 (mean ± standard deviation) % in 0-back and 57.7%±19.7% in 2-back (*Figure 1C*), and an RT (correct trials only) of 791±139 ms in 0-back and 988±138 ms in 2-back (*Figure 1D*). The CSI was significantly lower in 2- than in 0-back ($t$=−22.16, P<0.001, paired-sample $t$-test) and the RT was significantly longer in 2- than in 0-back ($t$=49.49, P<0.001, paired-sample $t$-test). *Table 1* shows age, years of education, drinking severity PC1, and behavioral performances of men and women separately.

Women as compared to men showed significantly lower drinking severity PC1, higher PSQI score, and lower $CSI_{2-0}$ (*Table 1*).

Across subjects, the differences in CSI between 2- and 0-back, i.e., $CSI_{2-0}$, were negatively correlated with the differences in RT between 2- and 0-back, i.e., $RT_{2-0}$ ($r$=−0.35, P<0.001, Pearson regression with age, sex and years of education as covariates, *Figure 1E*). That is, higher $CSI_{2-0}$ was associated with smaller $RT_{2-0}$. Neither drinking severity PC1 nor PSQI was significantly correlated with $CSI_{2-0}$ (PC1: $r$=−0.02, P=0.592; PSQI: $r$=0.04, P=0.209) or $RT_{2-0}$ (PC1: $r$=0.04, P=0.217; PSQI: $r$=0.01, P=0.751) in Pearson regression with same covariates.

Drinking severity PC1 was positively correlated with PSQI in entire sample ($r$=0.11, P<0.001), in men ($r$=0.10, P=0.034) and in women ($r$=0.13, P=0.004) alone with same covariates. No sex difference was noted in the correlation ($Z$=−0.44, P=0.660; slope test).

### *Regional activations to 2- vs. 0-back in correlation with PC1 and PSQI score in men and women combined*

Whole-brain linear regression of the contrast "2- minus 0-back" against PC1 for the entire sample revealed a positively correlated cluster in the DLPFC (x, y, z =34, 36, 22; $T$=4.47, 664 $mm^3$; *Figure 2A*). The β estimate of the DLPFC (DLPFC β) was significantly correlated with PC1 score ($r$=0.16, P<0.001; *Figure 2B*), as expected, and with $RT_{2-0}$ ($r$=0.31, P<0.001, *Figure 2C*) and $CSI_{2-0}$ ($r$=−0.15, P<0.001, *Figure 2D*) in linear regressions with the same covariates.

Whole-brain linear regression of the contrast "2- minus 0-back" against PSQI score for the entire sample did not reveal any clusters at same threshold.

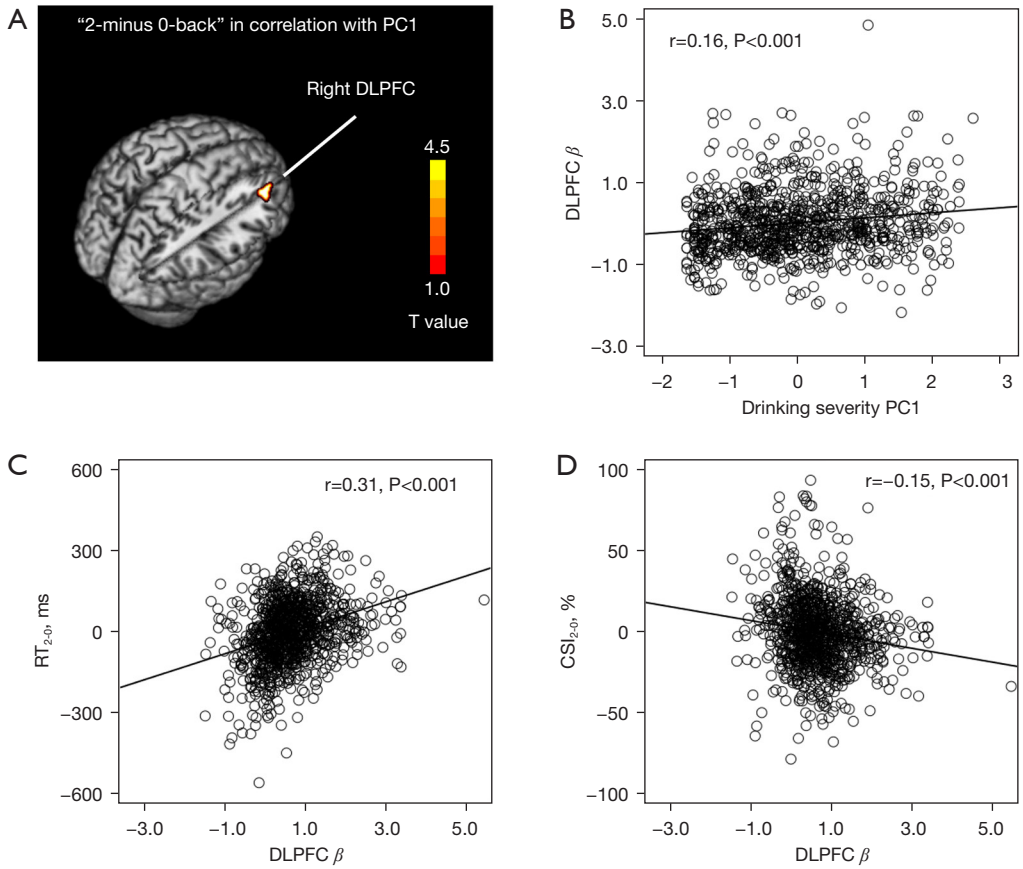


**Figure 2** Regional activations to 2- *vs.* 0-back in correlation with drinking severity. (A) DLPFC showed positive correlation with drinking severity PC1. Scatterplot of the DLPFC *β* *vs.* (B) drinking severity PC1; *vs.* (C) the $RT_{2-0}$; and *vs.* (D) the $CSI_{2-0}$. Note that the scatter plots show the residuals, after age, sex and years of education were accounted for. PC1, the first principal component from a principal component analysis of all drinking-related measures; DLPFC, dorsolateral prefrontal cortex; DLPFC *β*, *β* estimates of DLPFC; $RT_{2-0}$, difference in RT of correct trials between 2- and 0-back; $CSI_{2-0}$, difference in CSI between 2- and 0-back; CSI, critical success index; RT, reaction time.

### *Inter-relationship of PC1, DLPFC β, and behavioral performance in men and women combined*

DLPFC β, $RT_{2-0}$ and $CSI_{2-0}$ were significantly correlated pairwise. We performed a mediation analysis to examine the inter-relationship between the DLPFC β, $RT_{2-0}$ and $CSI_{2-0}$, with the same covariates. We considered all six models and employed a corrected $p$ (0.05/6=0.0083) to evaluate the mediation effects. The results showed the model DLPFC β → $RT_{2-0}$ → $CSI_{2-0}$ with the best fit (*Figure 3A*), suggesting that higher DLPFC activation in association with longer time for target switching during the stimulus stream and diminished target identification accuracy. Table S1 shows the statistics of all other models.

Based on the model DLPFC β → $RT_{2-0}$ → $CSI_{2-0}$, we performed path analyses to examine the inter-relationship between PC1, DLPFC β, $RT_{2-0}$ and $CSI_{2-0}$. The results of path analyses showed the model PC1 → DLPFC β → $RT_{2-0}$ → $CSI_{2-0}$ with the best fit [root mean square estimation of approximation (RMSEA) =0.000; 90% confidence interval (CI): 0.000–0.051], $\chi^2$/df =0.855, standardized root mean square residual (SRMR) =0.014, and comparative fit index (CFI) =1.000; *Figure 3B*). That is, greater severity of alcohol use led to higher DPFC activation for needed stimuli switching and impairment in accuracy. Table S2 shows the statistics of all other models.

### *Sex difference of regional activations to 2- vs. 0-back in correlation with PC1 and PSQI*

Whole-brain linear regression of the contrast "2- minus

 

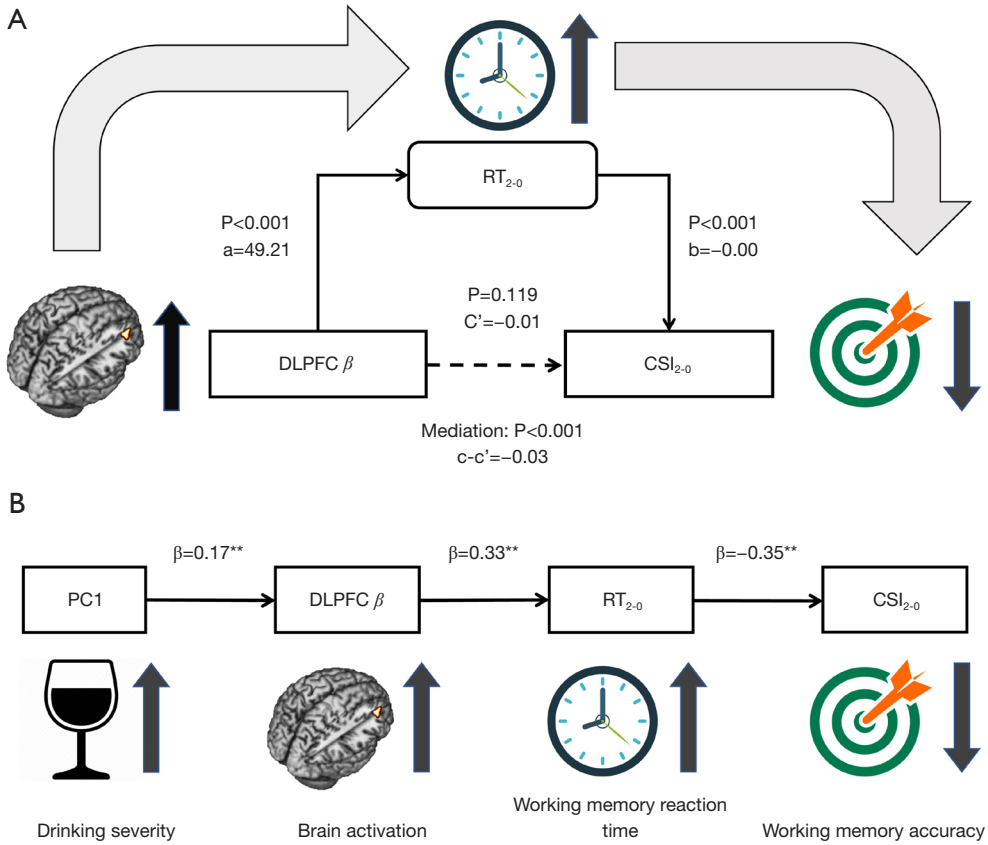


**Figure 3** Mediation and path analyses. (A) Mediation model to show the inter-relationship of DLPFC $\beta$, $RT_{2\text{-}0}$ and $CSI_{2\text{-}0}$. $RT_{2\text{-}0}$ completely mediated the relationship between DLPFC $\beta$ and $CSI_{2\text{-}0}$ in the N-back task. (B) Path model to show the inter-relationship of drinking severity PC1, DLPFC $\beta$, $RT_{2\text{-}0}$ and $CSI_{2\text{-}0}$. Higher alcohol drinking severity led to decreases in accuracy. **, P<0.001. $RT_{2\text{-}0}$, the difference in RT of correct trials between 2- and 0-back; DLPFC $\beta$, $\beta$ estimates of dorsolateral prefrontal cortex; $CSI_{2\text{-}0}$, difference in CSI between 2- and 0-back; PC1, the first principal component from a principal component analysis of all drinking-related measures.

0-back" against PC1 score for men alone did not reveal any clusters at voxel P<0.001, uncorrected in combination with cluster P<0.05, FWE-corrected. In women, a cluster in DLPFC (DLPFC_W, x, y, z =42, 32, 20; $T$=4.18, 496 $mm^3$; *Figure 4A*) shows a significant positive correlation with the PC1 with age and years of education as covariates. Please note that this cluster DLPFC_W was adjacent to the cluster DLPFC (x, y, z =34, 36, 22) identified from the entire sample. The β estimate of the DLPFC_W (DLPFC_W β) was significantly correlated with PC1 score ($r$=0.20, P<0.001), as expected, $RT_{2\text{-}0}$ ($r$=0.21, P<0.001), and $CSI_{2\text{-}0}$ ($r$=−0.17, P<0.001) with same covariates in women. The β estimate of the DLPFC_W (DLPFC_W β) was not significantly correlated with PC1 score ($r$=−0.00, P=0.924) but significantly with $RT_{2\text{-}0}$ ($r$=0.17, P<0.001) and $CSI_{2\text{-}0}$ ($r$=−0.12, P=0.009) with same covariates in men. Slope test confirmed sex differences in the slope of regression DLPFC_W β *vs.* PC1 score ($Z$=−3.19, P=0.001; *Figure 4B*), but not in the slope of regression DLPFC_W β *vs.* $RT_{2\text{-}0}$ ($Z$=−0.67, P=0.503) or DLPFC_W β *vs.* $CSI_{2\text{-}0}$ ($Z$=0.72, P=0.472).

Whole-brain linear regression of the contrast "2- minus 0-back" against PSQI score for men alone did not reveal any clusters at same threshold. In women, a cluster in the superior colliculus (SC_W, x, y, z =4, −34, −2; $T$ =−4.19, 1,200 $mm^3$; *Figure 4C*) showed a significant negative correlation with the PSQI score with same covariates. The β estimate of the SC_W (SC_W β) was significantly correlated with PSQI score ($r$=−0.23, P<0.001), but not correlated with $RT_{2\text{-}0}$ ($r$=0.04, P=0.346) or $CSI_{2\text{-}0}$ ($r$=−0.01, P=0.834) with same covariates. Slope test confirmed the sex differences in the slope of regression SC_W β *vs.* PSQI

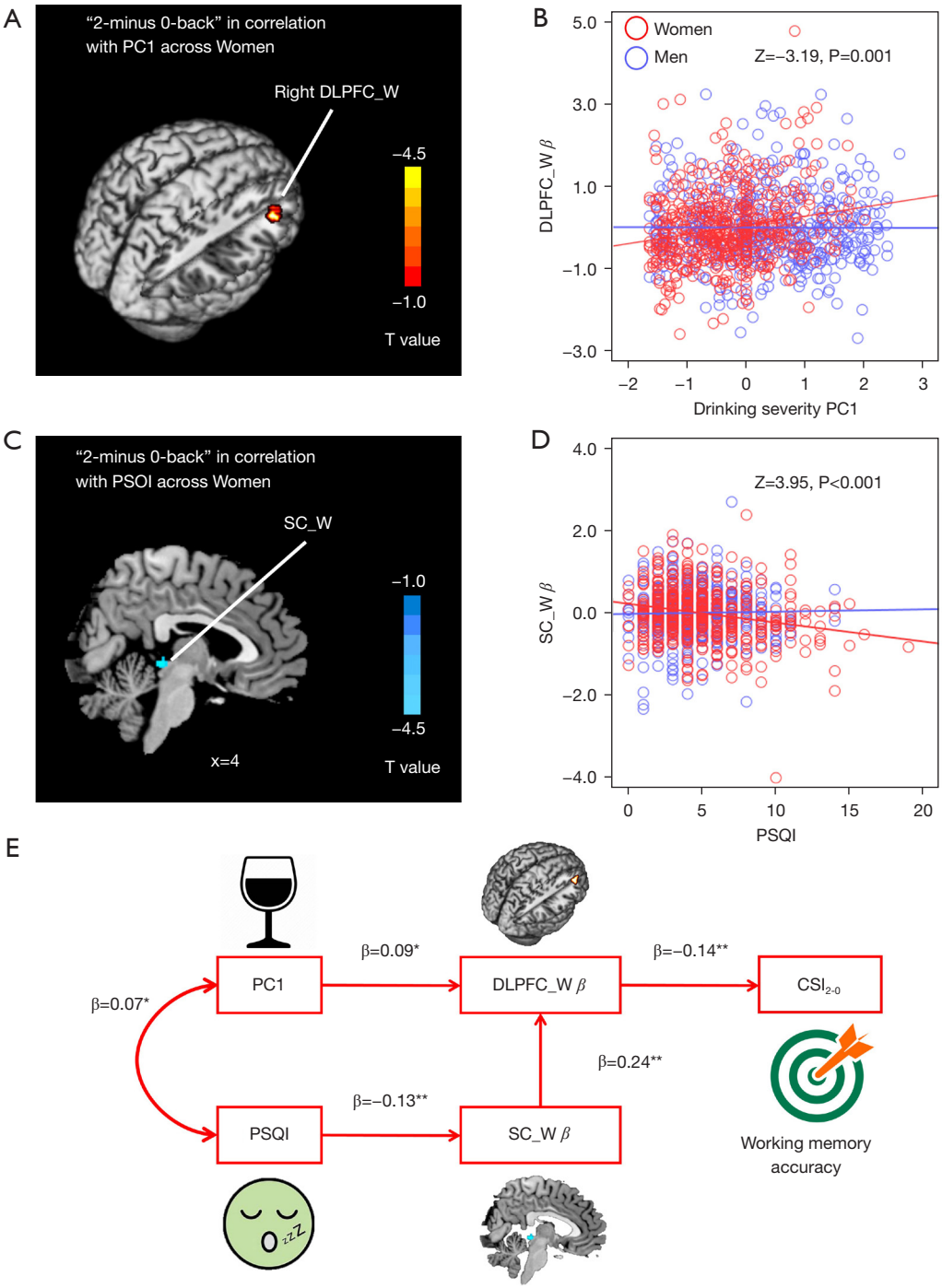


**Figure 4** Regional activations to 2- *vs.* 0-back in correlation with drinking severity and sleep deficiency. (A) In women only, DLPFC_W showed positive correlation with drinking severity PC1. (B) Scatterplot of DLPFC_W *c vs.* drinking severity PC1. (C) In women only, the SC_W showed activity in negative correlation with PSQI score. (D) Scatterplot of the SC_W *β vs.* PSQI. (E) Path model to show the inter-relationship of drinking PC1, DLPFC_W *β*, PSQI, SC_W *β* and $CSI_{2\text{-}0}$ in women. Note that the scatter plots show the residuals, after age and years of education were accounted for. *, P<0.05; **, P<0.001. PC1, the first principal component from a principal component analysis of all drinking-related measures; DLPFC, dorsolateral prefrontal cortex; DLPFC_W, a cluster located in dorsolateral prefrontal cortex and identified across women; DLPFC_W *β*, *β* estimate of DLPFC_W; PSQI, Pittsburgh Sleep Quality Index; SC_W, a cluster located in superior colliculus and identified across women; SC_W *β*, *β* estimate of SC_W; $CSI_{2\text{-}0}$, difference in critical success index between 2- and 0-back.

 

score ($Z$=3.95, P<0.001; *Figure 4D*).

We performed path analyses to examine the inter-relationship between PC1, PSQI, DLPFC_W β, SC_W β, and behavioral measures in women. *Figure 4E* shows the best fit model (RMSEA =0.000; 90% CI: 0.000–0.035), $\chi^2$/df =0.657, SRMR =0.015, and CFI =1.000). Figure S1 and Table S3 show the statistics of all other models.

## Discussion

In the current sample of neurotypical young adults, neither alcohol use severity nor sleep deficiency appeared to impact working memory. This "negative" finding may reflect the non-clinical sample of the HCP. However, drinking severity was associated with higher activation of the DLPFC during 2- *vs.* 0-back memory across men and women and in women alone, whereas sleep deficiency was associated with lower activation of the SC in women. With mediation and path analyses, we found the model PC1 → DLPFC β → $RT_{2\text{-}0}$ → $CSI_{2\text{-}0}$ with the best fit to highlight the inter-relationship amongst drinking severity, regional activities and performance during 2-back memory. In women alone, a model inter-relating PSQI and PC1 with each influenced SC and DLPFC activity, respectively, and SC activity influenced DLPFC activity and then $CSI_{2\text{-}0}$ showed the best fit.

### *The effects of alcohol use severity on working memory and the neural correlates*

Drinking severity was associated with higher DLPFC activation during working memory across men and women. The DLPFC contributes broadly to executive functions, including working memory, goal-driven attention, task switching, planning, problem-solving, and novelty-seeking (57). In a spatial memory task that requires active monitoring and manipulation of spatial information, additional activation foci are observed in DLPFC (58).

Alcohol suppresses the activity of the DLPFC as demonstrated by transcranial magnetic stimulation and EEG (59). Chronic alcohol use leads to diminished gray matter volumes (GMVs) (60) and cerebral hypoperfusion, as demonstrated by MRI with arterial spin labeling (61). However, studies with blood oxygenation level dependent (BOLD) imaging appeared to demonstrate contrasting findings of DLPFC activity during working memory. For instance, in a verbal N-back memory task individuals with AUD relative to non-drinking controls showed less activation in bilateral frontal and precentral, left superior temporal, left superior parietal, and left cerebellar cortex in the contrast of 2- *vs.* 0-back (62). However, another study of spatial working memory demonstrated higher activation of bilateral frontal cortices and insula and right postcentral cortex in AUD as compared to control group (63). Heavy drinking adolescents *vs.* controls showed higher activation in response to working-memory loads in the dorsal attention networks, including the DLPFC (44). Consistent with the latter report, the current findings suggest higher DLPFC activation in link with drinking severity and this may reflect a compensatory process in a non-clinical sample.

### *The effects of sleep deficiency on working memory and the neural correlates*

Despite the lack of a behavioral effect of sleep deficiency on working memory, higher PSQI score was associated with lower activation of the SC in women. The SC is a functionally conserved area of the mammalian midbrain that supports sensory perception and integration, cognition, and action (64,65). Many studies implicate the SC in attention, decision-making and working memory (66,67). Animal studies have highlighted the roles of the SC in maintaining sleep-wake behavior and regulating rapid eye movement (REM) sleep (68).

Studies have examined the effects of SD on working memory and the neural correlation of the effects (69,70). For instance, SD reduces activity in the prefrontal cortex, anterior cingulate gyrus, thalamus, and cerebellum (71) and enhances the functional connectivity between default mode and dorsal attention networks in relation to a decline in working memory performance (31). EEG recordings too have highlighted the neural effects of SD (72,73). However, to our knowledge, the current findings are the first to highlight diminution of SC activity during working memory in association with sleep deficiency.

### *The inter-related effects of alcohol use severity and sleep deficiency on working memory*

We employed mediation and path analyses to characterize the inter-relationship between the regional activities, severity of alcohol use and sleep deficiency, and working memory metrics. The best model showed PC1 → DLPFC β → $RT_{2\text{-}0}$ → $CSI_{2\text{-}0}$ with the best fit in men and women combined. In women alone, we were able to locate the neural correlation of PSQI in the SC and characterize the path model inter-relating PC1, PSQI score, DLPFC and

 

SC β's, and $CSI_{2-0}$.

These findings add to the literature of path modeling of alcohol misuse and sleep deficiency. A previous study employed mediation analysis to highlight the impact of prenatal alcohol exposure on memory as mediated by volumetric reduction, particularly in the right hippocampus (74). Suzuki *et al.* showed that the impact of modifiable risk factors of dementia, including alcohol misuse, on spatial memory impairment was mediated by posterior cingulate cortex volume in structural equation modeling (75). Another work reported that the left thalamus-mPFC resting-state connectivity strength mediated the relationship between the alcohol use disorders identification test (AUDIT) score and PSQI score in individuals with alcohol dependence (20). More recent studies reported that the volume of bilateral insula, right inferior frontal cortex, occipito-parietal cortex and a cluster including the anterior thalamus and hypothalamus significantly mediated the relationships between the percentage of slow wave (N3) sleep and executive performance (22) and that the GM density and cortical thickness in N3-related regions mediated the effects of chronic alcohol use on the duration of N3 (76) in AUD patients. Other investigators showed that the functional connectivities between the caudal cingulate gyrus and postcentral gyrus mediated the relationship between sleep quality and working memory deficits (77).

Together, it appears that a number of neural metrics can be used to characterize the inter-relationship amongst alcohol misuse, sleep problems, and cognitive deficits.

### *Sex differences*

In our study, we confirmed the sex differences in the slope of regression DLPFC_W β *vs.* PC1 score and SC_W β *vs.* PSQI by using slope tests. These results of slope tests showed that the inter-related effects of alcohol misuse and sleep deficiency on the neural processes of working memory were specific to women.

As compared to men, women are more susceptible to cognitive consequences of excessive alcohol consumption (78). An earlier study examined whether individual variation in working memory and biological sex modulates stress-induced alcohol craving. The results showed lower craving in women than in men but working memory function served to buffer against stress-induced craving in men but not in women (43). Although that is not directly related to the current findings, these results suggest sex differences in the roles of working memory and perhaps more broadly in executive functioning in manifesting a critical psychological process leading to alcohol misuse. Another study found that a greater number of standard drinks predicted smaller amygdala volume in men but not in women with AUD. Further, more monthly standard drinks were associated with larger cerebellum GMV, and this association was more marked in women as compared to men (79). Another study reported that a greater number of monthly standard drinks were associated with lower GMV in the right precentral gyrus in women, whereas the opposite (though weaker) relationship was found in men, with AUD. These studies underscore the importance of examining both sex-shared and specific neurobiological mechanisms associated with AUD. Sex differences in alcohol-related cerebellar and reward and executive network impairments might underlie the different relationships between alcohol use and affective and cognitive processes between females and males (80).

AUD and insomnia are highly comorbid. A recent study examined sex differences and showed that poorer sleep quality, as reflected in higher PSQI scores, was associated with more severe problem drinking (i.e., higher AUDIT scores) in women but not in men (81). Here, we noted more significant correlation between PC1 and PSQI score in women *vs.* men, though slope test failed to show sex differences. Sleep deficiency alters learning and memory. For instance, an animal study examined the effects of SD for 72 hours on spatial learning and memory, anxiety-like behavior, corticosterone levels, and the body weight in male as well as in intact and ovariectomized (OVX) female rats. SD did not significantly affect spatial learning and memory in male rats, whereas it significantly impaired the performance of both intact and OVX female rats (82). Thus, whether the mechanisms support sex differences in the influences of sleep deficiency on behavior and cognition need to be further investigated (83).

### *Limitations of the study*

A few limitations need to be considered. First, although the HCP was a largely neurotypical sample, the participants were heterogeneous in clinical characteristics, some of which, including depression and anxiety, may be relevant in modeling alcohol misuse and sleep deficiency (84,85). We did not account for these clinical characteristics in the current findings. Second, sleep deficiency was quantified by PSQI but not objective measures. As women and men may show differences in the frequency and manner they report

 

sleep problems, objective (e.g., EEG) measures would better characterize the quality of sleep. Third, attention and working memory are highly related, and we found earlier that the PSQI score was negatively related with SC activation during a sustained visual attention task in the same cohort (51). These findings together suggest broader impacts of sleep deficiency on subcortical processes that warrant more investigations.

## Conclusions

Alcohol misuse involves higher prefrontal cortical activation in functional compensation and, in women only, sleep deficiency affects 2-back memory by depressing the activity of the SC. In women only, drinking severity and sleep deficiency show inter-related impacts on 2-back memory. The study suggests potential sex differences in the influence of drinking and sleep problems on working memory.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-156/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).



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