EXAMINING THE ASSOCIATION BETWEEN EXTREME DRINKING AND PREFRONTAL CORTEX FUNCTIONING IN YOUNG ADULTS

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EXTREME DRINKING AND PFC FUNCTIONING

The undersigned, appointed by the dean of the Graduate School, have examined the thesis entitled

EXAMINING THE ASSOCIATION BETWEEN EXTREME DRINKING AND PREFRONTAL CORTEX FUNCTIONING IN YOUNG ADULTS

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# EXTREME DRINKING AND PFC FUNCTIONING

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Abstract

The aim of this thesis is to examine whether a single extreme drinking episode in young adults is associated with harmful effects on prefrontal cortex (PFC) functioning as assessed with task-based functional magnetic resonance imaging (fMRI). Animal research has found that heavy alcohol exposure damages the PFC, especially during adolescence. Prior correlational research in humans has also consistently found that heavy drinking is associated with PFC functional and structural alterations. However, it remains unclear whether damage can occur in humans after a single heavy drinking event. The current study is a novel natural experiment examining PFC activation during performance of a working memory task in 39 participants before and after their 21st birthday celebration, a single event that often involves extreme alcohol consumption.

Participants completed a visuospatial 3-Back task that has been found to strongly activate the PFC. Information about alcohol consumption during the participants’ birthday celebrations was obtained through a semi-structured interview to calculate peak estimated blood-alcohol content (eBAC). The results of this study indicate that peak eBAC is associated with changes in PFC maintenance activation on the N-Back task, yet not with changes in behavioral performance scores. It is hoped that this research will help us better understand the harmful effects of alcohol on PFC functioning.

*Keywords*: prefrontal cortex, alcohol, working memory, fMRI, N-Back task
Examining the Association Between Extreme Drinking and Prefrontal Cortex Functioning in Young Adults

**Introduction**

It has been well established in the literature that chronic heavy drinking is associated with functional and structural brain alterations as well as cognitive deficits (Rosenbloom et al., 2003; Sullivan & Pfefferbaum, 2005; Woods et al., 2016). However, whether heavy drinking plays a direct causal role in acute brain alterations in humans is still uncertain. For instance, it is not known whether a single heavy drinking episode causes changes in the brain. Rates of heavy drinking are very high in adolescence and young adulthood (Chung et al., 2018; National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2021). Further, brain regions such as the prefrontal cortex (PFC) are still developing well into young adulthood (Fuster, 2002), suggesting that emerging adulthood might be a time of heightened vulnerability to the harmful effects of drinking. It has been argued that a major public health concern is examining the consequence of heavy drinking in emerging adulthood (Ray & Grodin, 2021; Wechsler & Nelson, 2008). The current study is a novel natural experiment examining the direct consequences of heavy drinking in young adulthood on PFC functioning.

The PFC is a large brain region that is critically involved in complex, controlled aspects of cognition and behavior (Miller & Cohen, 2001). For example, the dorsolateral PFC is important for complex working memory and executive function (Crone & Steinbeis, 2017), and problems in dorsolateral PFC functioning may be related to impaired cognitive functioning, problems with daily life adjustment, and many neuropsychiatric disorders (Guo et al., 2019; Kerns et al., 2008; Roberts, 2020). The PFC is a brain region that matures relatively late in life, with pruning of synapses continuing well into adulthood (Selemon, 2013). Another important
feature about the human PFC is that there is a massive expansion of the PFC in humans relative to rodents, and even relative to other primates (Myers-Schulz & Koenigs, 2012). Further, there is uncertain (and perhaps to some extent non-comparable) homology, or similarity due to shared ancestry, between parts of the rodent PFC and the human PFC (Myers-Schulz & Koenigs, 2012; Roberts, 2020). Therefore, it is not possible to strongly infer the effects of alcohol on the PFC in humans based on previous rodent research.

PFC structure and function has been consistently associated with alcohol exposure (Abernathy et al., 2010; Hiller-Sturmhöfel & Spear, 2018; Zahr & Pfefferbaum, 2017). For instance, animal studies frequently show neural changes in the PFC after alcohol exposure. Human cross-sectional research also shows correlations between alcohol use and structural PFC imaging measures (Squeglia et al., 2015; Sullivan & Pfefferbaum, 2005). For instance, structural imaging studies have reported that alcohol use in adolescence and emerging adulthood is associated with decreased volume and cortical thinning in frontal regions (Squeglia et al., 2015). Longitudinal studies in emerging adults also have found associations between alcohol initiation and use with increased PFC thinning (Meda et al., 2017; Pfefferbaum et al., 2018; Squeglia et al., 2015).

In human functional magnetic resonance imaging (fMRI) research, cross-sectional correlational studies have found that alcohol use disorder (AUD) is associated with increased PFC activation (Sullivan & Pfefferbaum, 2005). This increase in PFC activation has been interpreted as decreased neural efficiency, as people might need to work harder to meet task demands (Sullivan & Pfefferbaum, 2005). This pattern of putative decreased neural efficiency in AUD is similar to results in other populations (e.g., in older adults) where PFC activation in some instances has been found to be increased (Grady, 2008; Yaple et al., 2019).
In contrast to cross-sectional fMRI AUD studies, one human longitudinal study reported a different although possibly compatible pattern of results. Specifically, in a human longitudinal study with adolescents, participants who later initiated heavy drinking had lower than normal baseline levels of prefrontal activation both on a visual working memory task and on a prepotent inhibition task. However, after drinking, now similar to results in AUD, these adolescents exhibited increased prefrontal activation (Courtney et al., 2019; Squeglia et al., 2012; Wetherill et al., 2013), again suggesting that alcohol use affected prefrontal neural efficiency. In addition, initiating heavy drinking did not affect behavioral performance, consistent with the idea that alcohol use caused people to increase activation to be able to meet task demands.

As previously mentioned, the PFC does not fully mature until well into young adulthood. Therefore, for adolescents and young adults, there may be a compounding negative effect of extreme alcohol exposure on brain development as well as numerous adverse psychosocial outcomes. About 30-35% of emerging adults (ages 18-25; Substance Abuse and Mental Health Services Administration [SAMHSA], 2021) report binge drinking in the past month, indicating that alcohol use could negatively impact the brains and lives of many emerging adults. Prior animal research has shown that adolescent rats are more sensitive than adult rats to the effects of extreme alcohol exposure, and one region where damage is particularly pronounced is in the PFC (Crews & Nixon, 2009; Crews et al., 2015). Further, there is animal evidence that harmful effects of alcohol on memory and learning are larger during development than in adulthood (Hiller-Sturmhöfel & Swartzwelder, 2005). For instance, in one preclinical animal study, researchers found that extreme alcohol consumption (15% alcohol solution provided every other day for 15 sessions) in adolescent mice was associated with a reduction in working memory performance (Salling et al., 2018).
Although PFC structure and function is associated with alcohol exposure, again it is still uncertain whether alcohol directly causes changes in the human brain. For instance, striking species differences do not allow for strong inferences from experimental animal research to human research. At the same time, previous human research has been correlational. Even in human longitudinal research, associations between alcohol use and PFC changes do not unambiguously prove causation. For instance, it is possible that people who differ in their propensity to drink might have differential brain maturation over time. Therefore, longitudinal changes in the brain between those who drink more versus those who drink less might occur even in the absence of drinking.

Given the limitations of previous research on whether and how alcohol affects the brains of emerging adults, there is a clear need for additional converging evidence regarding the harmful effects of alcohol on the brain. The current study employs a novel research strategy: a short-term longitudinal study examining the discrete effects of a single heavy drinking episode in emerging adulthood. The current research strategy starts by identifying a discrete episode when emerging adults are most likely to drink heavily and then examines neural measures immediately before and after the drinking event. If a single extreme drinking event affects the brain, then the amount that people drink during this one drinking event should be correlated with pre- versus post-brain imaging changes.

Potentially the one time in people’s lives when they are most likely to drink an extreme amount is on their 21st birthday. Previous research has found that many college students engage in extreme drinking on their 21st birthday (e.g., attempting to drink 21 alcoholic drinks on their 21st birthday; Rutledge et al., 2008). Hence, if a single heavy drinking episode has harmful
effects on PFC functioning, then extreme drinking on the 21st birthday could be associated with changes in PFC functioning and structure.

If a single heavy drinking episode is indeed associated with changes in PFC functioning, then it is expected that there would be changes in PFC activation during a task that strongly activates the PFC. In functional imaging studies, the PFC has been identified to be among the relevant areas activated during working memory tasks (Cohen et al., 1997; Funahashi, 2017; Smith & Jonides, 1997). Working memory refers to the online maintenance of a limited amount of information in a temporarily heightened state of availability for use in ongoing processing (Cowan, 1988). The PFC is activated during working memory tasks involving both the short-term storage of information (maintaining items in working memory) and in the processing of this information (working with these items within working memory; Cohen et al., 1997). The PFC has long been thought to play an important role in working memory, in part due to its ability to exhibit sustained neural activation for task-critical information (Miller & Cohen, 2001; Nee & D’Esposito, 2018). In accordance with this, human neuroimaging has consistently found that working memory tasks that involve the online maintenance and processing of information strongly activate the lateral PFC, especially the middle frontal gyrus (Nee et al., 2013). In addition, these working memory tasks also strongly activate other regions that are functionally connected with the middle frontal gyrus (i.e., the frontoparietal network; Cao et al., 2021; Darki & Klingberg, 2015).

Consistent with human longitudinal research findings that alcohol initiation and use is associated with PFC functional activation, the current study also examines whether 21st birthday drinking is associated with alterations in PFC functional activation. One working memory task that has consistently been found to strongly activate the PFC is the N-Back task (Owen et al.,
On this task, people must constantly maintain and periodically update information in working memory (Kirchner, 1958). Performance on this task is also strongly correlated with other measures of complex cognition, including measures of fluid intelligence (Shelton et al., 2009; Waiter et al., 2009). In an overview of the literature pertaining to the effects of alcohol on neural correlates of cognitive and emotional functioning during adolescence, heavy alcohol use has been associated with altered neural correlates of visual working memory in various cross-sectional studies (Courtney et al., 2019). Hence, if extreme alcohol exposure has harmful effects on PFC functioning, then it seems likely that extreme alcohol exposure could be associated with changes in PFC activation on a visuospatial version of N-Back task.

The current study used a 3-Back version of the task that strongly challenges working memory ability. In addition, given prior association of alcohol use with impaired spatial working memory (Courtney et al., 2019), we used a visuospatial version of the N-Back task (which requires participants to respond to the location of a visual stimulus). Further, to reliably assess PFC activation, participants completed 200 N-Back trials at each scanning session. In contrast, other prominent longitudinal studies (e.g., the Human Connectome Project) have been criticized for using task lengths too short to provide a reliable measure of functional activation (Turner et al., 2018). Our task length is sufficient to reliably estimate task activation (Nee, 2019).

Numerous prior research investigations have been conducted on the negative effects of extreme alcohol consumption on the brain. Although many have examined the effects of long-term alcohol exposure, to the best of my knowledge, there have been no investigations of the effects of a single heavy drinking episode on cognitive functioning in young adults. In the current study, I examine whether heavy 21st birthday drinking is associated with functional
activation changes in the PFC during performance of the N-Back task. Participants were scanned initially (Time 1) about 10-12 days before their 21st birthday and then again about 3-4 days after their 21st birthday (Time 2). At both scanning sessions, participants completed a 3-Back spatial working memory task, with approximately 30 minutes of task-based fMRI collected at each session. I examined whether changes in PFC activation after participants’ 21st birthday (i.e., from Time 1 to Time 2) are associated with the amount of alcohol consumed on their 21st birthday. I hypothesized that heavier 21st birthday drinking would be associated with a greater change in functional activation from Time 1 to Time 2.

Methods

Participants

This study enrolled volunteer participants from the Columbia, Missouri region. Analyses included data from thirty-nine participants who had usable N-Back data at the two time points (56.4% female, 92.3% Caucasian/White; Table 1). Recruitment primarily targeted university undergraduate juniors identified by publicly available information from the university registrar. However, student-status was not a requirement for participation, and there is a possibility that some non-students were recruited through word of mouth. All participants experienced a 21st birthday during the study period. Participants were excluded if they were unable or unwilling to be scanned due to MRI contraindications, reported having had a head injury with loss of consciousness for over two minutes, or were taking any prescribed medication (except for birth control). Participants were instructed not to smoke for at least 30 minutes before any scanning session, not to take any illicit drugs or use alcohol 24 hours before any scanning session, and not to take any ibuprofen or antihistamines 24 hours before any scanning session. Participants were paid $20 for their first scan and $50 for their second scan.
Ethical Considerations

Despite measuring the effects of extreme drinking, it is possible that individuals who participated in this study drank more or less than they would have if they were not enrolled in the study (although this could not be explicitly measured). All participants were told that the purpose of the study was to examine harmful effects of extreme drinking and were provided information on the dangers of extreme drinking. The study was reviewed and approved by the University of Missouri Institutional Review Board. All participants provided informed consent prior to participating in the study.

Procedures

This study aims to assess whether a single extreme drinking episode in young adults is associated with harmful effects on PFC functioning. Therefore, participants were recruited who were about to experience a 21st birthday since this is likely a single event when people are most likely to heavy drink (Geisner et al., 2017; Rutledge et al., 2008). PFC activation was assessed prior to and post-birthday celebration. Participants completed the N-Back task at two time points: approximately two weeks prior to their 21st birthday celebration (Time 1) and three to four days after their 21st birthday celebration (Time 2). On average, the pre-birthday scan occurred eleven days prior to participants’ 21st birthday. The post-birthday scan occurred three to four days after participants’ 21st birthday celebration in order to minimize the acute aftereffects of extreme alcohol consumption (e.g., hangover effects). Peak estimated blood-alcohol content during the birthday celebration was calculated for each participant.

Measures

N-Back Task

All participants completed a 3-Back version of the spatial N-Back task while in the fMRI
scanner, both before and after their 21st birthday. In this task, participants were shown a series of stimuli one after the other (in this case, circles positioned in one of eight locations forming the outer boxes of a 3 x 3 array). The stimulus was presented for 1.5s followed by an interstimulus interval varying between 1.5s and 12s to better assess fMRI signal. For every circle, participants indicated whether or not the circle was in the same location as the one shown three presentations previously. Not only did participants need to maintain several items in working memory, but they also needed to continuously update and re-order the items with each new presentation. The updating portion of the task corresponds to when the participant received the stimulus and responded to its location (1.5s period). The maintenance portion of the task corresponds to when the participant held the stimulus’ location in working memory for a varying amount of time (between 1.5s and 12s). To ensure that participants needed to specifically maintain prior locations and could not simply rely on a sense of familiarity to perform the task, the task included distraction trials. On these trials, the 3-Back circle’s location was in a 2-Back or 4-Back position. On 80 trials (40% of trials), the current circle’s location was the same as the one presented 3-Back. On 60 trials (30% of trials), the current circle’s location was the same as the circle presented 2- or 4-Back. A total of 40 trials in 6-minute scans were completed five times (totaling 200 trials for each participant at each time point, and around 30 minutes of N-Back data per scanning session). To assess working memory behavioral task performance on the N-Back, corrected recognition scores were calculated by subtracting the false alarm (guessing) rate for non-targets (i.e., when current location is not the same as one 3-Back) from the hit rate for targets (i.e., when current location is the same as the one 3-Back). Hence, perfect performance would be 100% hit rate without any false alarms. In contrast, chance performance would be indicated by a hit rate that was equal to the false alarm rate. In analyzing behavioral performance
over time, we found evidence of practice effects such that people improved in the first 6-minute scan of session 1 relative to the rest of session 1 scanning (with no further improvements thereafter). To remove the potential effects of practice from PFC activation, I excluded the first 6-minute session 1 scan for each participant from analyses.

_Birthday Celebration Structured Interview-21_

The Birthday Celebration Structured Interview-21 (BCSI-21; Stappenbeck et al., 2007) was conducted approximately three to four days after the participant’s 21st birthday celebration. The structured interview provided a detailed overview of the birthday celebration, including the number of locations visited during the celebration and how much time was spent at each location. For each location, the interview also assessed the number of standard-sized alcoholic drinks consumed, pace of alcohol consumption, and mood and subjective intoxication ratings. The interview also assessed whether and when participants vomited, number of blackouts, and information about any concurrent cannabis use during the birthday celebration (i.e., yes/no whether participants used cannabis at any point during their celebration). The developers of this interview provided training to research staff before conducting the current study.

_Peak Estimated Blood-Alcohol Content_

Peak estimated blood-alcohol content (eBAC) was calculated for each drinking episode using the equation given by Matthews and Miller (1979). A new drinking episode was defined if six or more hours elapsed between drinks. Drinking information used to calculate eBAC was obtained from the BCSI-21. The number of drinks consumed, period of time over which they were consumed, sex of the participant, and body weight of the participant were used to calculate peak eBAC.
Imaging Acquisition and Analysis

Imaging took place at the Brain Imaging Center at the University of Missouri using a 3T Siemens Trio scanner using an 8-channel head coil. Functional scanning involved a T2-weighted EPI pulse sequence, TR = 1500 ms, TE = 35 ms, flip angle = 70°, field of view (FOV) = 24 cm. T1 and T2 structural images were also collected. T1 structural images were acquired using a high-resolution T1-weighted sagittal scan (MPRAGE) with the following parameters: TR = 1920 ms, TE = 2.92 ms, flip angle = 9°, FOV = 256 × 256, matrix size = 256 × 256, slice thickness = 1 mm. T2 structural images were acquired using a high-resolution T2-weighted sagittal scan with the following parameters: TR = 3200 ms, TE = 402 ms, FOV = 256 × 256, matrix size = 256 × 256, slice thickness = 1 mm.

Data were analyzed using the FMRIB Software Library (FSL; Smith et al., 2004). Analyses include separate regressors for maintenance (i.e., when participants are maintaining previous spatial locations in working memory) and for updating (i.e., when participants are presented with the next spatial location and they must make a response as well as update the contents of working memory to maintain just the last three presented spatial locations). Parameter estimates for these two regressors were extracted for each participant using a region of interest (ROI) approach. Given my a priori interest in the PFC, I used an ROI that is the intersection of the middle frontal gyrus (from the Harvard-Oxford cortical atlas in FSL; Desikan et al., 2006) and the frontoparietal cortical network (Yeo et al., 2011).

Hypotheses and Predicted Results

If a single extreme drinking episode in young adults damages working memory performance, then I expected that those with a higher peak eBAC would do worse on the N-Back task during the post-birthday scan (Time 2). If a single extreme drinking episode in young adults...
is associated with harmful effects on PFC functioning, I expected altered PFC activation on the
N-Back task between Time 1 and Time 2. Specifically, I expected that more extreme 21\textsuperscript{st}
birthday drinking (i.e., higher eBAC) would be associated with a greater change in functional
activation from Time 1 to Time 2.

**Results**

**Alcohol Use Descriptive Statistics**

Consistent with previous studies assessing 21\textsuperscript{st} birthday drinking (Rutledge et al., 2008),
participants in the current study drank to extreme levels during their celebrations; mean peak
eBAC for participants with usable N-Back data is 0.22 g/dl ($SD = 0.14$), a level commonly
associated with vomiting and blackouts. Thirty-six percent of participants attained dangerously
high peak eBACs of greater than 0.25 during their 21\textsuperscript{st} birthday celebration. Peak eBAC ranged
from 0 to 0.45 (an upper limit of 0.45 was set as a BAC greater than 0.45 is considered a lethal
dose; Figure 1).

**Correlation Between Time 1 Activation and eBAC**

A bivariate correlation was run to examine whether peak birthday eBAC is associated
with Time 1 (i.e., pre-birthday) N-Back PFC activation, for both the updating and maintenance
portions of the task. There is no significant correlation between Time 1 PFC activation during the
updating portion of the N-Back task and peak birthday eBAC, $r = -.28$, $p = .083$ (Figure 2A).
However, there is a statistically significant negative correlation between Time 1 PFC activation
during the maintenance portion of the N-Back task and peak birthday eBAC, $r = -.41$, $p = .010$
(Figure 2B). Lower PFC activation during the maintenance portion at the Time 1 pre-birthday
scan is associated with a higher peak eBAC during the birthday celebration. A bivariate
correlation was run to examine whether peak birthday eBAC is associated with Time 1 N-Back
behavioral score. There is no significant correlation between Time 1 task performance and peak birthday eBAC, \( r = -.20, p = .223 \).

**Change in Post-Birthday Activation**

A paired-samples t-test was run to examine within-participant change in PFC activation for both the updating and maintenance portions of the N-Back task from Time 1 to Time 2. There is a significant decrease in updating activation from Time 1 \((M = 61.02, SD = 25.17)\) to Time 2 \((M = 50.74, SD = 21.65)\), \( t(38) = 3.32, p = .002 \). There is also a significant decrease in maintenance activation from Time 1 \((M = 18.29, SD = 14.00)\) to Time 2 \((M = 10.21, SD = 10.93)\), \( t(38) = 3.96, p < .001 \). Hence, for both updating and for maintenance there is evidence for a decrease in PFC activation over time.

A methodological concern with fMRI is possibly low test-retest reliability that in the current context could limit correlations with alcohol consumption (Chen et al., 2021). To examine test-retest reliability, I first examined bivariate correlations to test whether Time 1 PFC activation is associated with Time 2 activation, for both the updating and maintenance portions of the task. There is a statistically significant positive correlation between Time 1 and Time 2 PFC activation during the updating portion of the N-Back task, \( r = .67, p < .001 \), and during the maintenance portion of the N-Back task, \( r = .50, p = .001 \). To more directly examine test-retest reliability, I next examined intraclass correlations (ICC, examining absolute agreement and using the average of the two measures) for updating and maintenance activation across sessions. For updating, the ICC is .76 and for maintenance the ICC is .58. This level of reliability would be considered in the “good” range (Fleiss, 1986), with this level of reliability being higher than the average reliability in previous imaging or behavioral task studies (Chen et al., 2021).
Correlation Between Change in Post-Birthday Activation and eBAC

There is no significant correlation between change in post-birthday activation (i.e., Time 1 activation minus Time 2 activation) during the updating portion of the N-Back task and peak birthday eBAC, $r = -.18$, $p = .282$ (Figure 3A). However, there is a statistically significant negative correlation between change in post-birthday activation during the maintenance portion of the N-Back task and peak birthday eBAC, $r = -.36$, $p = .026$ (Figure 3B). Participants with a higher peak eBAC show a smaller difference in PFC activation from Time 1 to Time 2 during the maintenance portion of the task, with if anything Time 2 activation being greater than Time 1 activation. In contrast, participants with a lower peak eBAC exhibit a larger decrease in activation from Time 1 to Time 2.

Correlation Between Concurrent Cannabis Use, eBAC, and Change in Post-Birthday Activation

A bivariate correlation was run to examine whether endorsement of cannabis use is associated with peak birthday eBAC. There is no significant correlation between cannabis use and eBAC, $r = .01$, $p = .951$. There is also no significant correlation between cannabis use and Time 1 and Time 2 difference scores during the updating portion of the N-Back task, $r = -.07$, $p = .690$, or maintenance portion of the task, $r = .04$, $p = .823$. A partial correlation was run between eBAC and difference scores for maintenance and updating with cannabis use set as a control variable. There is no significant correlation between Time 1 and Time 2 difference scores during the updating portion of the N-Back task and peak birthday eBAC, $r = -.21$, $p = .202$. Even after controlling for cannabis use, there is a statistically significant negative correlation between Time 1 and Time 2 difference scores during the maintenance portion of the N-Back task and peak birthday eBAC, $r = -.41$, $p = .012$. 
**N-Back Behavioral Data**

Contrary to my initial hypothesis, there is no difference between participants’ Time 1 behavioral score \((M = .75)\) and Time 2 behavioral score \((M = .75)\), \(t(36) = .003, p = .997\). That is, participants did not perform any better at Time 2 compared to Time 1. Participants who achieved a higher eBAC during their birthday celebration show relatively higher Time 2 PFC activation yet maintain a consistent level of performance on the task. Difference scores were calculated to examine the difference between Time 1 behavioral score and Time 2 behavioral score. There is no significant correlation between the difference between Time 1 and Time 2 behavioral scores and peak birthday eBAC, \(r = .05, p = .763\).

**Discussion**

The primary aim of this thesis was to examine whether a single extreme drinking episode in young adults, defined as the 21\(^{st}\) birthday celebration, is associated with acute harmful effects on PFC functioning as assessed with task-based fMRI. Results from the current study support the hypothesis that a single heavy drinking event does indeed affect PFC functioning. The amount of birthday drinking (i.e., peak eBAC achieved) is associated with changes in PFC maintenance activation on the N-Back task, yet not with changes in behavioral performance scores. Concordant with prior research (Sullivan & Pfefferbaum, 2005), the increase in PFC activation associated with higher eBAC might reflect decreased neural efficiency in extreme drinkers. From this perspective, these participants likely needed to work harder to meet task demands in order to maintain a constant level of performance on the N-Back task from pre- to post-birthday scans.

At the baseline scan (Time 1), participants who showed lower PFC activation during the maintenance portion of the N-Back task reached a higher peak eBAC during their birthday celebration. In other words, lower maintenance PFC activation is associated with higher future
drinking. This finding is generally similar to prior research investigating the influence of alcohol use on brain functioning in adolescents before and after initiating heavy drinking. For instance, Squeglia and colleagues (2012) examined longitudinal fMRI data from 12- to 16-year-olds before the onset of drinking and again approximately three years later. Adolescents who later initiated heavy drinking (drinking on average 39 drinks per month) were matched to continuous nondrinkers on baseline alcohol risk and developmental factors. The researchers found that those who later initiated heavy drinking showed less PFC activation at baseline than people who would remain continuous nondrinkers. After onset of heavy drinking, the heavy drinking participants now had increased PFC activation, suggesting that heavy alcohol use affected prefrontal neural efficiency. Also similar to the results of the current study, participants who later initiated heavy drinking did not show differences in behavioral task performance compared to continuous nondrinkers. This is consistent with the idea that less efficient information processing results in increased PFC activation, enabling participants to continue to meet task demands and maintain a consistent level of performance on the task.

Regarding changes in PFC activation after the 21st birthday, participants with a lower peak eBAC show a decrease in PFC maintenance activation post-birthday while participants with a higher peak eBAC show an increase in PFC maintenance activation. This differential change in PFC maintenance activation based on eBAC has more than one potential interpretation. One interpretation is that heavier birthday drinking decreased the neural efficiency of PFC functioning, and participants who drank more had to work harder to maintain the same level of performance on the N-back task (as demonstrated by the lack of correlation between Time 1 and Time 2 behavioral difference scores and peak birthday eBAC). If this interpretation is correct, then it might be expected that an increase in PFC activation after birthday drinking would also be
associated with structural brain changes post-birthday. However, a different interpretation is that participants who drank more on their birthday received less benefit from practicing the task during the initial pre-birthday scan compared to those who drank less. Receiving less benefit from practice at Time 1 resulted in less of a decrease in activation from Time 1 to Time 2.

An issue for future research would be to further disentangle these two interpretations. One way to examine this is to examine whether changes in PFC activation are associated either with pre-birthday (baseline) structural imaging measures or with post-birthday structural brain changes. Prior findings from this research team have characterized structural brain changes related to birthday drinking and did not find evidence of changes in volume or surface area in the PFC (Hua, Piasecki, et al., 2020; Hua, Sher, et al., 2020). However, future research could investigate whether there are changes in other structural indices yet to be examined (e.g., white matter connectivity) and whether these are associated with changes in PFC activation.

Despite Time 1 PFC maintenance activation showing a significant correlation with peak birthday eBAC, we did not see this same result for PFC activation during the updating portion of the task. The updating portion of the task corresponds to the 1.5s period of time when the visual stimulus is presented and participants respond to its location. One possible explanation for the lack of significant correlation with eBAC could be related to insufficient statistical power to detect changes in PFC updating activation compared to maintenance activation (with the maintenance portion of the task varying between 1.5s and 12s). However, it should be noted that if anything activation during updating had higher test-retest reliability than activation during maintenance, which might suggest more power updating analyses. Another possible explanation could be related to evidence that the neural efficiency phenomenon in the context of working memory has been shown to be moderated by the complexity of task demands. For example, prior
research has demonstrated participants with higher intelligence show less cortical activation while solving moderately difficult working memory tasks yet not for simple or highly demanding tasks (Nussbaumer et al., 2015). In the current study, participants overall showed much greater activation during the updating portion of the task compared to the maintenance portion of the task, suggesting that the highly demanding updating portion may have obscured any significant differences in PFC activation related to peak eBAC.

**Limitations of Current Research**

One important limitation of this study is the relatively small sample size of 39 participants. Any results in the current study should be replicated with a much larger sample size. Another important limitation of this study is using the BCSI-21 to collect information about birthday drinking to estimate peak BAC. Limitations of this approach include being unable to precisely measure alcohol content in mixed drinks as well as needing to rely on participants’ retrospective memories for events when they have been heavy drinking, whereas alcohol is known to affect recall. To address the limitation of using the BCSI-21 to collect information about birthday drinking, future research should use more direct measures of alcohol consumption (e.g., portable breathalyzers) to record BAC throughout the birthday celebration. Additionally, there was evidence that participants’ performance on the N-Back task improved after the initial 6-minute scan, which suggests that this practice time was necessary for participants to become familiar with the task. Future research using this task should allow participants sufficient time to practice before the initial scan. Finally, the generalizability of this research is limited by the lack of demographic diversity in the study population, which was comprised of primarily Caucasian undergraduate college students. Future research should aim to recruit more diverse participants,
including those with diverse ethno-racial identities, non-college participants, and those from both urban and rural areas.

Conclusion

The current research is a novel natural experiment that examines the direct consequences of heavy drinking in young adulthood on PFC functioning. The fMRI data collected from participants before and after their 21st birthday celebration provide additional converging evidence that a single extreme drinking episode is associated with PFC activation changes during a working memory task. The unique short-term longitudinal nature of this study design has allowed for the examination of the discrete effects of a single heavy drinking episode, which cannot be achieved in a lab setting due to ethical considerations. It is hoped that the results of this research may help increase the understanding of the acute negative effects of alcohol on PFC functioning during an especially vulnerable period of brain development.
Tables and Figures

Table 1

*Participant Demographics*

<table>
<thead>
<tr>
<th></th>
<th>Frequency (N = 39)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17</td>
<td>43.6%</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>56.4%</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>36</td>
<td>92.3%</td>
</tr>
</tbody>
</table>
Figure 1

*Peak Estimated Blood-Alcohol Content (eBAC) of Participants*

- Number of Participants (N = 39)
- eBAC (g/dl)
- 0 - 0.050, 0.051 - 0.100, 0.101 - 0.150, 0.151 - 0.200, 0.201 - 0.250, 0.251 - 0.300, 0.301 - 0.350, 0.351 - 0.400, 0.401 - 0.450+

- Bars represent the number of participants in each eBAC range.
Figure 2

Correlations Between Time 1 Prefrontal Cortex (PFC) Activation for (A) Updating and (B) Maintenance with Peak Estimated Blood-Alcohol Content (eBAC)

A. Updating

B. Maintenance
Figure 3

Correlations Between Change in Post-Birthday Prefrontal Cortex (PFC) Activation (Time 1 Activation minus Time 2 Activation) for (A) Updating and (B) Maintenance with Peak Estimated Blood-Alcohol Content (eBAC)

A. Updating

B. Maintenance
References


