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Prospective Study Examining the Effects of Extreme Drinking on Brain Structure in Emerging Adults

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Abstract

Background: Emerging adulthood is a critical neurodevelopment period in which extreme drinking has a potentially pronounced neurotoxic effect. Therefore, extreme drinking, even a single episode, could be particularly harmful to the developing brain's structure. Relatedly, heavy alcohol use in emerging adults has been associated with structural brain damage, especially in the corpus callosum. However, it is unclear whether and how much a single extreme drinking episode would affect brain morphometry.

Methods: For the first time in the literature, the current study prospectively examined the impact of an extreme drinking episode (i.e., 21st birthday celebration) on the brain morphometry of emerging adults immediately following their birthday celebration ($n = 50$) and approximately five weeks post-birthday celebration ($n = 29$).

Results: We found evidence that a single extreme drinking episode was associated with structural changes immediately post-birthday celebration. Specifically, higher 21st birthday estimated blood-alcohol concentration (eBAC) was associated with decreased volume of the posterior and central corpus callosum immediately post-birthday celebration. This extreme drinking episode was not associated with further structural changes, or recovery, five weeks post-21st birthday celebration.

Conclusions: Overall, results suggest that a single episode of heavy drinking in emerging adulthood may be associated with immediate structural changes of the corpus callosum. Thus, emerging adulthood, which is characterized by high rates of extreme drinking, could be a critical period for targeted prevention and intervention.

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Authors Contribution

JGK, KJS, and TMP were responsible for the study concept and design. JGK contributed to the acquisition of data. CLB, CJT, YEM, and AMM were responsible for scoring the alcohol use variables. JPYH processed the structural neuroimaging data and performed the analyses. JPYH and JGK drafted the manuscript. All authors critically reviewed the manuscript and approved the final version for publication.

Disclosure of Conflicts of Interest

The authors report no conflicts of interest.

Data Accessibility

The data generated and analyzed during the current study are available in the Open Science Framework repository, osf.io/t2xwd.

Keywords

brain morphometry; corpus callosum; emerging adulthood; extreme drinking; longitudinal

Introduction

Emerging adulthood has been associated with the highest lifetime rates of extreme drinking (Chen et al., 2004). Additionally, emerging adulthood is a critical neurodevelopmental period during which the brain may be especially sensitive to the neurotoxic effects of extreme drinking (Jacobus and Tapert, 2013). Therefore, the effects of extreme drinking, even a single extreme drinking episode, may be especially harmful to the structure of the developing brain (Boness et al., 2019). Previous research has established that chronic alcohol use and dependence in emerging adulthood are associated with structural brain changes (Cservenka and Brumback, 2017; Jacobus and Tapert, 2013; Welch et al., 2013). However, to our knowledge, no previous study has prospectively examined the immediate changes that a single extreme drinking episode has on the morphometry of the brain (i.e., volume and gyrification) of emerging adults. Thus, for the first time, the current study examined the brain morphometry of emerging adults before and after an extreme drinking episode.

Damage associated with extreme drinking has been consistently found in the corpus callosum, hippocampal/parahippocampal regions, and the orbitofrontal cortex in both animal and human studies (Lawrimore et al., 2019; Pfefferbaum et al., 2008; Vargas et al., 2014). Specifically, in an animal model of extreme alcohol use, Pfefferbaum et al. (2008) exposed rats to vaporized ethanol (~400 mg%) for eight weeks in order to induce high levels of alcohol exposure, finding extreme alcohol exposure to be associated with decreased corpus callosum volume. Additionally, another animal model of binge drinking in young rats found binge drinking to be associated with decreased volume and damage to the myelin of the corpus callosum (Vargas et al., 2014). Consistent with these pre-clinical findings, alcohol-related corpus callosum atrophy has also been found in humans. Decreased volume of the corpus callosum has been found in individuals with alcohol use disorders (de Souza et al., 2019; Estruch et al., 1997; Harper, 2009; Pfefferbaum et al., 1996; Schulte et al., 2004). Additionally, both cross-sectional and longitudinal studies of heavy drinking in emerging adulthood have been associated with structural brain abnormalities (Cservenka and Brumback, 2017; Jones et al., 2018). Specifically, using diffusion tensor imaging (DTI), we found evidence suggesting that an episode of extreme drinking in emerging adults was associated with changes in multiple DTI measures (i.e., fractional anisotropy, radial diffusivity, and mean diffusivity) in the corpus callosum (Boness et al., 2019). Although DTI is often thought of as a measure of white matter integrity, it has been found to be weakly to moderately correlated with volume, with correlations across different subcortical regions going in both directions (Fjell et al., 2008). For example, a subcortical region could have increased volume but also more complex crossing of white matter fibers leading to decreased DTI values. Additionally, DTI measures are more sensitive than structural MRI to other properties, including variations in brain water content (Fjell et al., 2008). As such, DTI measures and volume have been posited to be sensitive to different neurobiological

processes (Fjell et al., 2008; Westlye et al., 2009), and it is important to examine if extreme drinking is also associated with changes in the corpus callosum. Critically, structural damage of the corpus callosum due to alcohol use has been associated with multiple clinical and functional impairments, including increased rates of drinking relapse (Vargas et al., 2014), decreased interhemispheric transfer of information (Schulte et al., 2004, 2005), and decreased cognitive performance (Estruch et al., 1997; Chanraud et al., 2007; Harper, 2009).

In addition to the corpus callosum, studies where rats were exposed to discrete episodes of high levels of ethanol (250 mg%–540 mg%) found atrophy of the hippocampal/parahippocampal formation and orbitofrontal cortex (Lawrimore et al., 2019). Alcohol-use associated damage to hippocampal/parahippocampal regions and the orbitofrontal cortex have also been associated with impairments in working memory, reward processing, and impulse control (Meda et al., 2018; Moorman, 2018).

Although these studies provide evidence that heavy drinking is associated with structural damage, it is unclear how a discrete episode of extreme drinking affects the brain morphometry in emerging adults. As mentioned previously, structural damage has been found in individuals with chronic heavy alcohol use (de Souza et al., 2019; Estruch et al., 1997; Harper, 2009; Pfefferbaum et al., 1996; Schulte et al., 2004); however, even habitual light drinkers may experience an occasional heavy drinking episode, and it is not known whether these individuals would also show structural brain damage. Thus, it is critical to disentangle whether this neurotoxicity is due to a chronic pattern of regular and heavy use or stems from a discrete episode of heavy drinking. To more directly examine the immediate effects of alcohol use, in the current study, we examined structural morphometry of participants before and after an extreme drinking episode.

A key lifetime event in which to naturalistically and prospectively examine the effects of a discrete extreme drinking episode is the 21st birthday celebration. In the United States, twenty-one is the minimum legal drinking age, and attainment of legal drinking status is the reason for the emphasis on alcohol use during the 21st birthday celebration. As such, the 21st birthday celebration is often characterized by extreme alcohol consumption, with one common drinking tradition, “21 for 21,” involving the consumption of 21 alcoholic drinks during the 21st birthday celebration (Brister et al., 2011; Neighbors et al., 2005; Rutledge et al., 2008). Previous research found that many celebrants reached dangerous peak estimated blood alcohol concentrations (eBACs) greater than .25 (Neighbors et al., 2005; Rutledge et al., 2008). Furthermore, the 21st birthday celebration is one such event in which a habitual light drinker might drink much more heavily. Consistent with this, a large proportion of celebrants endorsed consuming more alcoholic drinks during their 21st birthday celebration than at any previous point in their life (Brister et al., 2011; Rutledge et al., 2008). Hence, the 21st birthday celebration provides researchers with a rare opportunity to prospectively examine the effects of extreme drinking.

In the current study, we used a quasi-experimental design to examine the impact of an extreme drinking episode (i.e., 21st birthday celebration) on brain morphometry in emerging adulthood using multiple structural morphometric markers (volume and gyrification). To our knowledge, this is the first study to prospectively examine the impact of a discrete extreme

drinking episode on brain morphometry. By examining brain morphometry in participants less than two weeks before and again a few days after their 21st birthday celebration, we were able to more directly examine the immediate effects of extreme drinking while accounting for the age-related effects of morphometry. Based on previous animal (Crews and Nixon, 2009; Lawrimore et al., 2019; Pfefferbaum et al., 2008; Qin and Crews, 2012; Sripathirathan et al., 2009) and human research (de Souza et al., 2019; Meda et al., 2017, 2018; Moorman, 2018; Pfefferbaum et al., 1996), we hypothesized that extreme drinking would be associated with structural brain changes. In particular, we hypothesized that these changes would be most pronounced in the corpus callosum, which is the largest white matter tract that connects and facilitates communication between brain hemispheres (Fitsiori et al., 2011). We also hypothesized that these changes might be present in hippocampal/parahippocampal regions and in the orbitofrontal cortex. To examine the stability of any post-21st birthday structural changes, we also examined the impact of 21st birthday drinking on brain morphometry approximately five weeks post-21st birthday celebration.

Materials and Methods

Participants

Participants were recruited for a three-session study on extreme drinking in emerging adults. Participants were University of Missouri undergraduate students, who were about to celebrate their 21st birthday and who completed both a pre- and post-21st birthday session. Note that we report on DTI changes in the corpus callosum from this study in a separate publication (Boness et al., 2019). Of the 78 participants who completed the pre-21st birthday session, fifty-two participants returned for their post-21st birthday session. Two of these participants were missing peak eBAC data. Further, due to imaging software processing errors in calculating gyrification, one participant did not have useable gyrification data. This resulted in a final group of 50 participants for volume and 49 participants for gyrification. Participants ($n = 50$) were 52% female, 90% White/Caucasian 2% Black/African American, 2% other race/ethnicity, and 6% missing race/ethnicity information. Additionally, of these participants, twenty-nine participants returned for a final session five weeks after (see Supplemental Table 1 for demographics and alcohol descriptives of participants at each of the three scan sessions). Participants were not taking prescription medications other than birth control. Although recruitment for the current study was targeted to undergraduate students, there were some participants who did not identify as students. Thus, a few non-student participants may have potentially been recruited into the study through word of mouth.

Study Timeline

To examine brain morphometry, participants underwent a MRI scan at each of the three sessions in the study (see Fig. 1). The pre-21st birthday session occurred, on average, eleven days prior to participants' 21st birthday. The post-birthday scan occurred, on average, three to four days after the 21st birthday celebration to minimize acute after-effects of alcohol (i.e., within 24 hours; note that two participants completed their scans more than six days after, and results were very similar when these participants were removed from analyses) and hangover-related symptoms. During the post-21st birthday session, participants completed a

semi-structured interview (full details below) regarding their 21st birthday celebration alcohol consumption. As we were interested in examining stable neural changes rather than acute after-effects of drinking, most participants were scanned on a Monday or Tuesday to increase participants' compliance with the requirement for night-before drinking abstinence. Though the focus of the current manuscript is on structural morphometric changes from pre- to post-21st birthday, we also included analyses on the final scan session that occurred five weeks post-birthday celebration scan to examine the stability of any post-21st birthday structural changes (data for this study: Hua et al., 2019). In addition to the MRI scans, participants also completed two behavioral tasks (performance on these tasks was not associated with structural changes, and results will be presented in a separate paper).

Study procedures were approved by the University of Missouri's Institutional Review Board and were in accordance with the latest version of the Declaration of Helsinki. Additionally, all participants provided informed consent.

Estimated Blood-Alcohol Concentration (eBAC)

Participants completed the Birthday Celebration Structured Interview-21 (BCSI-21), a semi-structured interview that assesses 21st birthday celebration drinking (Stappenbeck et al., 2007), with current study personnel trained by the developer of the interview. The BCSI-21 involves a drink-by-drink reconstruction of the participants' primary 21st birthday celebration, including details, location, pace of each drink consumed, and other substance use. For participants reporting more than one celebration, the BCSI-21 was completed based on the participant's primary 21st birthday celebration (note that study results showed a similar pattern when modeling the number of excessive drinking episodes between the pre-21st birthday scan and the post-21st birthday celebration scan and when restricting analyses to participants with no more than one excessive drinking episode between scans). To facilitate accuracy of recall, interviewers provided participants with visual aids of standard drink sizes and types (Kaskutas and Kerr, 2008). When there was ambiguity about alcoholic content of a reported beverage, drinking establishments were contacted to obtain standard drink information. For cases in which participants reported partially consuming a drink, the standard drink was rounded down to the nearest half standard drink. Further, for cases in which participants reported only a number of standard drinks over a period of time (e.g., three standard drinks over two hours), it was assumed that consumption of these drinks was evenly spaced during that time period.

Using standard drink information from the BCSI-21, peak eBAC during the 21st birthday celebration was estimated based on the equation given by Matthews and Miller (1979). Because the median lethal dose (LD50) blood alcohol concentration has been estimated to be between .40–.50, eBACs in the current study greater than .45 were winsorized to a maximum of .45.

MRI Processing

Structural MRI scans were processed using a well-validated surface-based morphometric pipeline (FreeSurfer version 6.0.0; <https://surfer.nmr.mgh.harvard.edu>; full details on MRI acquisition and processing in Supplemental Methods). All scans were further processed

using the FreeSurfer longitudinal processing stream (<https://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing>; [Reuter et al., 2012]). In brief, using scans from each time point, an unbiased within-subject template was created through robust, inverse consistent registration (Reuter et al., 2010). Skull stripping, Talairach transformation, atlas registration, and generation of spherical surfaces maps and parcellations were conducted with common information from the unbiased within-subject template, which significantly increases reliability and statistical power (Reuter et al., 2012). All MRI surface reconstructions were manually checked for inaccuracies and artifacts by JPYH. Morphometric estimates (volume and local Gyrification Index [i.e., measure of regional gyrification]) were then calculated at each vertex of the tessellated cortical reconstruction (full details on morphometric estimates in Supplemental Methods).

Corpus Callosum and Hippocampus Regions of Interest (ROI)

In FreeSurfer, volume of the corpus callosum and hippocampus can only be examined using a ROI approach (i.e., it is not possible to do “whole-brain” analyses involving subcortical regions). Due to unique anatomical structure and functional connections (Fabri et al., 2014), the corpus callosum has often been divided into three subregions (splenium, body, and genu/rostrum). As such, we segmented the corpus callosum into three ROIs based on the atlas defined by Rosas et al. (2010): posterior (consisting of splenium and anterior splenium), central (body), and anterior (genu and rostrum). The hippocampus ROI was defined based on the Aseg Atlas provided by FreeSurfer (Fischl et al., 2002). See Table 1 for volumetric measurements at each scan.

Longitudinal Structural Morphometric Analyses

Recommended by FreeSurfer as being a principled and statistically powerful analytic approach, we implemented linear mixed effects models using the linear mixed effects Matlab toolbox (Bernal-Rusiel et al., 2013a, 2013b) distributed within FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/fswiki/LinearMixedEffectsModels>). To test for longitudinal brain morphometry changes, we fit our data using the following linear mixed effects model:

$$Y_{ij} = \beta_1 + \beta_2(\text{time}_{ij}) + \beta_3(\text{eBAC}_i) + \beta_4 * \text{eBAC}_i * \text{time}_{ij} + \beta_5(\text{gender}_i) + \beta_6(\text{intracranial volume}_i) + b_{1i} + b_{2i}(\text{time}_{ij}) + e_{ij}.$$

Time was the main effect of time between pre- to post-21st birthday celebration, *i* represents each of the individual participants, and *j* represents each of the measurement timepoints. When comparing pre- to post-21st birthday celebration, the intercept was modeled as a random effect, and all other terms were modeled as a fixed effect. The model included main effects of time ($\beta_2[\text{time}_{ij}]$) and eBAC ($\beta_3[\text{eBAC}_i]$) as well as an interaction term between eBAC and time ($\beta_4 * \text{estimated eBAC}_i * \text{time}_{ij}$). A significant interaction between higher eBAC and time was indicative of eBAC being associated with changes in cortical morphometry. Gender ($\beta_5[\text{gender}_i]$) and intracranial volume ($\beta_6[\text{intracranial volume}_i]$) were also included as fixed effects as previous research has found these variables to be associated with brain morphometry (Barnes et al., 2010; Hogstrom et al., 2013; Im et al., 2008; Luders et al., 2004; Ritchie et al., 2018).

To examine changes in mean subcortical volume of corpus callosum subregion and hippocampus ROIs, as recommended by FreeSurfer, we used univariate linear mixed effects models. To examine cortical changes in volume and gyrification, we examined whole-brain cortical changes using mass-univariate linear mixed effects models. Vertex-wise analyses were corrected for multiple comparisons using a two-step false discovery rate correction that accounted for both brain hemispheres ($q < .05$; Benjamini et al., 2006). As alcohol-related blackouts are also an indicator of a high-dose alcohol exposure, we followed-up significant results by analyzing whether participants who experienced a blackout during their 21st birthday celebration showed more structural damage than those who did not experience a blackout during their 21st birthday celebration.

We ran additional univariate linear mixed effects models that examined changes in mean volume of the lateral ventricles since changes in corpus callosum subregions could be a surrogate of lateral ventricular expansion. To test for longitudinal brain morphometry changes, we fit our data using the same linear mixed effects model described above. We also ran univariate linear mixed effects models that examined changes in mean subcortical volume of the corpus callosum subregions while accounting for lateral ventricular volume. To account for lateral ventricular volume, we fit our data using the following linear mixed effects model:

$$Y_{ij} = \beta_1 + \beta_2(\text{time}_{ij}) + \beta_3(\text{eBAC}_i) + \beta_4 * \text{eBAC}_i * \text{time}_{ij} + \beta_5(\text{gender}_i) + \beta_6(\text{intracranial volume}_i) + \beta_7(\text{lateral ventricular volume}_i) + b_{1i} + b_{2i}(\text{time}_{ij}) + e_{ij}.$$

To further examine whether a single extreme drinking episode, and not just chronic heavy alcohol exposure or other substance use, was associated with structural change, we ran additional univariate linear mixed effects models that accounted for individual participant differences in lifetime alcohol consumption, current cannabis use during the 21st birthday celebration, and lifetime history of cannabis use. Using the Lifetime Drinking History (Jacob, 1988) interview, which retrospectively assessed lifetime alcohol use patterns, *adjusted lifetime alcohol use* was calculated by summing the estimated total number of drinks across all drinking phases in a participant's life. Lifetime drinks greater than two standard deviations from the sample mean were winsorized to reduce the effect of outliers. To account for adjusted lifetime alcohol use and current/lifetime history of cannabis use, we fit our data using the following linear mixed effects model:

$$Y_{ij} = \beta_1 + \beta_2(\text{time}_{ij}) + \beta_3(\text{eBAC}_i) + \beta_4 * \text{eBAC}_i * \text{time}_{ij} + \beta_5(\text{gender}_i) + \beta_6(\text{intracranial volume}_i) + \beta_7(\text{other substance use variable}_i) + b_{1i} + b_{2i}(\text{time}_{ij}) + e_{ij}.$$

To examine whether changes between the post-21st birthday celebration scan and the five weeks post-21st birthday celebration scan were sustained, we used the same linear mixed effects model and parameters as in our pre- to post-21st birthday celebration analyses.

Results

Alcohol Use Descriptive Statistics

Consistent with previous studies of 21st birthday drinking (Neighbors et al., 2005; Rutledge et al., 2008), participants in the current study drank heavily during their 21st birthday celebration (see Fig. 2). For participants with useable volume data, mean peak eBAC was .22 g/dl ($SD = .14$), a level commonly associated with vomiting and blackouts. For participants with useable gyrification data, mean peak eBAC was .23 ($SD = .15$). Moreover, 44% of participants achieved dangerously high peak eBACs greater than .25 during their 21st birthday celebration, which is slightly higher than previous rates ranging between .23–.42 (Neighbors et al., 2005; Rutledge et al., 2008). Additionally, gender was not significantly associated with alcohol-induced brain volume changes (see Supplemental Table 2 and Supplemental Table 3).

Brain Morphometry Changes of the Corpus Callosum from Pre- to Post-21st Birthday Celebration Associated with Higher Peak eBAC

Changes in brain morphometry of corpus callosum subregions from pre- to immediately post-21st birthday celebration were associated with higher 21st birthday celebration peak eBACs as indicated by an interaction between eBAC and time (see Supplemental Table 2 for full model results). Specifically, higher 21st birthday peak eBAC was associated with decreased mean volume of posterior ($p = .0160$) and central corpus callosum subregions ($p = .0497$, result for central not significant after multiple comparison correction), immediately post-21st birthday relative to pre-21st birthday (see Fig. 3). Association with anterior corpus callosum was not significant (see Fig. 3). Hence, the more that people drank on their birthday celebration, the greater the decrease in mean volume of the posterior and central corpus callosum from session 1 (pre-birthday) to session 2 (on average three to four days post-birthday). Following-up on these interactions with chi-square analyses to test whether extreme alcohol use caused a change in volume, we found that these interactions were driven both by volumetric decreases in those with high eBACs as well as volumetric increases in those with low eBACs. Exploratory analyses of the posterior and central corpus callosum showed that participants who experienced an alcohol-related blackout during their 21st birthday celebration ($n = 17$) had significantly more damage of the posterior corpus callosum, but not the central corpus callosum, than those who did not ($n = 33$; Supplemental Table 4). Although there were interactions between peak eBAC and time, the main effect of time for corpus callosum subregions was not significant (all $ps > .1227$). Additionally, these longitudinal changes were specific to the corpus callosum and were not a secondary consequence of lateral ventricular expansion (see Supplemental Table 5).

To examine whether this interaction was associated with a single episode of extreme drinking or whether the interaction was better accounted for by lifetime chronic alcohol exposure, we also accounted for lifetime alcohol use (see Supplemental Table 3). When accounting for lifetime alcohol use, the interaction for posterior corpus callosum, but not central, remained significant. To further examine whether this interaction was associated with a single episode of extreme drinking, we also accounted for current cannabis use during the 21st birthday celebration (see Supplemental Table 6) and lifetime history of cannabis use

(see Supplemental Table 7). When accounting for current cannabis use during the 21st birthday celebration, results were very similar with there being an interaction of eBAC by time for both posterior and central corpus callosum. When accounting for lifetime history of cannabis use, the interaction for posterior corpus callosum, but not central, remained significant (note that lifetime cannabis use data on eight participants were missing, so these analyses should be interpreted with caution). Thus, these analyses provide further evidence that the damage to the corpus callosum was specific to this episode of extreme drinking and not a result of chronic heavy alcohol exposure or exposure to other substances.

In addition to the corpus callosum, we also examined changes in volume of the hippocampus. There was no significant interaction between peak eBAC and time for the hippocampus ($p = .9969$).

Additionally, dehydration has been associated with decreased volume, with reversal of these effects after rehydration (i.e., 30–90 minutes after drinking 1.5 liters of water; Nakamura et al. 2014). Although, it is unlikely that the effect of dehydration from drinking would confound the analyses since participants were instructed not to drink alcohol the day prior and because the rate of drinking the day prior to the scan was very low, we attempted to account for the dehydrating effects of alcohol by including eBAC from the two days prior to the post-21st birthday celebration scan as a covariate in analyses. Note that results were very similar when accounting for eBAC from the two days prior.

Brain Morphometry of the Corpus Callosum from Post-21st Birthday Celebration to Five Weeks After

Due to significant interactions between peak eBAC and time for the corpus callosum, we also examined whether there was evidence of structural changes in the corpus callosum five weeks post-21st birthday celebration. From immediately post-21st birthday to five weeks after, the interaction with 21st birthday peak eBAC was not associated with further changes, or recovery, in corpus callosum subregions (posterior: $F[1,27] = 0.33$, $p = .5704$; central: $F[1,27] = 0.0003$, $p = .9872$; anterior: $F[1,27] = 1.51$, $p = .2297$). Additionally, the main effect of time was not significant (posterior: $F[1,27] = 0.004$, $p = .9474$; central: $F[1,27] = 1.39$, $p = .2488$; anterior: $F[1,27] = 0.48$, $p = .4958$).

Cortical Whole-Brain Morphometry from Pre- to Post-21st Birthday Celebration and Five Weeks After

We also examined changes in cortical whole-brain morphometry (volume and gyrification). Whole-brain cortical results were not significant after multiple comparison correction. Given the novelty of the sample, in Fig. 4 and Fig. 5, we report exploratory analyses regions in which peak eBAC was associated with changes ($p < .01$) in volume and gyrification post-21st birthday and five weeks after (including clusters within parahippocampal regions and the orbitofrontal cortex).

Similar to the post-21st birthday analyses, we attempted to account for the dehydrating effects of alcohol by including eBAC from the two days prior to the five weeks post-21st birthday celebration scan as a covariate in analyses. Note that results were similar when accounting for eBAC from the two days prior.

Discussion

Due to high rates of extreme drinking, the 21st birthday celebration presents a unique opportunity to prospectively examine the neural effects of an extreme drinking episode. As previously mentioned, emerging adulthood is a critical period of neural maturation and development in which extreme alcohol use has been found to have a profound neurotoxic effect (Boness et al., 2019; Crews and Nixon, 2009; Heikkinen et al., 2017; Meda et al., 2017, 2018; Pfefferbaum et al., 1996). However, no previous study has examined the immediate changes that a single extreme drinking episode can have on the brain morphometry of emerging adults. For the first time, we prospectively examined the effects of a discrete extreme drinking episode (i.e., 21st birthday celebration) on the brain morphometry of emerging adults. We found support for our hypothesis that higher 21st birthday peak eBAC would be associated with brain morphometry damage, especially of the corpus callosum. We did not find evidence of decreased volume of the hippocampus. Additionally, there was evidence of structural changes to the parahippocampal gyrus and orbitofrontal cortex, but these were not significant after multiple comparison correction. Alcohol-induced brain volume changes were not significantly associated with gender.

We found important evidence of structural brain damage following an episode of extreme drinking in the corpus callosum. Specifically, higher 21st birthday celebration peak eBAC was associated with decreased mean volume of the posterior and central subregions of the corpus callosum at post-21st birthday celebration. To further examine whether this decrease in volume was not due to chronic heavy alcohol exposure or substance use, we also accounted for these variables in additional models. This interaction for the posterior corpus callosum remained significant after accounting for lifetime alcohol use and cannabis use, and individuals who experienced a 21st birthday blackout showed a greater volumetric decrease of this subregion than those who did not experience a 21st birthday blackout. We did not find a significant effect for the anterior corpus callosum subregion. Since corpus callosum subregions show differential patterns of development in emerging adulthood (e.g., Luders et al., 2010), it is possible that these subregions could be differentially affected by extreme alcohol use. Additionally, we found no evidence of further and continued structural changes five weeks post-21st birthday, nor did we find evidence of significant recovery. Hence, higher 21st birthday peak eBAC was related to immediate structural brain damage of the corpus callosum, and was not better explained by chronic heavy alcohol exposure or cannabis use.

Results are consistent with previous research finding abnormalities of the corpus callosum associated with extreme drinking in humans and non-human animals models of binge drinking (Pfefferbaum et al., 2008; Vargas et al., 2014). Using the same sample as the current study, Boness et al. (2019) found DTI changes in the corpus callosum, specifically increased fractional anisotropy and decreased radial diffusivity of the central subregion, immediately post-21st birthday. As DTI measures and volume have been posited to be sensitive to different neurobiological processes (Fjell et al., 2008; Westlye et al., 2009), current results provide further evidence that extreme alcohol use adversely affects the corpus callosum in multiple ways. Additionally, as no study to our knowledge has examined the effect of a discrete extreme drinking episode on corpus callosum volume in emerging adults,

we examined how our results fit within the broader alcohol literature. Consistent with our results, multiple studies of individuals with alcohol use disorder have found decreased volume of the corpus callosum (de Souza et al., 2019; Estruch et al., 1997; Pfefferbaum et al., 1996). Similar to de Souza et al. (2019), which had looked at subregions of the corpus callosum, we found decreased volume in the posterior and central corpus callosum. The posterior and central regions of the corpus callosum consist of interconnecting fibers associated primarily with primary motor, somatosensory, and sensory cortices (Fabri et al., 2014). Damage and volume loss of the corpus callosum related to alcohol use has been associated with increased rates of drinking relapse, reduced interhemispheric transfer of information (Schulte et al., 2004, 2005; Vargas et al., 2014), and decreased cognitive and executive performance (Chanraud et al., 2007; Estruch et al., 1997; Harper, 2009). Hence, the current study builds on previous alcohol use research and provides preliminary evidence that a single drinking episode is associated with immediate atrophy of the corpus callosum in emerging adults.

Contrary to our hypothesis and previous research, we did not find evidence of alcohol use-associated damage to the hippocampus in the current study. Arguably, the strongest evidence for binge-associated hippocampal damage is in animal studies (e.g., Crews and Nixon, 2009; Sripathirathan et al., 2009). In contrast to the current study design that included one binge episode, discrete binge episodes in animal studies typically range between 4–10 days and include multiple binge exposures each day. As such, it is possible that hippocampal damage may be a result of multiple binge exposures. It is also possible that alterations in the hippocampus might be specific to a particular hippocampal subregion and not the hippocampus as a whole. For example, previous studies have found evidence of preferential alcohol-associated damage in the ventral hippocampal dentate gyrus compared to the dorsal hippocampal dentate gyrus (Crews and Nixon, 2009). As such, future studies should segment the hippocampus and examine alcohol use associations with hippocampal subregions.

There were some limitations worth noting in the current study. One limitation was that we did not directly assess BAC and instead estimated BAC based on retrospective participant recall. Similar to other eBAC formulas, our calculation of eBAC did not include food consumption/vomiting and used a constant for alcohol metabolism rate, which could have led to inaccuracies in measurement of eBACs, especially overestimated eBACs in those at the high extreme. In future research, we plan to directly assess BAC with transdermal sensors or personal breath alcohol devices. Another potential limitation is the lower number of participants who came back for the post-21st birthday scan. To best capture a time period in which the brain is most likely to be sensitive to the neural effects of extreme drinking, participants came in, on average, three to four days after their 21st birthday celebration. Due to scheduling conflicts, not everyone from the pre-21st birthday session was able to complete the post-21st birthday scan. Moreover, it is possible that with a larger sample size and more power that we would have found evidence of cortical changes after 21st-birthday drinking. For instance, previous animal studies have found evidence of changes in the parahippocampal gyrus and orbitofrontal cortex after exposure to high doses of alcohol (Crews et al., 2000; Crews and Nixon, 2009; Lawrimore et al., 2019). However, we did not find any significant cortical changes after multiple comparison correction. Lastly, another

limitation was that the current study did not include a direct measure of hydration. Although it is unlikely that the effect of dehydration from drinking would confound the analyses since participants were instructed not to drink alcohol 24 hours prior to the scan and since the inclusion of eBAC two days prior to both the post-21st birthday celebration and the five weeks post-21st birthday celebration scans as a covariate yielded similar results. Nevertheless, future research should include a direct measure of hydration prior to scans.

Although there were some limitations, this is the first study to use a quasi-experimental prospective design to naturalistically examine extreme drinking in emerging adults. As mentioned previously, the 21st birthday celebration is a rare time in which to examine the effects of a discrete extreme drinking episode over a relatively short time window. Additionally, we examined for the first time how extreme drinking affected brain morphometry as assessed by multiple structural measures (i.e., volume and gyrification). There are few longitudinal structural studies of alcohol use, and no study has looked at the effects of alcohol on gyrification in emerging adulthood. Future research should expand upon this study by looking at mechanisms underlying these alcohol-related changes. Animal models of extreme drinking have implicated neuroinflammatory processes (Crews et al., 2017; Lawrimore et al., 2019; Qin and Crews, 2012), and human studies have implicated myelination thinning and axonal degeneration (Harper, 2009). As such, future research could examine whether and how these different processes play a role in brain changes after an extreme drinking episode in emerging adults.

Overall, the current study found novel evidence of structural brain changes of the corpus callosum, which is integral to the interhemispheric transfer of information, following an extreme drinking episode. Results from this study suggest that a single extreme drinking episode is enough to alter the brain morphometry of emerging adults a couple days after the drinking episode. Additionally, we did not find evidence of recovery in these brain regions five weeks post-21st birthday celebration. As such, these results underscore the importance of early prevention and intervention efforts of extreme drinking in emerging adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Study timeline.

Fig. 2.
Estimated peak blood-alcohol concentration (eBAC) of participants.

Fig. 3. Higher 21st birthday peak estimated blood-alcohol concentration (eBAC) associations with corpus callosum subregion volumes. a) Posterior corpus callosum; b) Central corpus callosum; c) Anterior corpus callosum. eBAC values were winsorized to a maximum of 0.45.

Fig. 4. Longitudinal cortical morphometry changes associated with higher peak estimated blood-alcohol concentration (eBAC) from pre- to post-21st birthday celebration. a) Cortical volume; b) Cortical gyrification.

Fig. 5. Longitudinal cortical morphometry changes associated with higher peak estimated blood-alcohol concentration (eBAC) from post-21st birthday celebration to five weeks after. a) Cortical volume; b) Cortical gyrification.

Table 1

Region of Interest Volumetric Means (SDs)

Volume (mm ³)	Pre-21 st Birthday Celebration (<i>n</i> = 50)	Post-21 st Birthday Celebration Session 2 (<i>n</i> = 50)	Five Weeks After Post 21 st Birthday Celebration (<i>n</i> = 29)	Pre- to Post-21 st Birthday Celebration Difference (<i>n</i> = 50)	Post-21 st Birthday Celebration to Five Weeks After Difference (<i>n</i> = 29)
Posterior Corpus Callosum	1,553.55 (273.06)	1,549.66 (271.06)	1,596.67 (263.47)	-3.89 (30.03)	4.51 (28.25)
Central Corpus Callosum	661.12 (129.54)	657.15 (124.28)	659.35 (133.61)	-3.97 (36.39)	-17.31 (39.75)
Anterior Corpus Callosum	1,475.16 (211.44)	1,479.89 (217.95)	1,523.99 (191.92)	4.73 (31.47)	-5.34 (39.71)
Hippocampus	8,608.84 (807.59)	8,608.26 (818.65)	8,564.82 (826.18)	-0.58 (160.71)	12.46 (142.12)