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Adolescent Drinking and Motivated Decision-Making: A Cotwin-Control Investigation with Monozygotic Twins

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Abstract

The present study used a monozygotic (MZ) cotwin-control (CTC) design to investigate associations between alcohol use and performance on the Iowa Gambling Task (IGT) in a sample of 96 adolescents (half female). The MZ CTC design is well suited to shed light on whether poor decision-making, as reflected on IGT performance, predisposes individuals to abuse substances or is a consequence of use. Participants completed structural MRI scans as well, from which we derived gray matter volumes for cortical and subcortical regions involved in IGT performance and reduced in adolescents with problematic alcohol use. Drinking was associated with poorer task performance and with reduced volume of the left lateral orbital-frontal cortex. CTC analyses indicated that the former was due to differences between members of twin pairs in alcohol use (suggesting a causal effect of alcohol), whereas the latter was due to factors shared by twins (consistent with a pre-existing vulnerability for use). Although these preliminary findings warrant replication, they suggest that normative levels of alcohol use may diminish the quality of adolescent decision-making and thus have potentially important public health implications.

Keywords

Adolescent; drinking; decision-making; cotwin-control; identical twins

Dual-systems models of adolescent decision-making and risk-taking have gained traction in recent years (cf. Casey and Jones 2010; Steinberg 2010). Such models are based on differences in the respective developmental trajectories of the brain regions underlying cognitive control processes on one hand and reward sensitivity and incentive motivation on the other. Whereas cognitive control, which depends critically on prefrontal cortex (PFC) and its connections with other regions, develops gradually throughout adolescence and into early adulthood, reward sensitivity and incentive motivation are based in limbic-striatal systems and develop earlier, reaching a peak in adolescence before declining by early adulthood (Luciana et al. 2012; Steinberg 2010; Urošević et al. 2012). This difference between systems in respective developmental course is thought to bias adolescents to seek out rewarding, novel, and sensation-enhancing stimuli, and may predispose to substance use.

Heightened reward sensitivity makes cognitive control more difficult (Luciana and Collins 2012), particularly in the context of situations offering potential reward, further strengthening this bias.

The Iowa Gambling Task (IGT; Bechara et al. 1994) involves just such a situation. On each trial, subjects select a card from one of four decks of playing cards. Two of the decks are ultimately advantageous despite resulting in small immediate gains. The other two decks yield larger wins but large losses as well, with losses outweighing wins in the long run. To maximize winnings, subjects must learn which decks are advantageous across trials. Investigations with adults who abuse alcohol and other substances consistently indicate a compromised ability to maximize winnings on the IGT (Bechara et al. 2001; Bechara and Martin 2004; Bolla et al. 2003; Dom et al. 2006; Goudriaan et al. 2007; Goudriaan et al. 2005; Hanson et al. 2008; Hermann et al. 2009; Le Berre et al. in press; Moreno et al. ; Verdejo-Garcia et al. 2007). However, very few studies of the association between adolescent performance on the IGT and substance use exist, and these lead to different inferences. A study of 10th graders in China reported that binge drinking was related to IGT performance (Johnson et al. 2008). Because frequency of recent drinking was unrelated to performance, the authors speculated that poor decision-making, as reflected in IGT performance, predisposes adolescents to misuse alcohol. This interpretation was supported by results of a one-year follow-up, which found that poor performance predicted subsequent levels of binge drinking, including ongoing drinking (Xiao et al. 2009). However, a study of 12- to 14-year-old adolescents in the US administered the IGT at study intake and found that those who subsequently initiated substance use did not have a decision-making deficit prior to their drug use (Ernst et al. 2010). This finding is inconsistent with the notion that such a deficit predisposes to substance use and abuse.

An alternative explanation for poor performance among adolescent binge drinkers is that alcohol misuse disrupts the development of decision-making processes. Experimental rodent research consistently indicates that alcohol exposure is especially neurotoxic when it occurs during adolescence, compared to adulthood, with deleterious long-term effects (e.g., Crews et al. 2000; Hiller-Sturmhofel and Swartzwelder 2004; Markwiese et al. 1998; Nixon and Crews 2002; Obernier et al. 2002; Shors et al. 2001; Silvers et al. 2006; Sircar and Sircar 2005). Chronic intermittent exposure, an analog of binge drinking, is particularly harmful, leading to reduced neurogenesis (Nixon and Crews 2002) and neurochemical changes (Obernier et al. 2002) in the hippocampus, which can be permanent (Monti et al. 2005). A burgeoning body of research motivated by these findings suggests that alcohol use and abuse are associated with a variety of neurocognitive anomalies among adolescents as well, such as poor performance on neuropsychological tests, structural brain anomalies, and altered white-matter structure (reviewed in Jacobus and Tapert 2013; Welch et al. 2013). Of particular relevance to the present study, gray matter volume is reduced in adolescents with alcohol use disorders (AUDs) relative to demographically-matched controls in hippocampus (De Bellis et al. 2005; Nagel et al. 2005) and PFC, especially its anterior aspect (De Bellis et al. 2000; Medina et al. 2008). However, the majority of studies in this area have been cross-sectional, and whether a causal relationship between alcohol use and neurocognitive anomalies exists remains largely unanswered.

Of course, disentangling effects of substance abuse from correlates that predispose to abuse is challenging. Adolescents who demonstrate problematic alcohol use differ from those who do not on a number of factors, many of which predate the initiation of alcohol use and are also associated with poor decision-making (Cantrell et al. 2008; Crone and van der Molen 2004; Ernst et al. 2003; Fairchild et al. 2009; Hobson et al. 2011; Kim et al. 2006; Lovallo et al. 2006). Research designs that permit stronger causal inferences are needed. “Natural experiments,” such as twin- or sibling-difference designs, offer a powerful test of causal influence in observational research (Rutter et al. 2001). For example, the cotwin-control (CTC) design (McGue et al. 2010) can be used to examine outcomes in twins who differ with respect to their alcohol use. Because identical twins share their genetic endowment, as well as their pre- and postnatal rearing environments, they serve as ideal controls for both genetic predisposition and shared environmental effects. When twins are discordant for exposure to an environmental influence, the CTC design approximates a randomized experiment. The CTC difference design, which is based on *differences* between twins in the magnitude of continuous measures of exposure (McGue et al. 2010), can provide an especially sensitive test of the effects of alcohol use on neurocognitive functioning; the lesser-using twin provides a close approximation of expected functioning of the greater-using twin had s/he used less. Thus, the CTC difference design fits comfortably within current perspectives on causality, which define the true causal effect of exposure as the difference in the exposed individual’s measured outcome and her outcome had s/he not been exposed (the unobserved, counterfactual case).

The present study uses a CTC difference design to investigate associations between alcohol consumption and IGT performance in 48 pairs of adolescent monozygotic (MZ) twins between 15 and 18 years of age. This was complemented by propensity score adjustment to control for unshared confounders. We also examined the volume of selected brain areas. To reduce the likelihood of Type I error, we limited ourselves to regions implicated both in adolescent alcohol abuse and IGT performance. As noted above, volume of the hippocampus and PFC is reduced in adolescents with AUDs. Lesion studies implicate the hippocampus and the orbital aspect of PFC in IGT performance as well (Bechara et al. 1994; Gupta et al. 2009; Tranel et al. 2002). We therefore examined gray matter volume in these two areas. Our CTC difference design allows us to begin to disentangle competing hypotheses regarding effects of alcohol exposure on task performance and gray matter volume. Although this is a preliminary investigation, its contribution to the existing literature derives from the use of a powerful design that permits stronger statements about causality than are possible in the typical correlational analysis, even with a longitudinal design.

Method

Participant recruitment and characteristics

Participants consisted of the sample of the AdBrain study, part of the Minnesota Center for Twin and Family Research (MCTFR). Twin pairs were drawn from a pool of twin births in the state of Minnesota between 1991 and 1994 and including all 571 families not already participating in a separate MCTFR study (Keyes et al. 2009). The design called for 16 pairs

in each of three age cohorts, and 147 families living within approximately one hour from the University of Minnesota were contacted randomly within cohort until the target enrollment of 48 pairs had been reached. Twenty-one (14%) refused a phone interview to determine eligibility, and another 75 (51%) were ineligible, primarily because the twins were not MZ or were ineligible for MRI (owing almost exclusively to orthodontia). One eligible pair refused to participate, and two were not included because the target sample size had been achieved.

The final sample of 48 pairs of MZ twins (half female) completed a comprehensive multimodal assessment twice in a one-year interval (referred to here as baseline and wave 2). Mothers also participated in the study, providing information about their own mental health, their family, and the twins. All adolescents provided informed assent to participate in the project, and mothers provided informed consent to their twins' participation as well as their own. Because there was greater variability in alcohol use at wave 2, we used wave-2 data for the present analysis. Twins ranged in age from 14.9 to 17.7 years (mean, 16.4).

Assessment

The comprehensive assessment was modeled on that of other MCTFR studies (Iacono et al. 1999; Iacono and McGue 2002; Keyes et al. 2009; McGue et al. 2007). Twins completed interview and laboratory assessments simultaneously in different rooms. During a separate visit to the Center for Magnetic Resonance Research (CMRR), one twin completed computerized tasks and a drug screen while the other completed the MRI scans. The vast majority of scans (83%) were completed within 2 weeks of the initial visit (mean, 10.6 days; range, 1 to 49 days, the latter being due to a scanner problem that required rescheduling).

Iowa Gambling Task—Participants completed a computerized version of the IGT (Bechara et al. 1994) in which they viewed four decks of playing cards equally spaced horizontally on the screen and face down. They were instructed to choose one card at a time by clicking on it with a computer mouse. Each card resulted in winning money but some cards also resulted in losses, with the magnitude of gains and losses and the frequency of losses varying across decks. Two decks were associated with small gains (\$0.10 or \$0.15) but selecting from these decks results in an average net gain of money (\$12.50), whereas the other two decks paid more (\$0.25) but were associated either with frequent losses or large, infrequent losses, such that selecting from them results in a net loss of money equivalent to the gain yielded by the advantageous decks. The two advantageous and disadvantageous decks differed from each other with respect to the frequency of losses and therefore in the overall ratio of gains to losses. Participants began with \$5 and were instructed that their goal was to win as much money as possible or, if unable to win, to avoid losing as much as possible. Participants were informed that they would win real money by playing well. After each trial their accumulated total was displayed on screen. We computed the number of cards chosen from advantageous decks minus the number chosen from disadvantageous ones, deriving this for each of five blocks of 20 consecutive trials in order to characterize learning, as is typical.

Alcohol use—Adolescents completed a version of the Substance Abuse Module (SAM; Robins et al. 1987) of the Composite International Diagnostic Inventory (CIDI; Robins et al. 1987). The MCTFR-expanded SAM includes questions about drinking frequency, quantity, misuse, and density (e.g., the maximum number of drinks in a 24-hr period). Our primary measure of alcohol use was derived from four items from the modified SAM: frequency of drinking, number of drinks typically consumed per occasion, the maximum number of drinks consumed in a single 24-hr period, and the number of times intoxicated. All questions were asked about the preceding 12 months. Because responses to each question were highly skewed and sparse, in that relatively few of the possible responses were represented, we transformed them into ordinal measures, with five or six categories for each measure. This also has the effect of reducing noise due to uncertainty in recall. We derived a summary measure of past-year alcohol exposure by summing the four ordinal scales, yielding a measure of exposure with a maximum possible score of 23. Internal consistency of the scale was high, Cronbach's $\alpha = .95$. The intraclass correlation, measuring twin similarity, was .54, corrected for age and sex effects.

Structural MRI—Anatomical images were collected on a Siemens 3T Tim Trio scanner (Siemens Medical Systems, Erlangen, Germany), using a 12-channel array head coil. Three-dimensional T1-weighted images were acquired in the sagittal plane using a magnetization prepared rapid gradient echo sequence (MP-RAGE) (TR of 2530 ms, TE of 3.65 ms, flip angle 7°, matrix size of 256 by 256 with a FOV of 256, and 240 sagittal slices with 1-mm isomorphic voxels). One caregiver elected not to have her twins complete the wave-2 scan. Data for the remaining 94 subjects were processed using the standard pipeline as implemented in the Freesurfer suite (Fischl et al. 2002; Fischl et al. 2004) (<http://surfer.nmr.mgh.harvard.edu>). This consisted of motion correction (Jenkinson et al. 2002); removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al. 2002); intensity normalization (Sled et al. 1998); tessellation of the boundary between gray and white matter, and identification of the borders between gray and white matter and between gray matter and cerebrospinal fluid (Fischl et al. 1999). One subject's data could not be properly segmented in Freesurfer, leaving 93 subjects with valid MRI data. As indicated previously, we selected two regions of interest — OFC and hippocampus — based on previous findings indicating that structural lesions of these areas affect IGT performance and that volume of these areas is reduced among adolescents with AUDs.

Statistical analyses

We conducted linear mixed models (LMMs) to determine whether our index of drinking was significantly associated with IGT performance. Trial block was included as a fixed effect, and participant age, gender, and full-scale IQ were included as covariates. IQ was derived from the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scales of Intelligence (WASI; Wechsler 1999). It was included to rule out differences among adolescents in intelligence as an explanation of IGT performance. Random intercepts were included at the level of individuals and pairs to account for the within-individual and within-pair correlations, respectively.

Cotwin-control analysis—We followed up any significant drinking effect with the CTC approach, in which each individual's alcohol exposure score is re-expressed in terms of two components (Begg and Parides 2003; Neuhaus and Kalbfleisch 1998): the average for each twin pair and each individual's deviation from the twin-pair mean. The twin-pair mean represents associations between drinking and performance attributable to influences that MZ twins share, *whether measured or not*. These include genetic and shared environmental influences that might predispose some adolescents to choose cards on the basis of immediate reward on one hand *and* to drink alcohol on the other. Because it captures the mean level of exposure for two individuals with the same genetic makeup and shared environmental influences, it is conceptually comparable to what is assessed in studies of non-twins. The twin-deviation score provides a measure of alcohol use unconfounded by shared influences, and it is therefore a more appropriate test of exposure effects (Begg and Parides 2003; Neuhaus and Kalbfleisch 1998). We will refer to these interchangeably as the between- and within-pair effects, or twin-pair mean and twin-deviation score. Analyses were conducted in R (R Development Core Team, 2013). LMMs were conducted using `lme` from the `nlme` package.

Propensity score adjustment—As powerful as it is, the CTC design can only control for confounding factors that twins share; it cannot control for unshared differences among adolescents in the propensity to be exposed to alcohol in the first place. Any such factors that are also related to IGT performance create a spurious association between alcohol use and task performance. For instance, individuals low in risk-taking tendencies may not drink alcohol in adolescence and may also avoid selecting cards from decks with large punishments, or adolescents whose peer group is deviant may engage in risky behavior, such as drinking alcohol, and may become prone to making risky decisions on the IGT. A propensity score estimates each adolescent's probability of having been exposed to alcohol conditional on covariates reflecting prior characteristics that predispose to alcohol use (Rosenbaum and Rubin 1983).

Propensity score covariates were available in the form of measures from the baseline assessment tapping domains that were conceptually related to drinking: externalizing behavior and symptoms; impulsivity and undercontrolled personality; peer influences; and academic performance, problems, and engagement. Spearman correlations confirmed that these were associated with drinking, ranging in absolute value from .20 to .44 (approximate p -values $< .05$). Measures included information from both the adolescents and their caregivers, and used different methods (questionnaire, verbal report, and clinical interview). Measures, and internal consistency or interrater reliability estimates, are briefly detailed in Table 1.

Propensity score estimation and balance—We modeled exposure (any alcohol use) using a covariate balancing propensity score approach (CBPS), as implemented in the R package by the same acronym. CBPS derives a propensity score while simultaneously optimizing “covariate balance” between exposure groups (Imai and Ratkovic 2013). This mimics for observational research what random assignment does in experimental designs, which is to ensure that experimental groups differ only randomly with respect to important

background variables (covariates). Covariate balance essentially creates a virtual population in which risk is equated between exposed and unexposed groups (Stuart et al. 2009).

CBPS produces a J-statistic to assess this, which is distributed as a chi-square and which should not deviate appreciably from 0 if the groups are well balanced (Imai and Ratkovic 2013). The J-statistic for our covariates was trivially nonzero (.22 on 9 df). Examining standardized mean differences between groups with respect to each covariate used to estimate the propensity score is a common diagnostic tool. (These are familiar to psychologists as Cohen's *d* effect size measure.) Whereas standardized mean differences between exposed and unexposed adolescents on the original covariates ranged from .32 to .73 (Mdn = .57), after propensity score weighting they ranged from less than .01 to .06 (Mdn = .02), well below the threshold (0.25) proposed as an indication that adjustment might not be trustworthy (Rubin 2001). Therefore, the degree of covariate balance attained by CBPS appears quite satisfactory.

Propensity score weighting—We used the inverse probability of treatment weighting (IPTW) method to adjust for individual differences in propensity to use alcohol, where the weight for individual *i*, w_i , equals $1/p_i$ for exposed individuals and $1/(1-p_i)$ for unexposed individuals, where p_i is the propensity score (Austin 2011; Stuart 2010). IPTW weighting thus assigns larger weights to exposed individuals with small probabilities of exposure and unexposed individuals with large probabilities of exposure. These are the individuals who are most informative about the counterfactual case — decision-making in alcohol-exposed adolescents who (counterfactually) *have not* been exposed and in alcohol-naïve adolescents who (counterfactually) *have*. Software for estimating LMMs that can incorporate IPTW weights is limited. We used the GLLAMM package written for Stata (Rabe-Hesketh et al. 2004), with IPTW weighting based on propensity scores derived with CBPS. GLLAMM produces robust (sandwich) standard errors, which are required for valid inference.

Results

Association between alcohol exposure and task performance

Thirty-three subjects reported having had at least one drink in the previous year at wave 2 (34.3% of the sample). The mean score on our composite measure of alcohol exposure was 5.4 among drinkers (SD, 3.6), with a range from 1 to 13. The overall mean was 1.9 (SD, 3.3). Despite the youth of this community sample, variation in alcohol use was evident. For instance, nine subjects had scores of at least 9, and their average alcohol exposure (median values) consisted of having been intoxicated 20 times, having consumed a maximum of 10 drinks at one time, having “binged” (defined as 5 or more drinks at one time) 12 times, and having experienced 3 physical consequences of drinking (withdrawal and hangover symptoms). The difference in mean IGT performance between drinkers and non-drinkers is presented in graphic form in Figure 1, which indicates that both groups increasingly preferred the advantageous decks during the first 60 trials. Whereas this continued among non-drinkers, drinkers “regressed” somewhat, favoring the disadvantageous decks in the later trials.

We conducted a three-level LMM to examine this pattern statistically. Age, gender, and IQ were included as covariates, and random intercepts at the level of individuals and twin pairs, to account for within-individual and within-pair correlations. The main effect of trial block was significant, $F(4, 380) = 10.38, p < .0001$, indicating significant change in performance over the 100 trials. *t*-statistics corresponding to each level of the block factor (relative to the first trial block, which served as the reference category) ranged from 3.13 to 5.51, *p*-values $< .002$, indicating rapid improvement in performance. The left-hand side of Table 2 gives parameter estimates and associated *F*-statistics for the drink index as well as the covariates in our statistical model. Only the drink index was significant, $F(1, 46) = 5.06, p < .029$. Each unit increase on the drink index corresponded to approximately $\frac{1}{2}$ fewer advantageous card choices per trial block, on average. Based on a mean score of 5.4, this indicates that the average adolescent drinker thus selected 15 fewer advantageous cards over the course of the task. A pseudo- R^2 statistic, in the sense of the proportional reduction in variance accounted for (cf. Snijders and Bosker 1999), equaled .021.

Two subsequent LMMs tested for interaction effects associated with the effects of drinking on the pattern of learning over trial blocks and sex differences in the drink index effect, respectively. Despite the apparent difference between drinkers and non-drinkers on later trials (see Figure 1), the interaction between trial block and the drink index was not significant, $F(4, 376) = 1.04, p < .388$. A separate LMM indicated that the interaction between sex and the drink index was also not significant, $F(1, 45) = 0.29, p < .590$. Thus, only a main effect of drinking was observed.

The unconfounded drinking effect and task performance

As described previously, we decomposed each individual's drink index into two components: the twin-pair mean, which yields the between-pair effect, and each individual twin's deviation from it., which yields the within-pair effect. The right-hand side of Table 2 gives results of the CTC analysis. Parameter estimates and associated *F*-statistics are provided for the covariates in our statistical model as well as for the between- and within-pair effects. Both components were inversely associated with performance, but only the within-pair twin-deviation effect was significant, $F(1, 46) = 5.59, p < .022$. Figure 2 illustrates this. For this purpose, a total IGT score for each individual across all 100 trials is plotted against twin-deviation score, not including pairs who do not differ in drinking (all but one because neither twin had initiated drinking). Those with positive difference scores in Figure 2 drink more than their co-twin, while those with negative scores drink less. The figure gives a line of best fit, illustrating that the lesser drinking twins in a pair (those with values on the left side of the figure) tend to have higher IGT scores. It also indicates that there were no obvious outliers to account for our findings.

Weighting cases by IPTW in GLLAMM using propensity scores indicated that the within-pair effect was still significant even when adjusted for propensity to drink alcohol, Wald *z*-statistic = 2.00, *p* = .045. Thus, the twin-deviation, or within-pair, effect could not be accounted for by potential differences between twins with respect to the likelihood of being exposed to alcohol.

Associations between drinking and MRI measures

We conducted a series of LMMs with gray matter volume as the dependent measure, drink index as the predictor of interest, and gender, age, and total intracranial volume as covariates. A random intercept at the twin-pair level accounted for the correlation between twins with respect to volume of each region. Gender was the only covariate significantly associated with gray matter volume; males had larger volumes for all regions. There were no sex differences in the effect of drinking on brain volume; adding interaction terms between gender and drink index to the statistical model were not significant, F -statistics on 1 and 43 $df < 1.70$, p -values $> .20$.

Table 3 gives parameter estimates and associated test statistics for the drink index, with left-hemisphere values on the left-hand side and right-hemisphere values on the right. The drink index was significantly associated only with lateral OFC volume in the left hemisphere, with a trend toward a significant association with medial OFC volume in the left hemisphere as well. Each unit increase in the drink index was associated with a reduction in left lateral OFC volume of approximately 62 mm^3 . We followed up this significant drink effect with a CTC analysis, which indicated that the within-pair effect on volume was not significant, $F(1, 44) = 0.15$. However, the between-pair effect was, $F(1, 43) = 6.76$, $p < .013$. This pattern suggests that drinking is not causally related to left lateral OFC volume. Rather, reduced volume is likely to reflect a preexisting characteristic of those adolescents in the sample who were drinking.

Does volume account for task performance?

To determine whether reduced volume of lateral OFC might account for the observed drinking effects on IGT performance, we conducted an additional LMM with the relative number of advantageous cards selected as the dependent measure and age, gender, brain volume, and drink index as predictors. We collapsed across all 100 trials to simplify analyses. We first fit a model without the drink index to assess effects of left lateral OFC volume, which was not significantly associated with task performance, $F(1, 44) = 1.69$, $p < .200$. Mediation can still occur in the absence of a significant relationship with the potential mediator, and we therefore tested for it. However, the effect of drinking on task performance, net effects of the volume of left lateral OFC, remained significant, $F(1, 42) = 6.30$, $p < .016$, and the magnitude of its regression coefficient was largely unchanged.

Discussion

Our findings are consistent with the little research that exists, which shows that adolescent binge drinking is associated with poor performance on the IGT, a widely used measure of decision-making under ambiguity (Johnson et al. 2008; Xiao et al. 2012; Xiao et al. 2009). We extend previous research by virtue of our CTC difference design. The twin-deviation effect, which reflects influences of alcohol exposure that are unconfounded by genetic and environmental influences shared by twins and which might in turn predispose them to drink, was significantly associated with IGT performance. This implies that poor decision-making on the IGT reflects a causal effect of drinking, rather than something that predisposes adolescents to drink. The CTC design cannot control for factors not shared by twins that are

confounded with alcohol exposure and IGT performance. We used propensity scores to adjust for such unshared confounders, modeling exposure to alcohol using a newly developed approach that optimizes the balance between exposed and unexposed adolescents on covariates at the same time that it derives a propensity score (Imai and Ratkovic 2013). Weighting cases by the (inverse) probability of drinking did not attenuate the twin-deviation effect, which strengthens our confidence in it.

Although the distribution of our drink index was clearly skewed, reflecting the fact that many adolescents had not yet initiated alcohol use, this is unlikely to account for our findings. Figure 1 suggests that *any* alcohol exposure was associated with poor performance, which argues against our findings being a simple artifact of distributional properties of the drink index. Moreover, twin-deviation scores are symmetric by definition and were not skewed. Our CTC analysis, which is the novel feature of this study, was therefore unaffected.

That subjects knew that a real monetary reward was at stake may have contributed to our finding of an association between alcohol use and task performance. In general, monetary incentives have a strong effect on performance in decision-making tasks (Camerer and Hogarth 1999; Hertwig and Ortmann 2001). Performing for real versus imaginary rewards has been found to result in reduced variance in responses on the IGT (Bowman and Turnbull 2003), as on other tasks (Camerer and Hogarth 1999; Hertwig and Ortmann 2001). The opportunity to win money may have elicited individual decision-making biases to a greater degree than would have been the case had participants been playing for an imaginary reward.

Our finding that the within-pair component accounted for the association between alcohol use and task performance does not necessarily implicate a neurotoxic effect, which seems unlikely given the relatively low levels of exposure to this point in their lives. It simply suggests that drinking is a link in a causal chain that leads to poor decision-making under conditions of ambiguity. Alcohol exposure during adolescence in rats modulates the normal reinforcement learning process by altering risk appraisal, thereby producing long-term changes in decision-making (Clark et al. 2012; Nasrallah et al. 2011). Whether a similar process occurs in humans is unknown. However, acute alcohol administration in social drinkers affects discrimination of the magnitude of potential gains when the probability of winning is high, even if potential losses are large (George et al. 2005), which is at least broadly consistent with this hypothesis.

Of course, our finding does not argue against the notion that poor decision-making influences the decision to initiate drinking and alcohol consumption. The between-pair effect on performance within-pair was in the same direction as the within-pair effect, suggesting that a shared liability may also underlie poor performance. That this was not significant may reflect the relatively small sample size of this study and restriction in the range of drinking in this sample.

We also found that adolescent drinking is associated with reduced volume of the left lateral OFC, with a trend toward a significant reduction in the left medial OFC as well. OFC has

been implicated in IGT performance through studies of patients with lesions (Bechara et al. 1994; Bechara et al. 2000; Tranel et al. 2002). This finding is also consistent with studies of adolescents with AUDs, which have reported reduced gray-matter volume in PFC, particularly its anterior aspect (De Bellis et al. 2005; Medina et al. 2008). Volume reductions were significant only for the left hemisphere, which was unexpected. Studies of brain structural correlates of alcoholism have yielded inconsistent findings in this regard, with some studies finding that reductions in OFC volume are only significant for the left hemisphere (Laakso et al. 2002) or are greater in magnitude in the left hemisphere (Tanabe et al. 2007), but others not finding a significant reduction in either hemisphere (Makris et al. 2008). On the other hand, lesser right-left difference in OFC volume has been found among individuals at high risk for alcoholism than those at low risk, implying (relatively) greater left-hemisphere volume (Hill et al. 2009). Further study is required with larger normative samples and perhaps with finer-grained methods (e.g., vertex based) to determine to what extent the reduction we observed, if replicated, is truly specific to the left hemisphere.

In contrast to our analysis of IGT task performance, analyses of OFC gray-matter volume indicated that it was the between-pair effect, or that component of our drink index shared by members of a pair, that was significantly associated with reduced volume. Although by definition this includes the mean level of alcohol exposure, in the CTC design it primarily reflects a shared liability. The reductions in volume of OFC we observed therefore most likely reflect a factor that predisposes to alcohol use in the first place. This inference is consistent with a recent report that smaller volume of OFC measured early in adolescence, when subjects were 12 years old, predicted initiation of cannabis use by age 16 (Cheetham et al. 2012).

OFC is important for processing emotional and motivational characteristics of a stimulus context (Hill et al. 2009) and for integrating expectancies about the outcomes of actions over time and comparing alternative actions (Camille et al. 2004; Schoenbaum et al. 2006). It appears to be critical for stimulus–reinforcement learning that is sufficiently flexible to adjust to changes in contingencies (Tsuchida et al. 2010), and the process of evaluating punishers, which is necessary for adjusting behavior in this way, appears to be specific to the lateral aspect of OFC (Kringelbach and Rolls 2004). Relative reductions in OFC volume could indicate in part that fewer synapses are available to be sculpted by experience, potentially interfering with the adolescent’s capacity to adapt to changing contingencies in the environment and leading to poor decision-making, such as initiating drinking at an early age. Of course, this is highly speculative, and the relationship between structure and function is far from straightforward. Nevertheless, these findings highlight the possibility offered by the CTC design for beginning to disentangle cause and effect.

Limitations

The sample in this study was relatively small, and, although variability in alcohol exposure was evident, the majority of twins had not yet initiated drinking, which reduces variability in our drink index and in its between- and within-pair components. This is undoubtedly due in part to secular trends in adolescent alcohol use; Monitoring the Future recently reported that adolescent alcohol use had fallen to “historic lows” (Johnston et al. 2011). Our propensity

score adjustment may not have captured important sources of unshared confounding that influenced exposure and performance *and* were uncorrelated with the measures included. In particular, the measures of environmental influence we had available from the baseline assessment were somewhat limited. These factors clearly call for caution in interpreting the results.

Conclusion

Nevertheless, this study has a number of strengths. Foremost among them is its use of a MZ CTC difference design. We found that adolescent alcohol use was associated with impaired performance on the IGT, a widely used task of decision-making. Our CTC design indicates that the association between alcohol use and poorer performance likely reflects a causal effect of alcohol exposure on the processes tapped by the IGT. Adolescent drinkers failed to learn, in that, unlike nondrinkers, they did not display a significant preference for advantageous decks relative to disadvantageous ones in any of the five trial blocks. We also found that drinking was associated with reduced volume of gray matter in left lateral OFC. In contrast to our IGT findings, this effect was due to the twin-pair mean. Although we cannot completely rule out effects of alcohol, this finding is consistent with an inference that reduced gray-matter volume in OFC constitutes part of the constellation of characteristics that predispose adolescents to drink alcohol. This difference in findings highlights the usefulness of the CTC design in observational and epidemiological research in permitting researchers to begin to disentangle causal and etiological influences. If normative levels of alcohol use, such as those observed here, truly have causal effects on adolescent decision-making, this has significant public health implications. Our findings, although clearly preliminary, thus call for follow-up and further investigation.

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Advantageous – Disadvantageous Choices

Figure 1.

Performance on the Iowa Gambling Task plotted separately for adolescents reporting having consumed alcohol in the past year and those who did not drink. For each consecutive block of 20 trials, the mean number of choices from long-term advantageous decks relative to (minus) long-term disadvantageous ones is plotted, along with standard errors.

Advantageous – Disadvantageous Choices

Figure 2.

To illustrate the twin-deviation effect on task performance, the number of choices from advantageous decks relative to disadvantageous ones is plotted on the ordinate against the twin difference in drink index on the abscissa. For purposes of illustration, overall performance is plotted, although our regression analysis examined performance across trial blocks. Only pairs in which twins differed in self-reported drinking are included; those who do not differ do not affect estimates of the twin-deviation effect in our regression model. A

line of best fit indicates that twins drinking more than their cotwin choosing relatively fewer cards from advantageous decks.

Table 1

Measures used for propensity score estimation

Measures	Instrument and source
DSM-IV symptoms of ADHD, CD, and ODD (Cohen's κ reliability estimates = .71–.84)	Diagnostic Interview for Children and Adolescents, Revised, parent and child versions (DICA; Reich 2000), modified to include DSM IV A best-estimate procedure was used to assign symptoms if endorsed by either parent or adolescent (Kosten and Rounsaville 1992; Leckman et al. 1982)
Impulsivity ($\alpha = .75$)	Short version of Barratt Impulsiveness Scale (Spinella 2007)
Aggressive-undercontrolled personality (Hicks et al. 2011) ($\alpha = .61$ –.65 for Aggression and .76–.82 for Constraint)	Multidimensional Personality Questionnaire (MPQ; Tellegen and Waller 2008), 2008), adolescent self report Multidimensional Personality Ratings (MTR; Cukrowicz et al. 2006; Oliva et al. 2012; Taylor et al. 2000), parent report
Academics: grade point average, behavior problems ($\alpha = .78$), academic problems ($\alpha = .86$), academic motivation ($\alpha = .85$)	Academic History Interview (AHI; Johnson et al. 2006; Johnson et al. 2007), parent report

Note: The presence of DSM symptoms was determined by consensus of pairs of individuals with advanced clinical training. The total number of symptoms of externalizing disorders was log-transformed to reduce skew. The measure of aggressive-undercontrolled personality was constructed by adding together scores on the Aggression and Constraint scales. Both were first transformed to T-scores and the Constraint scale was reflected. This was separately done for each respondent (adolescent and caregiver). One adolescent's mother did not complete all items making up the personality scales and was not included in propensity score adjustment.

Table 2

Associations between drink measures and IGT performance

Parameter	Test of Any Drinking Effect			Between- and Within-Pair Effects		
	Estimate (SE)	F-statistic (df)	p-value	Estimate (SE)	F-statistic (df)	p-value
Age	0.78 (1.03)	<0.01 (45)	.968	0.44 (1.06)	<0.01 (44)	.967
Sex (Male)	0.03 (1.73)	0.08 (45)	.772	0.31 (1.73)	0.09 (44)	.771
Full-scale IQ	0.07 (0.07)	0.80 (46)	.377	0.08 (0.07)	0.81 (46)	.373
Drink Index	-0.55 (0.24)	5.06 (46)	.029			
Twin-pair mean				-0.30 (0.32)	0.92 (44)	.343
Twin deviation				-0.89 (0.38)	5.59 (46)	.022

Note: F-statistics have 1 numerator df, and denominator df in parentheses. Age is relative to (centered at) the mean age in the sample. Sex is a dummy variable coding for male gender. Full-scale IQ is based on two subtests of the WASI and is centered at the sample mean. Twin-pair mean and twin deviation represent the two components obtained in the cotwin-control design by decomposing the drink index. The twin-pair mean reflects all influences shared by members of a twin pair, including all measured or unmeasured influences that are confounded with alcohol exposure. This is the component of the drinking index that varies between pairs. The twin-deviation score reflects environmental influences specific to each twin, independent of all factors that twins share and that are related to adolescent alcohol use. It is thus a more accurate reflection of the effects of alcohol exposure unconfounded by any shared pre-existing liability to drink.

Table 3

Associations between drink index and MRI measures of gray-matter volume

Region of interest	Left Hemisphere			Right Hemisphere		
	Estimate (SE)	F-statistic	p-value	Estimate (SE)	F-statistic	p-value
Lateral orbital-frontal cortex	−62.0 (28.6)	7.08	.011	−27.9 (26.5)	2.32	.134
Medial orbital-frontal cortex	−36.9 (24.6)	3.23	.079	−15.0 (20.9)	0.93	.340
Hippocampus	3.4 (9.8)	0.36	.549	5.2 (11.8)	0.01	.909

Note: F-statistics have 1 and 44 df