

Testing the effects of adolescent alcohol use on adult conflict-related theta dynamics

A Thesis  
SUBMITTED TO THE FACULTY OF THE  
UNIVERSITY OF MINNESOTA  
BY

Jeremy Harper

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS  
FOR THE DEGREE OF  
MASTER OF ARTS

Adviser: William G. Iacono

February 2017

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## **Acknowledgements**

I would like to thank my advisor, Bill Iacono, and co-mentor, Steve Malone, for their invaluable guidance and support throughout this project and many other aspects of my graduate career. I am indebted to my partner, Amanda Unruh, for her love, support, and encouragement.

The author was supported by the National Science Foundation Graduate Research Fellowship (Grant No. 00039202). This work was supported by the National Institute of Health grants DA005147 and AA009367.

## Abstract

While adolescent alcohol use (AAU) has been associated with poor neurocognitive outcomes, few studies have utilized prospective samples, leaving uncertain any potential long-term neurocognitive effects of AAU. In addition, despite theoretical models linking AAU to diminished cognitive control, empirical work testing the relationship between AAU and specific neural correlates of cognitive control remains scarce. Recent work indicates that demands of cognitive control (e.g., response conflict) involve EEG theta-band dynamics, including medial frontal cortex (MFC) power and MFC-dorsal prefrontal cortex (dPFC) functional connectivity, which may be related to AAU-related neurocognitive dysfunction. The present study tested the hypothesis that greater AAU is associated with diminished adult conflict-related EEG theta-band dynamics in a large ( $N = 718$ ) population-based prospective twin sample assessed at the target ages of 11, 14, 17, and 29. Two complementary analytic methods (cotwin control design; bivariate biometric modeling) were used to disentangle the genetic/shared environmental premorbid risk towards AAU from the potentially causal nonshared environmental effects of alcohol exposure. AAU was negatively associated with adult (age 29) theta MFC power and MFC-dPFC connectivity during a flanker task, suggesting that early drinking is associated with diminished cognitive control-related theta dynamics in adulthood. Both the CTC and biometric modeling results indicated that genetic influences primarily accounted for the association between AAU and reduced theta-band dynamics. Taken together, these findings suggest that the link between AAU and diminished adult cognitive control-related theta dynamics is likely a consequence of

heritable genetic factors, rather than causal nonshared environmental effects.

*Keywords:* Adolescent Alcohol Use; Cognitive Control; Cotwin Control; Functional Connectivity; Endophenotype; Theta.

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## **Introduction**

While cross-sectional work suggests that adolescent alcohol use (AAU) is associated with structural prefrontal cortex anomalies and poor neurocognitive performance (Jacobus and Tapert, 2013), less is known regarding any potential long-term neurocognitive effects of AAU. In addition, recent theoretical models of substance misuse have implicated weak cognitive control processes as a risk factor for AAU (Iacono et al., 2008; Zucker et al., 2011), yet there is a lack of empirical work testing the relationship between AAU and specific cognitive control-related neural correlates. Electrophysiological research implicates frontal theta-band (3-8 Hz) dynamics, including local medial frontal cortex (MFC) power and interregional MFC-dorsal medial/lateral prefrontal cortex (dPFC) functional connectivity, as candidate neurophysiological mechanisms underlying the execution of adaptive cognitive control (e.g., response conflict; Cavanagh and Frank, 2014; Clayton et al., 2015). Therefore, diminished theta-band dynamics may be theoretically plausible mechanisms linking AAU and weak prefrontal cognitive control processes. Disentangling the potential causal effects of early alcohol exposure from a genetic/shared environmental propensity towards early drinking is often difficult, and evidence supports both the potential neurotoxic effects of early alcohol exposure (Jacobus and Tapert, 2013) and the heritability of alcohol-related brain dysfunction (Iacono et al., 2008). As most prior work on AAU has relied on purely observational/correlational research designs (which cannot establish causal mechanisms), the etiology of AAU-related neurocognitive dysfunction remains largely ambiguous. To address this unknown, data collected from prospective quasi-experimental designs

(Vaidyanathan et al., 2015), such as comparing members of a twin pair who differ in their level of adolescent alcohol exposure, are needed to test etiological hypotheses.

A large body of work suggests that AAU is associated with a variety of neurocognitive anomalies, including structural/functional brain abnormalities and poor neuropsychological test performance (reviewed in Jacobus and Tapert, 2013; Welch et al., 2013). Specifically, heavy drinking adolescents exhibit reduced grey and white matter prefrontal cortex volume (Bellis et al., 2005; Medina et al., 2008; Malone et al., 2014; Wilson et al., 2015) and suboptimal performance on laboratory tasks of executive functioning (Nigg et al., 2006; Squeglia et al., 2009), than adolescents with no or limited history of alcohol exposure. In addition, recent theoretical models of alcohol and substance abuse implicate dysregulation of cognitive control processes, mediated by the prefrontal cortex, as an important risk factor of early alcohol engagement and misuse (Iacono et al., 2008; Zucker et al., 2011). During normative adolescent development, the early maturation of limbic and striatal systems associated with reward-seeking and appetitive motivation occurs concomitantly with the gradual development of control-related prefrontal cortex areas (Casey et al., 2008). Protracted prefrontal cortex maturation may be exacerbated in adolescents with a familial liability towards behavioral disinhibition/undercontrol, which predisposes them towards engaging in immediately gratifying, yet harmful, behaviors (e.g., excessive alcohol use) that may further potentiate prefrontal dysfunction (e.g., deleterious causal effects of alcohol exposure; Goldstein and Volkow, 2002; Iacono et al., 2008; Zucker et al., 2011). However, despite these

influential models, empirical work testing the association between AAU and specific neural correlates of cognitive control remains scarce.

Situations requiring cognitive control, such as when competing responses are activated but only one should be selected (response conflict), have been consistently associated with theta-band electrophysiological signatures thought to underlie conflict detection and control-related processes (reviewed in Cavanagh and Frank, 2014). Theta-band power enhancement over the MFC has been consistently observed following demands of response conflict/interference (Cohen et al., 2008; Nigbur et al., 2011; Nigbur et al., 2012; Cohen and Donner, 2013), and current models of cognitive control implicate the MFC in monitoring the environment for situations of conflict/uncertainty (Ridderinkhof et al., 2004a; Ridderinkhof et al., 2004b; Ullsperger et al., 2014). Upon conflict detection, the MFC is thought to signal the need for increased control to regions of the dPFC, which further implements top-down control/behavioral adaptation processes to resolve response conflict (Ridderinkhof et al., 2004a; Ridderinkhof et al., 2004b; Cavanagh and Frank, 2014; Clayton et al., 2015). Empirical and theoretical work suggests that this interregional communication between MFC and dPFC is biophysically realized through coordinated theta-band rhythmic activity (phase synchronized oscillations; Fries, 2005), which forms a dynamic functional network for information transfer among distant cortical areas (Cavanagh and Frank, 2014; Clayton et al., 2015).

Given the importance of theta-band MFC power and MFC-dPFC functional connectivity during response conflict and cognitive control, and research suggesting a link between AAU and reduce grey and white matter prefrontal cortex volume (Jacobus

and Tapert, 2013), reduced theta dynamics may be a plausible neurophysiological mechanism linking AAU and suboptimal cognitive control.

The majority of previous studies on AAU have utilized cross-sectional observational research designs, leaving unknown whether AAU has any long-term association with prefrontal cortex neurocognitive functioning. Additionally, the etiology of AAU-related neurocognitive dysfunction remains largely ambiguous, as disentangling the potential causal effects of early exposure from a premorbid genetic/shared environmental vulnerability is difficult using purely observational/correlational research. Observing that individuals who engage in heavy drinking during adolescence show worse neurocognitive functioning/brain abnormalities than lesser-drinking individuals (or non-drinking controls) does not specify any causal mechanism, and because of this, quasi-experimental research designs/methods, such as comparing twins who differ in their degree of early alcohol exposure, are needed to permit stronger etiological inferences (Vaidyanathan et al., 2015).

One such design is the cotwin control (CTC) method, which capitalizes on the genetic and rearing environment similarity of twins discordant for their level of environmental exposure to some agent (e.g., alcohol; McGue et al., 2010). In this design, since monozygotic (MZ) twins share all genetic and shared environmental influence, comparisons between members of an MZ twin pair account for all familial genetic/shared environmental influences, whether measured or not, that may confound any potential nonshared environmental causal effect of AAU on some outcome (e.g., EEG dynamics). As dizygotic (DZ) twins share half of their genetic material, comparisons between

members of a DZ twin pair account partially for genetic and fully for shared environmental influence. The CTC method provides a powerful test of the causal effects of alcohol exposure on the brain, since the neural dynamics of the lesser-drinking twin are a close approximation of the expected dynamics of the heavier-drinking twin had he/she drank less. When testing the causal effects of AAU on neurocognitive functioning, if early alcohol exposure has a deleterious causal effect on cognitive control-related theta-band dynamics, the twin who drank more during adolescence should display less activity than the cotwin who consumed less alcohol. In contrast, if a familial vulnerability towards both AAU and weak theta-band dynamics underlies the association, the brain dynamics of both the heavier- and lesser-drinking twins should not differ (McGue et al., 2010).

A second complementary method to examine etiology is biometric modeling, which estimates the amount of genetic and environmental influence shared across both AAU and theta-band dynamics that explains their observed phenotypic association. In this method, the genetic (or environmental) factors underlying AAU are allowed to correlate with the same genetic (or environmental) factors underlying theta activity. Evidence of a causal effect of AAU on reduced theta dynamics would be consistent with a significant overlap between the same nonshared environmental influences on both AAU and theta activity. In contrast, evidence for a genetic (or shared environmental) influence underlying the AAU-theta association would be consistent with a significant overlap between the same genetic (or shared environmental) factors shared across AAU and theta dynamics.

The current study was designed to evaluate whether normative levels of adolescent alcohol exposure are associated with reduced cognitive control-related theta dynamics in adulthood, and if so, whether the association is consistent with the potentially causal effects of AAU or a premorbid familial risk characteristic. A large prospective population-based sample of same-sex twins was assessed throughout adolescence and into adulthood, with comprehensive assessments of alcohol use (e.g., number of intoxications; maximum consumption; frequency/quantity of drinking) obtained at multiple points spanning adolescence (ages 11/14/17), and EEG correlates of cognitive control processes recorded at age 29. This prospective, genetically-informed twin design is thus well suited to test etiological hypotheses regarding the genetic and/or environmental influences underlying the link between adolescent alcohol exposure and adult cognitive control-related EEG components.

We hypothesized that greater AAU would be associated with reduced adult conflict-related theta-band MFC power and MFC-dPFC connectivity, which if true, would support a link between adolescent drinking and diminished cognitive control-related processes in adulthood. Significant drinking effects were followed up using two complementary methods to test etiological hypotheses. First, a cotwin control analysis of within-twin-pair differences in AAU, where the lesser-drinking twin provides a natural control for the heavier-drinking cotwin (McGue et al., 2010), was conducted to test the potential causal effects of AAU on adult theta dynamics. Second, biometric modeling was used to estimate the specific nature of any potential familial (genetic/shared environmental) or nonshared environmental influence underlying the AAU-EEG

relationship. Given research supporting both the heritability of alcohol-related brain dysfunction (Iacono et al., 2008) and the potential causal effects of adolescent drinking on the brain (Jacobus and Tapert, 2013), we had two hypotheses regarding etiological influences:

1. If adolescent drinking has a causal effect on theta-band dynamics in adulthood, then a) within a twin pair, the heavier drinking twin should exhibit decreased theta activity than the lesser drinking twin (reflected by a significant within-pair CTC effect), and b) biometric modeling should be consistent with a significant nonshared environmental correlation between AAU and theta.
2. If familial factors underlie the association between adolescent drinking and reduced adult theta dynamics, then a) within a twin pair, theta activity should not differ between the heavier and lesser drinking twin (reflected by a non-significant within-pair CTC effect), and b) biometric modeling should be consistent with a familial influence underlying the AAU/theta covariation, with the relative magnitude of genetic/shared environmental correlations casting light on the specific nature of the familial influence.

## **Methods**

### **Participants**

Participants were MZ and same-sex DZ twins drawn from the community-based Minnesota Twin Family Study, who were initially assessed at age 11 and then followed

up approximately every three or four years (for details, see Iacono and McGue, 2002; Iacono et al., 2006). Twins who had adolescent alcohol use data at the target assessment ages of 11 (age:  $M [SD] = 11.7 [0.4]$ ), 14 ( $14.7 [0.5]$ ), and 17 ( $18.1 [0.7]$ ), and flanker EEG data at age 29 ( $29.1 [0.5]$ ) served as participants for the present study. The sample consisted of 718 twins (395 females), with 459 MZ (196 complete pairs) and 259 DZ twins (105 complete pairs).

### **Adolescent alcohol use at ages 11, 14, and 17**

To quantify adolescent alcohol use (AAU), a composite drinking index was calculated by summing responses from four self-report drinking items: (1) total number of times intoxicated from alcohol (0 = never to 6 = 150 times or more), (2) frequency of drinking in the past 12 months (0 = never to 5 = two or more times every day), (3) typical number of drinks consumed in one session in the past 12 months (0 = none to 6 = 30 or more), and (4) the maximum number of drinks consumed in a 24-hr period since last assessment (0 = none to 6 = 30 or more). At ages 11 and 14, the participants reported on their history of alcohol, nicotine, and other substance use using a computerized substance use (CSU) inventory that was conducted in a private room. At age 17, alcohol and other substance use history was obtained with the Substance Abuse Module (SAM) of the Composite International Diagnostic Interview (Robins et al., 1987), which was administered by trained interviewers. The composite drinking index was calculated separately for each adolescent assessment (11, 14, 17), and then the sum of the three drinking index scores was calculated (possible range: 0–69; see Table S1 in Supplement for descriptive statistics) and used as the measure of AAU in the current report.



Each of these four measures tap different aspects of alcohol exposure and exhibited high within-age item-level correlations (Table S2 in Supplement), and combining them into a single composite measure both produces a measure of AAU that arguably has greater construct validity than any single item and decreases the risk of observing false-positive findings by conducting item-wise tests. Prior research offers strong support for the construct and psychometric validity of this composite index, including high internal consistency and expected parent-offspring correlations when assessed throughout adolescence (McGue et al., 2014). In addition, higher index scores have been associated with reduced prefrontal grey matter volume and neurocognitive performance in adolescents (Malone et al., 2014; Wilson et al., 2015), and diminished response inhibition-related theta-band MFC power and MFC-dPFC connectivity in young adults (Harper et al., 2016).

Furthermore, we examined the degree to which this composite index of AAU is related to pathological alcohol use during adolescence. At the age 17 assessment, lifetime presence of Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (American Psychiatric Association, 1994), alcohol abuse or dependence was established using a best-estimate approach, which uses both adolescent self-reported symptoms as well as parental report on the child (see Iacono et al., 1999, for interviewing and diagnostic details). By age 17, 4.3% ( $n = 31$ ) participants met criteria for alcohol dependence, and 11.8% ( $n = 85$ ) met criteria for abuse. AAU scores were significantly higher in those individuals diagnosed with an alcohol use disorder (AUD; collapsed across dependence/abuse) by the age 17 assessment ( $M [SD] = 16.65 [6.15]$ ,  $n = 116$ ) than those

without ( $M [SD] = 5.16 [5.12]$ ,  $n = 602$ ;  $F(1,696) = 307.34$ ,  $p < 0.001$ ), and AAU scores were highly correlated with total AUD symptom counts ( $r = 0.61$ ). These results indicate that a portion of this sample were problematic drinkers by age 17 (at a rate comparable to those reported in similar samples [Elkins et al., 2006]), and suggest that the continuously distributed composite AAU index is related to psychopathological measures of alcohol misuse.

### **Flanker task and EEG recording at age 29**

Behavioral and EEG data were collected at age 29 during a modified version of the Eriksen flanker task (Eriksen and Eriksen, 1974). During each trial, a target letter (S or H) was flanked by distractor letters that were either congruent or incongruent with the center target, which created a set of four stimulus array that occurred with the following frequencies: SSSSS (33.3%), HHHHH (33.3%), SSHSS (16.7%), and HHS HH (16.75%). Letters were presented centrally in white text on a black background. Participants were asked to respond quickly and accurately by making a right or left button press to each target. The task consisted of three blocks of 150 pseudorandomized trials (100 congruent / 50 incongruent), and the target-stimulus hand mapping alternated across blocks (Blocks 1 and 3:  $S = \text{right}$ ,  $H = \text{left}$ ; Block 2:  $S = \text{left}$ ,  $H = \text{right}$ ). Short breaks and feedback regarding accuracy were given after each block. The stimulus duration was 100 ms, response window was 1150 ms, and intertrial interval (fixation point) varied between 900 and 1100 ms. Participants completed a set of practice trials before EEG recording.

EEG signals were recorded from 61 scalp electrodes (10/10 placement) at 1024 Hz with an analog DC to 205 Hz bandpass filter using the BioSemi ActiveTwo system

(Biosemi, Amsterdam, Netherlands). Vertical and horizontal electrooculogram (EOG) signals were recorded from four electrodes placed above and below the right eye and bilaterally on the temples, respectively, and electrodes were placed on both earlobes to serve as an offline average reference.

### **EEG signal processing**

Signals were processed offline using MATLAB (version 7.1, Mathworks, Inc.) and EEGLAB software (Delorme and Makeig, 2004). First, continuous signals were down sampled to 256 Hz, highpass filtered at 0.1 Hz (*firfilt* EEGLAB plugin; Kaiser window, order of 1286), and re-referenced to the averaged earlobe signals. An automated pipeline was used to identify and remove instances of artifacts and inter-electrode electrolyte bridging (Tenke and Kayser, 2001). Descriptive statistics (e.g., absolute temporal variance) were calculated for each electrode and 1s time-range in the continuous data, and data that exceeded four normalized median absolute deviations relative to the median (Rousseeuw and Croux, 1993) in 25% or 75% of a 1s time-range or electrode, respectively, were deleted. To correct for ocular artifacts, EEG signals were decomposed into independent components (ICs) with the Infomax algorithm (Bell and Sejnowski, 1995). The spatial and temporal characteristics of each IC were correlated with the time course of a criterion channel (bipolar vertical or horizontal EOG) and the prototypical topography (inverse weight) of a blink or saccade IC. Components were subtracted from the data if the squared correlation coefficient exceeded an empirically derived threshold derived by an expectation maximization algorithm (Mognon et al., 2011).

Next, epochs of  $\pm 2$  s aligned to stimulus onset were taken, and screened for artifacts (as detailed above). Deleted electrodes were interpolated via a spherical spline method (Perrin et al., 1989) within epochs containing  $\geq 75\%$  of the original data/electrodes; otherwise, the trial/epoch was discarded. Error trials were excluded to avoid mixing processes related to conflict processing with error-related processes, and trials within blocks with accuracy  $\leq 50\%$  were excluded (3.5% across all subjects/blocks). Epochs were baseline corrected by subtracting the mean prestimulus activity from -200 to -1 ms, and down sampled to 128 Hz. Finally, trial-level EEG signals were scalp Laplacian (current source density) transformed (Lagrange order = 50;  $m = 4$ ;  $\lambda = 10^{-5}$ ) using a spherical spline surface (Kayser and Tenke, 2006). The Laplacian is a reference-free spatial filter recommended for connectivity analyses (Cohen, 2015a), which attenuates spatially-broad volume-conducted activity (e.g., single source projected to multiple electrodes) that can positively bias functional connectivity estimates (Winter et al., 2007).

### **EEG time-frequency analysis**

Single-trial signals were transformed into time-frequency representations via wavelet convolution (Cohen, 2014) by multiplying the EEG power spectrum (calculated via fast Fourier transform [FFT]) by the power spectrum of complex Morlet wavelets [ $e^{i2\pi ft} e^{-t^2/(2\sigma^2)}$ ], where  $f$  is frequency (ranging from 2 to 40 Hz in 25 logarithmic steps),  $t$  is time, and  $\sigma$  defines the width of each frequency band, which was set according to  $c/(2\pi f)$ , where  $c$  is the number of wavelet cycles (increasing from 3.5 to 8 in 25 logarithmic steps to obtain comparable time/frequency precision), and then taking the

inverse FFT. The complex signals were down sampled in time to 64 time bins/second. Since unequal trial numbers between conditions can bias power and functional connectivity estimates, for each subject, a random sample (without replacement) of incongruent trials was selected to match the number of congruent trials ( $M$  [ $SD$ ] = 132.90 [34.35]) before calculating power and interelectrode connectivity. This was performed 25 times, and the results were averaged.

**Time-frequency power.** From the resulting complex signal  $Z_t$ , an estimate of the frequency-specific power at each time point was calculated as  $[\text{real}(Z_t) + \text{imag}(Z_t)]^2$ . The trial-averaged power was decibel transformed ( $\text{dB Power}_{tf} = 10 \times \log_{10}[\text{Power}_{tf}/\text{Baseline Power}_f]$ ), where, for each channel, frequency, and condition, the average prestimulus power from  $-250$  to  $-50$  ms served as the baseline power.

**Functional connectivity.** Interelectrode functional connectivity was calculated with the weighted phase-lag index (wPLI; for a discussion and mathematical definition, see Vinck et al., 2011), which is defined as:

$$\frac{|E\{\Im\{X\}|\text{sgn}(\Im\{X\})\}|}{E\{\Im\{X\}\}}$$

where  $E\{\cdot\}$  is the expected value operator,  $X$  is the cross-spectrum of the complex signals (obtained from the wavelet analysis) between two electrodes,  $Z_1$  and  $Z_2$ , which is equal to  $Z_1$  multiplied by the complex conjugate of  $Z_2$ ,  $\text{sgn}$  is the sign function, and  $\Im\{X\}$  is the imaginary component of the cross-spectrum. In other words, the wPLI is the absolute value of the average sign of phase differences over trials between two electrodes, weighted by the average distance of the phase differences from the real axis, and values can range from 0 (no connectivity, or  $0^\circ/180^\circ$  phase lag differences due to volume

conduction) to 1 (perfect non-0°/180° phase-lagged functional connectivity). Because single source volume conducted activity creates a cross-spectrum that has no phase lag (0°/180°) and can spuriously inflate connectivity estimates, the wPLI partials out no and random phase lag differences and is thus a measure of connectivity largely insensitive to volume conduction artifacts compared to other measures (Vinck et al., 2011; Cohen, 2015b). To remove tonic interelectrode connectivity not modulated by task demands, the wPLI values were baseline corrected for each electrode/frequency/condition by subtracting the mean prestimulus wPLI between -250 to -50 ms ( $wPLI_{tf} = wPLI_{tf} - \text{Baseline } wPLI_f$ ).

### **Time-frequency component selection**

As depicted in Figure 1A, theta power values were calculated as the average power over a region of interest (ROI) spanning 3-8 Hz and 250-578 ms post-stimulus separately for each condition and subject, defined by the grand average time-frequency power representation. As expected, the topographic map of theta power incongruent–congruent condition contrast demonstrated a focal increase over midfrontal electrode FCz, and power at this electrode was chosen for statistical analysis of medial frontal cortex (MFC) theta power.

Guided by prior work (Cohen and Cavanagh, 2011; Nigbur et al., 2012) and a priori hypotheses regarding theta-band functional connectivity between MFC and dorsal prefrontal cortex (dPFC) electrodes during response conflict/cognitive control (Clayton et al., 2015), pairwise wPLI values were calculated between MFC seed electrode FCz and all other channels. As seen in Figure 1B, the grand average plots of connectivity between

FCz and a cluster of dPFC electrodes (Fz/F1-4/AFz/AF3-4) revealed a focal connectivity enhancement across a 3-8 Hz and 250-578 ms post-stimulus window (the same ROI used for the power analysis). The incongruent–congruent contrast topographic map of mean wPLI values across this ROI demonstrated robust connectivity between the MFC seed electrode FCz and dPFC electrodes. The mean wPLI across this ROI was calculated and pooled across dPFC electrodes for each subject and condition. For convenience, this measure is referred to as MFC-dPFC connectivity below. While MFC-based connectivity was observed with other areas, particularly midcentral/lateral parietal regions, the decision to focus on dPFC connectivity was guided by a priori hypothesis regarding MFC-dPFC connectivity during cognitive control (Cavanagh and Frank, 2014; Clayton et al., 2015).

### **Statistical analyses**

Statistical analyses were conducted in R (R Core Team, 2015). Linear mixed models (LMMs) were fit using lmer from the lme4 package (Bates et al., 2015) with Kenward-Roger adjusted denominator degrees of freedom from the lmerTest package (Kuznetsova et al., 2014). Random intercepts at the individual and twin-pair level accounted for within-individual and -pair correlations, respectively. The fixed effect of stimulus category (incongruent, congruent) on behavior and the EEG measures was evaluated with one-level LMMs.

To examine the individual-level association between adolescent alcohol use and theta-band MFC power, MFC-dPFC connectivity, or behavioral measures, separate

LMMs were fit to incongruent or congruent data with a fixed effect of drinking index scores.

Significant AAU effects were followed up with a cotwin control analysis, where LMMs were fit with a fixed effect for the within-pair AAU effect (Begg and Parides, 2003), which is the deviation of each individual twin's drink index score from his/her twin-pair drink index mean. The within-pair effect reflects the nonshared environmental effects of AAU unconfounded by shared genetic/environmental influences, and is therefore a more appropriate test of causal exposure effects (Begg and Parides, 2003; McGue et al., 2010). Within-pair comparisons of MZ and DZ pairs provide a complete shared environmental control, while MZ pairs provide complete genetic control and DZ pairs provide partial (50%) genetic control. A significant within-pair effect for theta dynamics suggests a causal effect of AAU on the EEG measure, while observing an effect at the individual level in the absence of a significant within-pair effect suggests that the individual-level effect is due primarily to familial factors shared by twins that are confounded with exposure and theta dynamics (McGue et al., 2010).

Bivariate Cholesky models, which treat the twin pair as the unit of analysis, were estimated to determine the respective roles of genes and environment on the association between AAU and each respective theta measure. Figure 2 provides a graphical depiction of these models, which decompose the phenotypic correlation between theta dynamics and AAU into that due to additive genetics (A), shared environment (C), and nonshared environment (E), and allow the ACE influences on AAU to correlate with the same influences on adult theta dynamics. The magnitude of the genetic, shared environmental,



and nonshared environmental correlations between AAU and theta indexes the degree to which such influences are common to both phenotypes. The nonshared environmental correlation is analogous to the within-pair effect in CTC analyses, whereas the genetic and shared environmental correlations reflect the familial factors underlying AAU-EEG associations in the absence of a significant nonshared environmental (within-pair) effect. These models also estimate the proportion of the phenotypic correlation between AAU and theta dynamics that is explained by genetic and environmental factors. Biometric models were fit to the raw data using full information maximum likelihood to adjust parameters for missing data in the OpenMx package in R (Boker et al., 2011). Initially, a base model was fit that estimated all ACE influences, and the associated genetic and environmental correlations, on AAU and theta-band dynamics. Next, to test the overall relative influence of the two sources of familial influence on the AAU-theta associations, the fit of the base model was compared to more restrictive and parsimonious nested models dropping either A or C (i.e., CE and AE models) on two metrics. First, change in model fit was assessed via the difference in the  $-2$  log-likelihood values ( $-2LL$ ), which approximates a  $\chi^2$  distribution, between the base and nested models using a 1 degree of freedom likelihood ratio test. A non-significant change in  $-2LL$  is considered evidence that the nested model (e.g., AE) does not significantly worsen model fit. In addition, change in model fit was compared using the Bayesian Information Criterion (BIC), which is a combined metric of goodness of fit and model parsimony, where a difference in BIC of 0–2 is considered weak evidence in support of the model with lower BIC value, and a difference of  $> 2$  is considered positive evidence (Raftery, 1995).

## Results

### Behavioral results

The expected conflict effect on behavior was observed, with greater error rates and longer reaction times in the incongruent than the congruent condition. Specifically, error rates were higher for incongruent ( $M [SD] = 4.50\% [5.58]$ ) than for congruent stimuli ( $M [SD] = 3.14 [4.54]$ ;  $t(717) = 13.26, p < 0.001$ ). Mean reaction time was slower following incongruent ( $M [SD] = 564.39 \text{ ms} [66.87]$ ) than congruent stimuli ( $M [SD] = 519.38 \text{ ms} [67.24]$ ;  $t(717) = 63.05, p < 0.001$ ). Adolescent alcohol use was not related to error rates or reaction time in either condition ( $ps \geq .19$ ).

### Descriptive statistics and intraclass correlations

Table 1 presents descriptive statistics and twin intraclass correlations for adolescent alcohol use, MFC theta power, and MFC-dPFC theta-band connectivity. In all cases, the MZ intraclass correlations were highly significant, and larger than the DZ correlations, suggesting a genetic influence on these measures.

### Response conflict modulation of theta-band dynamics

As depicted in the incongruent minus congruent difference plots in Figure 1A, MFC theta power was greater during incongruent trials than congruent trials [ $t(717) = 26.09, p < 0.001$ ]. Incongruent trials were also associated with greater theta-band functional connectivity between MFC electrode FCz and a cluster of electrodes over the dorsal prefrontal cortex (Figure 1B) than congruent trials [ $t(717) = 17.27, p < 0.001$ ].

### Adolescent alcohol use (AAU) and adult theta-band EEG dynamics

Table 2 presents the results from the separate LMMs between AAU and adult theta-band dynamics. Adolescent alcohol exposure was negatively associated with incongruent and congruent power, and incongruent MFC-dPFC connectivity. The association between AAU and congruent MFC-dPFC connectivity was not significant. These results suggest that AAU is associated with diminished cognitive control/conflict-related theta-band dynamics in adulthood.

Two complementary analytic methods (cotwin control analysis; bivariate biometric modeling) were used to investigate the etiological basis of these three significant AAU–EEG associations.

#### **Cotwin control analysis of potential causal AAU effects**

The cotwin control analysis was conducted with 301 complete twin pairs (196 MZ pairs) to test if within-twin-pair differences in AAU are related to adult theta dynamics, which if significant, would suggest a causal nonshared environmental effect of AAU on the adult EEG measures. In contrast, a non-significant within-pair effect (in the presence of the significant individual-level effects reported above) suggests that the association between AAU and EEG dynamics is likely due to familial (genetic/shared environmental) factors (McGue et al., 2010).

Within all three separate CTC models, the within-pair effect was not significantly associated with incongruent MFC power [ $t(300) = -1.07, p = 0.286$ ], congruent MFC power [ $t(300) = -0.53, p = 0.594$ ], or incongruent MFC-dPFC connectivity [ $t(300) = -1.03, p = 0.306$ ]. In all cases, the within-twin pair effect did not differ between MZ and DZ twins; adding fixed-effect terms for zygosity and the zygosity by within-pair

interaction did not improve model fit [ $\Delta\chi^2_s(2) \leq 2.23$ ,  $ps \geq 0.328$ ]; thus, these terms were removed from the final models reported above. This pattern of CTC results is consistent with a preexisting familial risk, and not a causal effect of early drinking, underlying the association between AAU and reduced adult theta-band dynamics.

### **Bivariate biometric modeling of AAU and adult theta-band dynamics**

Bivariate Cholesky models were fit to determine the respective roles of genes and environment on the association between AAU and each respective theta measure. These models decompose the phenotypic correlation between theta and AAU into that due to additive genes (A), shared environment (C), and nonshared environment (E), and allow the genetic and environmental influences on AAU to correlate with the same respective influences on adult theta dynamics. The magnitude of the genetic, shared environmental, and nonshared environmental correlations reflect the degree to which such influences are common across both two measures.

Model fitting results for the three separate bivariate Cholesky models of AAU and either incongruent MFC power, congruent MFC power, or incongruent MFC-dPFC connectivity are presented in Table 3. In all cases, the model fitting results indicated that dropping A from the models significantly worsened fit, as evidenced by significant likelihood ratio tests and more positive BIC values compared to the base ACE model. In contrast, dropping C from all three models had a negligible effect on model fit, as indicated by non-significant likelihood ratio tests and more negative BIC values than the base ACE model, which suggests no significant contribution of shared environmental effects to AAU or adult theta-band dynamics.

Table 4 presents the parameter estimates and 95% confidence intervals derived from the best fitting bivariate AE models for each separate theta-band measure. Both AAU and theta-band dynamics showed significant genetic heritability. There were modest but statistically significant negative phenotypic correlations between AAU and adult theta-band measures. As expected given the cotwin control results, the nonshared environmental correlations ( $rE$ ) between each EEG measure and AAU were effectively zero, while the genetic correlations ( $rG$ ) were modest and statistically significant. In addition, a large majority (79-99%) of the phenotypic correlation between AAU and each respective theta measure was due to common genetic influences.

Overall, the results of the bivariate biometric modeling are consistent with those obtained from the cotwin control analysis, which together suggest that heritable genetic factors, and not a nonshared environmental alcohol exposure effect, underlie the association between AAU and diminished adult theta-band dynamics.

### **Discussion**

The present study evaluated the association between adolescent alcohol use and adult EEG correlates of cognitive control processes in a large population-based twin sample prospectively assessed at ages 11, 14, 17, and 29. Consistent with past work reporting an association between AAU and various brain anomalies, we found that greater adolescent alcohol exposure was negatively associated with reduced theta-band MFC power and MFC-dPFC functional connectivity during demands of response conflict/cognitive control at age 29. A novel contribution of the current study derived from our use of a longitudinal twin design to examine the genetic and environmental

influence on the prospective association between AAU and adult theta. Findings from two complementary tests of etiology (cotwin control analysis of within-twin-pair differences in drinking; bivariate biometric modeling) jointly suggested that the relationship between diminished adult theta-band dynamics and AAU was best explained by heritable genetic influences. The current report provides, to the best of our knowledge, the first evidence that adolescent drinking is related to reduced adult cognitive control-related theta dynamics, and that a premorbid genetic risk towards early alcohol use, and not the direct causal effect of alcohol exposure, likely underlies the relationship between adolescent drinking and diminished adult theta dynamics. As such, deviations in theta dynamics appear to possess key characteristics required of an endophenotype for AAU (Iacono et al., 2016). Should genetic variants associated with theta dynamics be identified, our findings have the potential to provide insights into how these variants are related to brain function associated with AAU liability.

Heavier adolescent drinking was negatively associated with reduced adult theta-band power over the MFC during incongruent and congruent trials, and functional connectivity between the MFC and dPFC regions during incongruent trials. This finding supports the hypothesis that AAU is related to diminished cognitive control and prefrontal cortex processes, and is consistent with previous work detailing prefrontal cortex dysfunction in early drinkers (Jacobus and Tapert, 2013; Welch et al., 2013). In the context of recent models of cognitive control (Cavanagh and Frank, 2014; Clayton et al., 2015), the consequence of diminished theta-band dynamics may be a reduced ability to ignore irrelevant distracting information to suppress an inappropriate competing

response (MFC power), and decreased execution of behavioral adaptation/cognitive control processes to resolve conflict (MFC-dPFC connectivity). Overt behavioral performance did not relate to AAU, which suggests that EEG correlates of response conflict/cognitive control may be more closely associated with adolescent drinking than performance-based measures.

Converging evidence from the cotwin control analysis of within-pair differences in adolescent alcohol exposure and bivariate biometric modeling suggested that the association between AAU and theta dynamics was consistent with a premorbid genetic risk towards both early drinking and reduced theta in adulthood. Results of the cotwin control analysis suggested that within-pair differences in AAU were not related to MFC power or MFC-dPFC connectivity; in other words, within a twin pair, the heavier drinking twin exhibited MFC power and MFC-dPFC connectivity comparable to his/her lesser drinking cotwin. The CTC results argue against a causal effect of adolescent alcohol exposure on adult theta-band dynamics, as a deleterious causal effect should produce a difference between heavier- and lesser-exposed twins (e.g., decreased theta in the greater exposed twin), and these findings are instead consistent with a familial confounding underlying the individual-level association (McGue et al., 2010). In addition, the bivariate biometric modeling provided corroborating support for a familial association between AAU and theta-band dynamics. The modeling suggested that AAU and theta-dynamics were heritable, and, though the genetic correlations between AAU and each theta measure were modest in size, shared genetic factors accounted for a majority of the phenotypic association between AAU and reduced adult theta. Taken

together, the results of these two methods of testing etiological hypotheses provide strong evidence that the association between adolescent alcohol use and reduced theta-band correlates of cognitive control in adulthood is better explained by genetic influences common to both phenotypes, rather than a direct effect of alcohol exposure on the brain.

The finding that conflict-related theta-band EEG activity and AAU share a common premorbid genetic liability is consistent with recent theories of alcohol and substance use disorder development, which broadly propose that a core risk pathway to substance misuse is through poor cognitive control processes and behavioral disinhibition. In these models, a genetic vulnerability towards early-onset substance misuse is partly expressed through a preexisting dysregulation of cognitive control-related brain mechanisms, which may then lead to difficulty inhibiting inappropriate responses/impulses and/or a bias towards immediate over long-term rewards (Iacono et al., 2008; Dick et al., 2010; Zucker et al., 2011). Given the established role of MFC theta power and MFC-dPFC connectivity during demands of cognitive control (Cavanagh and Frank, 2014), it is plausible that these EEG dynamics may be candidate brain-based mechanisms or expressions of this genetic vulnerability towards alcohol/substance misuse. Taken together, these findings reflect a step towards understanding the neurophysiological correlates/potential mechanisms of alcohol-related cognitive control dysfunction and disinhibition (Iacono et al., 2008; Dick et al., 2010; Zucker et al., 2011), and strongly suggest that diminished cognitive control-related theta dynamics are part of a constellation of heritable characteristics associated with adolescent drinking.



There are of course some limitations to this study. As this report focused on normative levels of adolescent drinking in an epidemiologically-derived sample, the results may not easily generalize to clinical populations or adolescents with severe alcohol exposure. However, it should be noted that 16% of our sample ( $n = 116$ ) did meet clinical criteria for an alcohol use disorder by age 17, suggesting that problematic adolescent drinking was represented in our sample. Similarly, these results may not generalize to cases of very early exposure, as very few twins reported any alcohol use prior to age 11. Additionally, given our focus on adolescent drinking, we did not explore the effects of adult alcohol use on brain dynamics. As the genetic and environmental influences on alcohol use behaviors changes with age (Vrieze et al., 2012), future work should explore whether the etiological influence underlying the AAU-theta association changes across the lifespan. Finally, despite the large sample size, the failure to find an environmental influence may be due to a lack of power, and thus a potential environmental influence cannot be unequivocally ruled out.

These results provide strong evidence suggesting that a heritable genetic vulnerability underlies the comorbidity between adolescent drinking and diminished adult conflict-related prefrontal theta-band dynamics, and offer empirical support for theoretical models implicating poor cognitive control processes as an expression of the genetic liability towards behavioral disinhibition and early-onset substance misuse.

## Tables

**Table 1.** Descriptive statistics and twin intraclass correlations

	Mean (SD)	Intraclass Correlations (95% CI)	
		MZ	DZ
AAU	7.01 (6.78)	0.79 (0.74, 0.83)	0.53 (0.40, 0.63)
Incongruent MFC theta power	2.42 (1.40)	0.54 (0.45, 0.62)	0.20 (0.04, 0.34)
Congruent MFC theta power	1.71 (1.07)	0.57 (0.48, 0.64)	0.24 (0.09, 0.39)
Incongruent MFC-dPFC theta functional connectivity	0.10 (0.09)	0.34 (0.22, 0.44)	0.22 (0.07, 0.37)
Congruent MFC-dPFC theta functional connectivity	0.06 (0.06)	0.32 (0.21, 0.43)	0.18 (0.02, 0.33)

*Notes:* Abbreviations: AAU = adolescent alcohol use; MFC = medial frontal cortex (electrode FCz); dPFC = dorsal prefrontal (electrodes Fz/F1-4/AFz/AF3-4); MZ = monozygotic; DZ = dizygotic; CI = confidence interval. Values are in decibels for power, and weighted phase lag index units for theta-band connectivity (all relative to a -250 to -50 baseline). Sample sizes for intraclass correlations were 459 MZ twins (196 full pairs) and 259 DZ twins (98 full pairs).

**Table 2.** Relationship between medial frontal theta-band dynamics and adolescent drinking

	MFC Power Incongruent		MFC Power Congruent		MFC-dPFC FC Incongruent		MFC-dPFC FC Congruent	
	<i>t</i> (df)	<i>p</i> -value	<i>t</i> (df)	<i>p</i> -value	<i>t</i> (df)	<i>p</i> -value	<i>t</i> (df)	<i>p</i> -value
AAU	-2.71 (643)	0.007	-2.34 (652)	0.026	-2.78 (599)	0.006	-1.56 (592)	0.120

*Notes:* Results of the separate linear mixed models of the relationship between AAU and theta-band MFC power or MFC-dPFC functional connectivity for incongruent or congruent Flanker conditions. *P*-values were calculated via Kenward-Roger approximation.

Abbreviations: AAU = adolescent alcohol use; MFC = medial frontal cortex; dPFC = dorsal prefrontal cortex; FC = functional connectivity.

**Table 3.** Fit statistics for full and nested bivariate models

Models	-2LL	df	BIC	$\Delta$ BIC	$\Delta$ -2LL	<i>p</i> -value
AAU – MFC Power Incongruent						
Base ACE Model	6999.38	1425	7065.75			
<b>Drop C</b>	<b>7001.67</b>	<b>1428</b>	<b>7049.94</b>	<b>-15.81</b>	<b>2.29</b>	<b>0.515</b>
Drop A	7040.58	1428	7088.84	23.09	41.20	< 0.001
AAU – MFC Power Congruent						
Base ACE Model	6609.65	1425	6676.02			
<b>Drop C</b>	<b>6611.86</b>	<b>1428</b>	<b>6660.12</b>	<b>-15.90</b>	<b>2.21</b>	<b>0.531</b>
Drop A	6654.07	1428	6702.33	26.31	41.42	< 0.001
AAU – MFC-dPFC FC Incongruent						
Base ACE Model	7430.10	1425	7496.47			
<b>Drop C</b>	<b>7433.01</b>	<b>1428</b>	<b>7481.27</b>	<b>-15.20</b>	<b>2.91</b>	<b>0.407</b>
Drop A	7462.36	1428	7510.63	14.16	32.26	< 0.001

*Notes:* Model fit indices for the bivariate models. To test the relative contribution of genetic/shared environmental influence, relative fits for the nested models dropping C or A influence (AE or CE models, respectively) were compared to the base ACE models on two metrics: 1) change in BIC ( $\Delta$ BIC), which is a combined metric of goodness of fit and model parsimony, with lower BIC values indicating better relative fit, and 2) change in the -2LL ( $\Delta$ -2LL), which follows a  $\chi^2$  distribution, using a likelihood ratio test. The best-fitting models are in bold. In all cases, dropping the shared environmental influence did not worsen fit, whereas dropping the additive genetic influence significantly degraded model fit.

Abbreviations: -2LL = -2 log likelihood value; df = degrees of freedom; BIC = Bayesian information criteria (parameter-adjusted); A = additive genetic effects; C = shared environmental effects; E = nonshared environmental effects; AAU = adolescent alcohol use; MFC = medial frontal cortex; dPFC = dorsal prefrontal cortex; FC = functional connectivity.

**Table 4.** Genetic and environmental influences on the association between AAU and theta-band dynamics

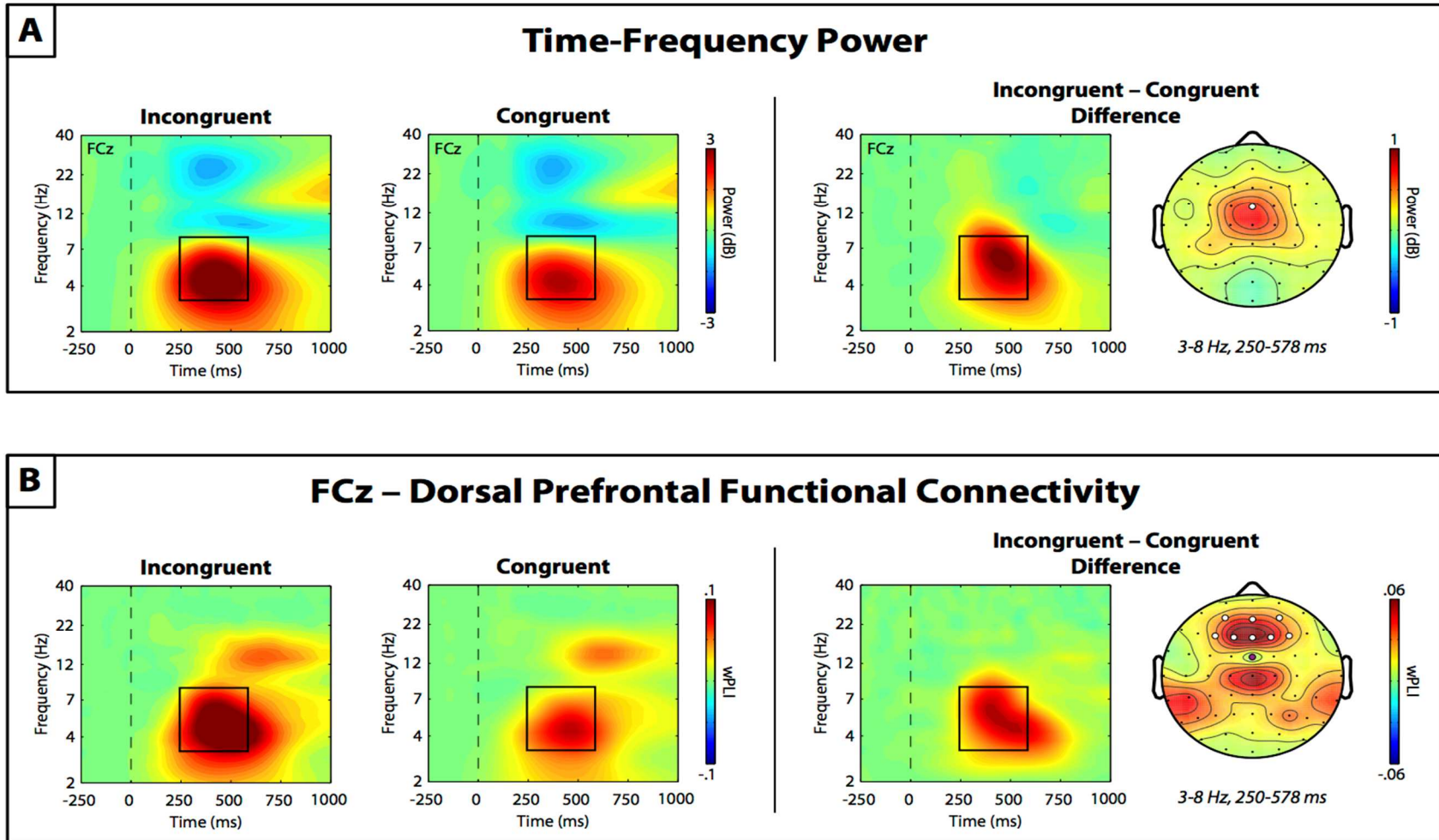
Phenotype 1 – Phenotype 2	<i>r</i>	AAU		Theta-band Phenotype		Model-implied correlations			Proportion (%) of <i>rP</i> due to	
		A	E	A	E	<i>rP</i>	<i>rG</i>	<i>rE</i>	<i>A</i>	<i>E</i>
AAU – MFC Power Incongruent	-.11	.80 (.75, .84)	.20 (.16, .25)	.52 (.42, .61)	.48 (.39, .58)	-.11 (-.19, -.03)	-.15 (-.28, -.02)	-.04 (-.17, .10)	90	10
AAU – MFC Power Congruent	-.10	.80 (.75, .84)	.20 (.16, .25)	.56 (.47, .64)	.44 (.36, .53)	-.09 (-.17, -.01)	-.14 (-.27, -.01)	-.01 (-.14, .13)	99	1
AAU – MFC-dPFC FC Incongruent	-.12	.80 (.75, .84)	.20 (.16, .25)	.34 (.22, .45)	.66 (.55, .78)	-.11 (-.19, -.03)	-.17 (-.33, -.01)	-.06 (-.19, .07)	79	21

*Notes:* Parameter estimates from the separate bivariate AE Cholesky models between AAU and each theta-band EEG measure.

Abbreviations: AAU = adolescent alcohol use; MFC = medial frontal cortex; dPFC = dorsal prefrontal cortex; FC = functional connectivity; *r* = observed phenotypic correlation; A = additive genetic effects with 95% confidence intervals (CIs); E = nonshared environmental effects; *rP* = model-implied phenotypic correlation; *rG* = genetic correlation; *rE* = nonshared environmental correlation.

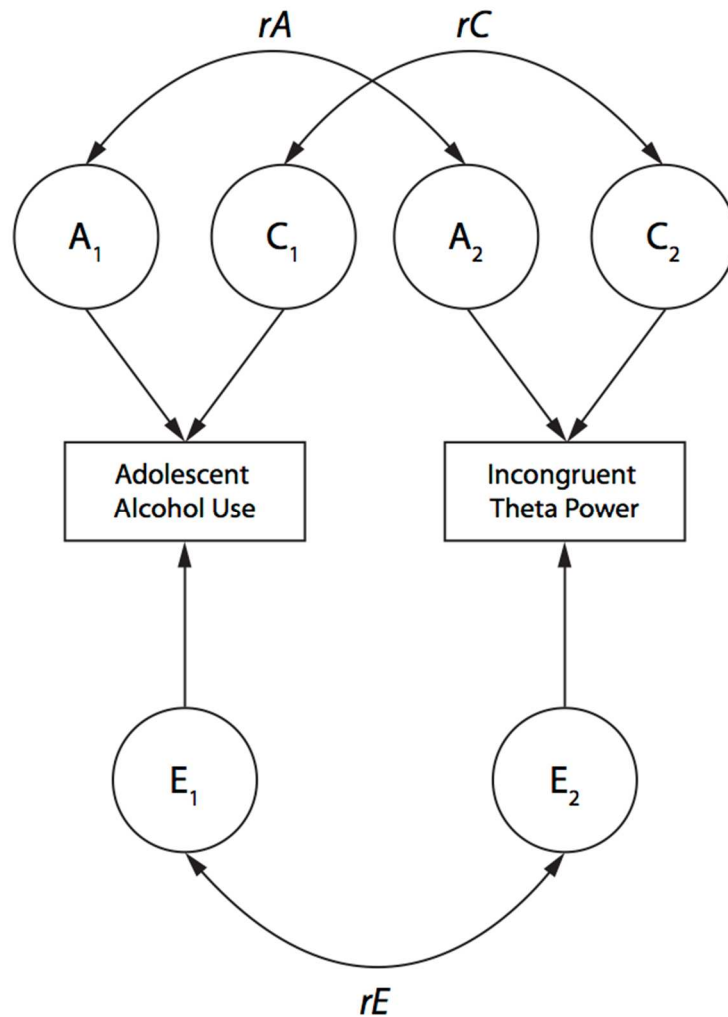
## Figures

**Figure 1.** Time-frequency theta-band (3-8 Hz) EEG dynamics.



**(A)** Left: The grand average time-frequency plots of stimulus-locked (time = 0, dashed line) power at medial frontal cortex channel (FCz) for incongruent and congruent conditions. Note the strong increase in theta-band power following incongruent stimuli. Right: The response conflict effect (difference between incongruent and congruent trials) on time-frequency power. The time-frequency plot of the response conflict effect for power at FCz (white electrode) and the associated topographic distribution of theta-band power, which show robust theta power enhancement over the medial frontal cortex for incongruent trials. **(B)** Left: Same as (A), but for FCz-seeded (purple electrode) functional connectivity as measured by the weighted phase lag index (wPLI). These plots illustrate enhanced connectivity between a medial frontal cortex channel (FCz) and a cluster of dorsal medial and dorsolateral prefrontal channels (dPFC; white electrodes), which is augmented during incongruent trials. The black outline boxes denote the region of interest used for statistical analyses.

**Figure 2.** Graphical depiction of a general bivariate ACE model.



Graphical depiction of a general bivariate ACE model illustrating the variance in each individual phenotype parsed into that explained by additive genetic ( $A$ ), shared environmental ( $C$ ), and nonshared environmental ( $E$ ) effects, and the associated genetic ( $rA$ ), shared environmental ( $rC$ ), and nonshared environmental ( $rE$ ) correlations, between adolescent alcohol use and incongruent theta-band power. The  $rE$  correlation is analogous to the within-pair exposure effect in the cotwin control analysis, while  $rA$  and  $rC$  capture the familial risk effect.



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## **Supplemental Materials**

### **Composite drinking index**

Since responses to each of the four composite index items were sparse and skewed, scores were transformed into ordinal measures (see Table S1) before summation. Table S1 presents frequency counts for each item at ages 11, 14, and 17. Bivariate associations among the four items at each assessment are presented in Table S2, which demonstrate the high degree of overlap across the four alcohol exposure measures.

At the age 17 assessment, a subset of twins ( $n = 635$ ) completed both the SAM and CSU measures, which allowed us to assess the consistency of the drinking index across the two report formats. The correlation between the two indexes was 0.89, suggesting a high degree of overlap across interview-based and computerized formats.

**Supplemental Tables**

**Table S1.** Frequency counts (%) for each item of the drinking index as a function of assessment age

<b>Frequency of drinking (past 12 months)</b>	<b>Never Drank [0]</b>	<b>“Less than once a year” or “Less than once a month, but at least once a year” [1]</b>	<b>“About once a month” or “2 or 3 times a month” [2]</b>	<b>“1 or 2 times a week” or “3 or 4 times a week” [3]</b>	<b>“Nearly every day” or “Every day” [4]</b>	<b>“2 times a day” to “3 or more times a day” [5]</b>	
Age 11	712 (99.16)	5 (0.70)	1 (0.14)	0 (0.00)	0 (0.00)	0 (0.00)	
Age 14	566 (78.83)	85 (11.84)	55 (7.66)	10 (1.39)	2 (0.28)	0 (0.00)	
Age 17	201 (27.99)	266 (37.05)	171 (23.82)	60 (8.36)	20 (2.79)	0 (0.00)	
<b>Lifetime Number of Intoxications</b>	<b>Never [0]</b>	<b>1-5 [1]</b>	<b>6-10 [2]</b>	<b>11-20 [3]</b>	<b>21-50 [4]</b>	<b>51-149 [5]</b>	<b>≥150 [6]</b>
Age 11	717 (99.86)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.14)	0 (0.00)
Age 14	644 (89.69)	48 (6.69)	11 (1.53)	11 (1.53)	3 (0.42)	1 (0.14)	0 (0.00)
Age 17	332 (46.24)	184 (25.63)	55 (7.66)	47 (6.55)	59 (8.22)	19 (2.65)	22 (3.06)
<b>Average amount consumed per drinking session (past 12 months)</b>	<b>None [0]</b>	<b>1-3 [1]</b>	<b>4-6 [2]</b>	<b>7-10 [3]</b>	<b>11-20 [4]</b>	<b>21-29 [5]</b>	<b>≥30 [6]</b>
Age 11	712 (99.16)	5 (0.70)	0 (0.00)	0 (0.00)	1 (0.14)	0 (0.00)	0 (0.00)
Age 14	566 (78.83)	91 (12.67)	39 (5.43)	13 (1.81)	9 (1.25)	0 (0.00)	0 (0.00)
Age 17	255 (35.52)	216 (30.08)	137 (19.08)	78 (10.86)	32 (4.46)	0 (0.00)	0 (0.00)
<b>Max number of drinks consumed in a 24-h period (since past assessment)</b>	<b>None [0]</b>	<b>1-3 [1]</b>	<b>4-6 [2]</b>	<b>7-10 [3]</b>	<b>11-20 [4]</b>	<b>21-29 [5]</b>	<b>≥30 [6]</b>
Age 11	712 (99.16)	5 (0.7)	0 (0.00)	0 (0.00)	1 (0.14)	0 (0.00)	0 (0.00)
Age 14	566 (78.83)	73 (10.17)	43 (5.99)	16 (2.23)	20 (2.79)	0 (0.00)	0 (0.00)
Age 17	202 (28.13)	96 (13.37)	113 (15.74)	116 (16.16)	137 (19.08)	38 (5.29)	16 (2.23)

**Table S2.** Association among alcohol use items within assessment age.

	Age 11				Age 14				Age 17			
	1	2	3	4	1	2	3	4	1	2	3	4
1. Frequency of drinking	–				–				–			
2. Average amount consumed per drinking session	.95	–			.80	–			.79	–		
3. Max number of drinks consumed in a 24-h period	.95	1.0	–		.84	.92	–		.80	.81	–	
4. Lifetime Number of Intoxications	.67	.87	.87	–	.66	.65	.69	–	.76	.73	.78	–

*Note:* Bivariate correlations between each drinking measure at each assessment age. All associations were significant at the  $p < 0.0001$  level, which was calculated via linear mixed models with random intercepts at the twin-pair level and Kenward-Roger adjusted degrees of freedom.