Psychological Medicine

cambridge.org/psm

Parietal P3 and midfrontal theta prospectively predict the development of adolescent alcohol use

Jeremy Harper, Stephen M. Malone and William G. Iacono

Department of Psychology, University of Minnesota, 75 East River Road, Minneapolis, MN 55455, USA

Original Article

Cite this article: Harper J, Malone SM, Iacono WG (2021). Parietal P3 and midfrontal theta prospectively predict the development of adolescent alcohol use. *Psychological Medicine* **51**, 416–425. https://doi.org/10.1017/S0033291719003258

Received: 29 July 2019
Revised: 11 October 2019
Accepted: 22 October 2019
First published online: 18 November 2019

Key words:
Adolescent alcohol use; EEG/ERP; endophenotype; longitudinal design; P3; theta

Author for correspondence:
Jeremy Harper, E-mail: harpe300@umn.edu

Abstract

Background. Subclinical adolescent alcohol use is highly prevalent and may have deleterious effects on important psychosocial and brain outcomes. Prior research has focused on identifying endophenotypes of pathological drinking, and the predictors of normative drinking remain understudied. This study investigated the incremental predictive value of two potential psychophysiological endophenotypes, P3 amplitude (an index of decision making) and midfrontal theta power (a correlate of attentional control), for prospectively predicting the expression and initiation of alcohol use emerging in adolescence.

Methods. A large ($N = 594$) epidemiological sample was prospectively assessed at ages 11/14/17. Alcohol/substance use was assessed at all ages via a computerized self-report inventory. EEG was recorded at age-14 during a visual oddball task to elicit P3 and theta.

Results. Reduced target-related P3 and theta at age-14 prospectively predicted drinking at age-17 independent of one another. Among alcohol-naive individuals at age-14, attenuated P3 and theta increased the odds of new-onset alcohol behaviors 3 years later. Importantly, the endophenotypes provided significant incremental predictive power of future non-clinical alcohol use beyond relevant risk factors (prior alcohol use; tobacco/illicit drug initiation; parental alcohol use disorder).

Conclusions. The current report is the first of our knowledge to demonstrate that deviations in parietal P3 and midfrontal theta prospectively predict the emergence of normative/non-pathological drinking. P3 and theta provide modest yet significant explanatory variance beyond prominent self-report and familial risk measures. Findings offer strong evidence supporting the predictive utility of P3 and theta as candidate endophenotypes for adolescent drinking.

Introduction

Alcohol is one of the most commonly used substances by adolescents, with 59% reporting initiation and 43% reporting having been intoxicated by late adolescence (grade 12) (Johnston *et al.*, 2019). Early alcohol use is a reliable predictor of negative outcomes later in life, including worsened mental health and psychosocial functioning, increased likelihood of adult antisocial behavior, legal problems, escalation to alcohol/drug misuse, and development of substance use disorders (Poikolainen *et al.*, 2001; Flory *et al.*, 2004; Malone *et al.*, 2004; Wells *et al.*, 2004; Iacono *et al.*, 2008; Hicks *et al.*, 2010; Foster *et al.*, 2014; Irons *et al.*, 2015; Savage *et al.*, 2018). Evidence suggests that many of these prospective associations may be due (in part) to the potential causal effects of early drinking (Deutsch *et al.*, 2013; Irons *et al.*, 2015), and the developing adolescent brain may be particularly sensitive to the potential effects of alcohol exposure (Crews and Boettiger, 2009; Jacobus and Tapert, 2013), even at non-pathological levels (Luciana *et al.*, 2013; Squeglia *et al.*, 2015; Pfefferbaum *et al.*, 2018) (although see Malone *et al.*, 2014; Wilson *et al.*, 2015). Identifying the biological/neurocognitive factors conferring risk for the development of normative drinking is of significant importance given the high prevalence of non-pathological (relative to pathological) adolescent alcohol use (Substance Abuse and Mental Health Services Administration, 2018) and its potential deleterious outcomes, and yet this remains an under-studied area.

Alcohol and substance use are associated with individual differences in the prefrontal cortex and related neurocognitive mechanisms, including variations in decision making and control-related attentional processes (Field and Cox, 2008; Casey and Jones, 2010; Koob and Volkow, 2010; Luciana and Collins, 2012; Jacobus and Tapert, 2013; Wiers *et al.*, 2015) that may amplify risk toward alcohol initiation/use (Iacono *et al.*, 2008; Tessner and Hill, 2010; Zucker *et al.*, 2011; Wiers *et al.*, 2015). Laboratory-based neurobehavioral endophenotypes can serve as useful tools to identify the neural mechanisms involved in the development and expression of a clinical phenotype such as alcohol use (Gottesman and Gould, 2003; Anokhin, 2014; Salvatore *et al.*, 2015; Iacono *et al.*, 2017). As indicated in a recent extensive

© Cambridge University Press 2019

CAMBRIDGE UNIVERSITY PRESS

review of psychiatric endophenotypes (Iacono *et al.*, 2017), one of the most compelling but under-researched characteristics of endophenotypes is their ability to predict onset of a clinical phenotype before its presentation. Endophenotypes that can potentially identify those at high risk for alcohol use well before initiation may have important clinical utility for early identification and prevention efforts. Despite this promising quality, more research is needed to better understand the prospective clinical utility and incremental predictive power of endophenotypes.

Arguably the most well-replicated neurobiological risk factor for alcohol use is the parietal target/oddball P3 event-related potential (ERP) (Iacono and Malone, 2011; Euser *et al.*, 2012). P3 is elicited by the detection of rare targets and is a neural correlate of decision making and signal matching, such as monitoring whether the classification of a stimulus and the associated chosen response choice is appropriate (Başar-Eroglu *et al.*, 1992; Nieuwenhuis *et al.*, 2005; Verleger *et al.*, 2005; Barry *et al.*, 2016) (for a detailed review, see Verleger and Śmigasiewicz, 2016). Among adolescents with little to no substance exposure, reduced P3 amplitude increases the odds of prospectively developing an alcohol use disorder by late adolescence/young adulthood (AUD) (Berman *et al.*, 1993; Hill *et al.*, 1995, 2009; Iacono *et al.*, 2002; Carlson *et al.*, 2004; Habeych *et al.*, 2005; Perlman *et al.*, 2013; Yoon *et al.*, 2015). From a neurocognitive perspective, diminished parietal P3 may contribute to disadvantageous decisional processes or action-monitoring processes that contribute to inappropriate actions/choices and suboptimal or problematic behaviors such as adolescent drinking. The majority of prospective P3 studies have focused on predicting pathological alcohol use in predominantly male samples (Iacono and Malone, 2011; Euser *et al.*, 2012), and work is needed to address whether P3 reduction prospectively predicts the development of normative adolescent drinking and if these effects vary by sex.

While P3 is arguably the most well-studied candidate endophenotype indexing genetic risk for alcohol use development (Iacono and Malone, 2011; Euser *et al.*, 2012; Iacono *et al.*, 2017), it is primarily an index of parietal activation (Barry *et al.*, 2019) and it is unclear whether prefrontal EEG/ERP components predict adolescent drinking. Given its suggested role in facilitating motivated behavioral responses (Delorme *et al.*, 2007; Cohen and Cavanagh, 2011; Cavanagh and Frank, 2014), individual differences in midfrontal theta rhythms may reflect an electrophysiological index of dysregulated control-related processes (e.g. attentional control, action monitoring) relevant to adolescent drinking (Iacono *et al.*, 2008; Casey and Jones, 2010; Koob and Volkow, 2010; Zucker *et al.*, 2011). Current cognitive models suggest that variations in theta, likely mediated by medial frontal/cingulate cortical sources (Makeig *et al.*, 2004; Delorme *et al.*, 2007; Cavanagh and Frank, 2014), reflect a reactive processing mechanism signaling the need for enhanced attentional allocation, orienting, and control-related processes toward salient events (e.g. rare targets; Başar-Eroglu *et al.*, 1992; Cavanagh *et al.*, 2012; Clayton *et al.*, 2015; Harper *et al.*, 2017*b*; Bachman and Bernat, 2018) during action monitoring and behavioral control (Cavanagh *et al.*, 2012; Cohen, 2014*b*; Clayton *et al.*, 2015). Prior work from our group and others suggests that reduced target-related theta power is associated with alcohol and substance use/externalizing psychopathology (Jones *et al.*, 2006; Andrew and Fein, 2010; Yoon *et al.*, 2013; Burwell *et al.*, 2014). Diminished target-related theta is also observed in the high-risk adolescent offspring of alcoholics (Rangaswamy *et al.*, 2007), and is heritable and shares genetic variance with problematic alcohol/substance use (Harper *et al.*, 2019), which offer evidence that theta represents a potential candidate endophenotype for alcohol use. However, it is unknown whether reduced midfrontal theta before alcohol initiation can prospectively predict the development of alcohol use emerging in adolescence. This key standard must be met to establish that the candidate endophenotype is state-independent and provides potential clinical utility by predicting development of the clinical phenotype.

The current study was designed to test whether reductions in parietal P3 and midfrontal theta elicited during a visual oddball task predict the normative expression and initiation of alcohol use emerging in adolescence in a large epidemiological sample prospectively assessed throughout adolescence (ages 11, 14, and 17). We hypothesized that diminished P3 and theta at age-14 would each independently predict greater self-reported alcohol use at age-17. We expected that this prospective relationship would be specific to the rare target/oddball condition due to its demands on attentional control and decision-making processes as indexed by theta and P3, respectively. We tested whether any significant effects held after accounting for prominent risk factors (parental AUD; alcohol/tobacco/illicit drug initiation by age-14). We also addressed the question of whether reduced P3 and midfrontal theta in alcohol-naive individuals at age-14 predict new-onset alcohol use by age-17. Follow-up analyses were conducted to determine if the prospective P3/theta effects held for both males and females.

Significant findings would support the hypothesis that reductions in midfrontal theta and parietal P3 are present before alcohol initiation and contribute to the development of adolescent normative drinking in late adolescence; that is, the range of alcohol use behavior and consumption arising in a community-based representative sample of children first recruited for study during the year they turned 11 years old.

Methods

Sample

Participants were adolescent same-sex twins from the longitudinal population-based Minnesota Twin Family Study Enrichment Sample (Keyes *et al.*, 2009). Participants with relevant EEG data (described below) at age-14 were considered for the present study ($N = 780$). Fifty-two were excluded for EEG recording issues; 13 were excluded for task performance ⩽50%. Of the remaining 715, 594 (303 females) had complete alcohol use data at the target ages of 11 (age: mean [S.D.] = 11.80 years [0.40]), 14 (14.93 [0.49]), and 17 (17.76 [0.36]) (see online Supplementary Material for attrition analyses). Participants were recruited from the State of Minnesota birth certificate registry and were broadly representative of Minnesota families with children living at home according to the 2000 US Census. Families were eligible to participate if they lived within a day's drive of the University of Minnesota and if the children had no physical or psychological impairment that would interfere with their providing informed assent and completing the intake assessment. Using publicly available databases (e.g. phone books, Internet directories), 82% of living registry twins were located and invited to participate, and 83% of those asked to join the study agreed to do so. For the purpose of the current study, we treated the twins as individuals while accounting for the nested structure of familial data in statistical analyses.

https://doi.org/10.1017/S0033291719003258 Published online by Cambridge University Press

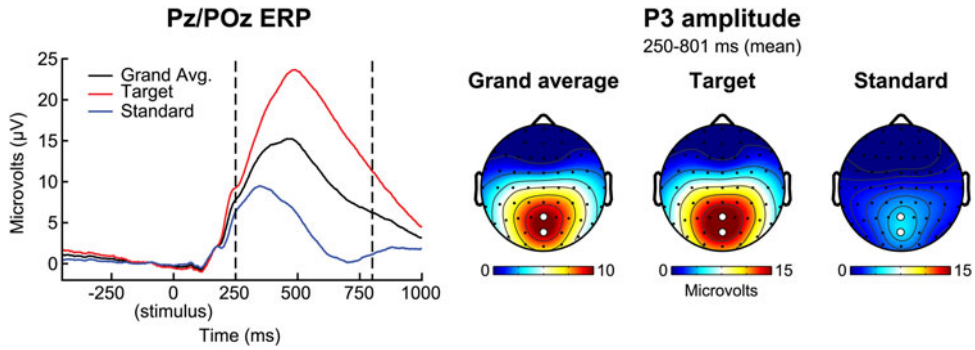


Fig. 1. Parietal P3. (Left) Grand-averaged and condition-averaged event-related potentials (ERPs) plotted as the mean across parietal electrodes Pz and POz. Dashed lines indicate the P3 time window. Stimulus onset corresponds to 0 ms. (Right) The topography of grand-averaged and condition-averaged mean P3 voltage (250–801 ms) indicating a parietal maximum at Pz and POz (white electrodes). The reader is referred to the web version of this article for the full color figure.

Alcohol and substance use assessment

At each assessment, individuals reported on lifetime and past 12-month substance use using a computerized substance use inventory (McGue *et al.*, 2014; Saunders *et al.*, 2017) administered in a private room. Age-11 and age-14 measures were aggregated to measure cumulative use/initiation by age-14.

A composite drinking index (Malone *et al.*, 2014; McGue *et al.*, 2014; Harper *et al.*, 2017*a*) measuring past 12-month alcohol use was computed by summing four items: frequency of drinking; typical number of drinks per occasion; maximum number of drinks consumed at one time; and frequency of intoxications (possible range: 0–18; see online Supplementary Table S1 for details). The index had excellent internal consistency (Cronbach's α: age-11/14 = 0.93, age-17 = 0.94; item-wise correlations: age-11/14 = 0.65–0.96, age-17 = 0.75–0.91).

Binary (yes/no) measures were used to investigate new onset of alcohol use behaviors, specifically: ever using alcohol (without parental permission); ever being intoxicated from alcohol; and ever engaging in binge drinking (consuming five or more drinks for males/four or more drinks for females, at one time) (Substance Abuse and Mental Health Services Administration, 2018).

Parents reported on their history of alcohol dependence/abuse symptoms (DSM, Fourth ed.; American Psychiatric Association, 1994) at the adolescent's age-11 and age-17 assessments (see online Supplementary Material). For each adolescent, parental alcohol use disorder (AUD) status was defined as positive if at least one parent met criteria for AUD at either assessment; 304 adolescents (169 out of 337 individual families) were positive for parental AUD.

To control for other forms of substance use initiation by age-14, tobacco use was defined as ever using tobacco (more than a small amount, e.g. at least a full cigarette/cigar), and illicit drug use was defined as ever using any of the following substances to get intoxicated (ordered in decreasing endorsement frequency): cannabis, inhalants, stimulants, psychedelics (e.g. PCP, LSD), steroids, cocaine, Quaaludes, heroin or other opiates, tranquilizers.

Oddball task

At the age-14 assessment, EEG and behavioral data were collected during a visual rotated heads oddball task (Begleiter *et al.*, 1984). Eighty target trials [stimuli: white schematic heads (oval with stylized nose and a single ear on the left or right side)] were pseudo-randomly interspersed among 160 standard trials (stimuli: white oval). Participants were asked to respond with either a right or left button press to indicate the side of the head on which the ear appeared for targets (equal number of left- or right-response targets), and to not respond to standards. The nose pointed up (easy/unrotated condition) for half of the target trials, and pointed down (hard/rotated condition) for the remainder (the easy and hard target trials were combined in all analyses). Stimulus duration was 100 ms, the response window was 1500 ms, and after the complete response window, a randomized intertrial interval (central fixation dot) separating trials varied between 1000 and 2000 ms. Relevant behavioral measures include target hit rate, mean target reaction time, and reaction time variability (intraindividual standard deviation of RT).

EEG recording, processing, and signal analysis

Continuous 61-channel EEG was collected at age-14 and processed as described in our previous reports (Harper *et al.*, 2017*b*, 2019) (see online Supplementary Material).

Trial-averaged ERPs were computed separately for target and standard trials/conditions (error trials were excluded from analyses). Based on the grand averaged ERP (Fig. 1), P3 amplitude was quantified as the mean amplitude between 250 and 801 ms (relative to a −450 to −250 ms average baseline) pooled across electrodes Pz/POz.

Trial-level signals were transformed into time-frequency representations using complex Morlet wavelet convolution (Cohen, 2014*a*) (see online Supplementary Material). Trial-averaged power was calculated separately by condition and baseline adjusted (decibel transform; separately across conditions/frequencies) relative to the mean −450 to −250 ms prestimulus power.

As shown in Fig. 2, grand averaged post-stimulus time-frequency power increased in the theta-band (3.1–6.3 Hz) between 219 and 500 ms with a midfrontal peak at FCz. Theta was quantified as the average power across this region of interest at FCz.

Statistical analyses

Statistics were conducted in R (R Core Team, 2018). Linear mixed models (LMMs) were fit using the lme4 package (Bates *et al.*, 2015) using Kenward–Roger approximated denominator degrees of freedom (Kuznetsova *et al.*, 2017). Random intercepts at the individual and family levels accounted for within-individual and within-twin-pair correlations, respectively.

https://doi.org/10.1017/S0033291719003258 Published online by Cambridge University Press

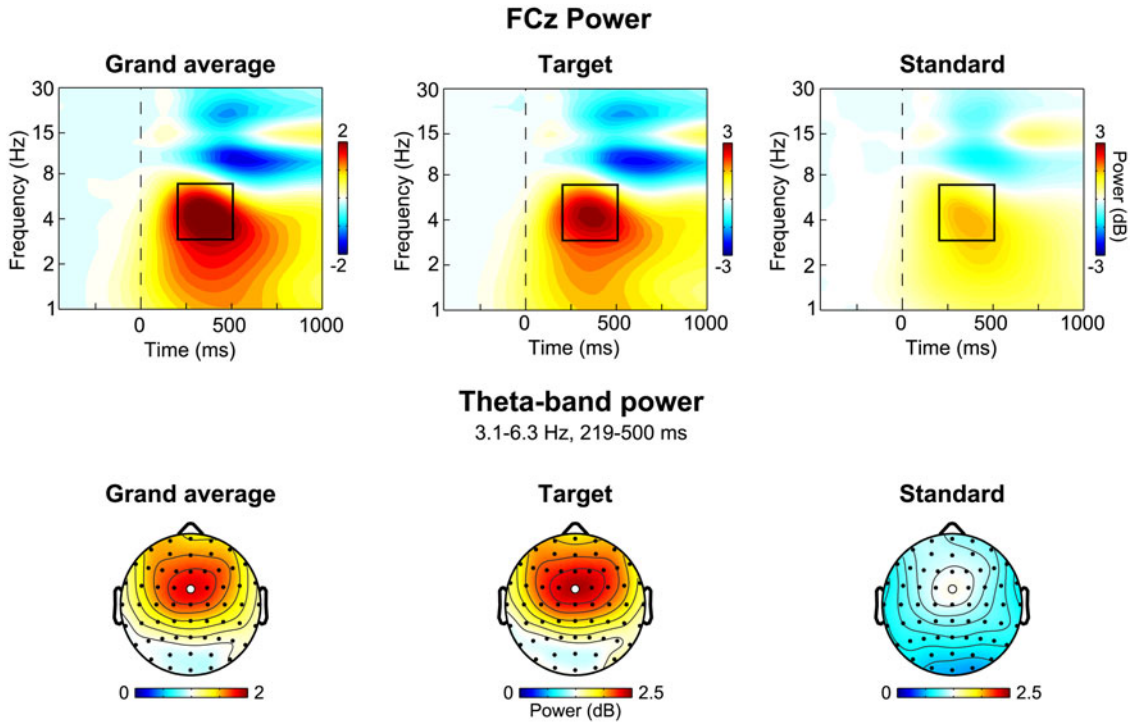


Fig. 2. Midfrontal theta power. (Top) Grand-averaged and condition-averaged time-frequency power at midfrontal electrode FCz. Black boxes denote the region of interest used for theta in statistical analyses. Stimulus onset corresponds to 0 ms. (Bottom) The corresponding topography of theta-band power (3.1–6.3 Hz, 218–500 ms) indicating a spatial maximal at midfrontal electrode FCz (white electrode). The reader is referred to the web version of this article for the full color figure.

To test if age-14 P3 and theta predicted age-17 alcohol use, a prospective LMM (*lmer* function) was initially fit as a covariate-only model with age-17 drinking index scores as the dependent variable and sex, parental AUD, and age-11/14 drinking index scores as fixed-effect predictors. Next, age-14 P3 and midfrontal theta were entered (separately for targets and standards). The fit of this model was compared to the covariate-only model using a likelihood ratio test on the difference in the −2 log-likelihood (χ^2 distribution approximation); a significant change provides evidence that P3 and theta improved model fit/prediction. Standardized regression coefficients (β) with 95% confidence intervals (Lüdecke, 2019) are presented as effect size estimates. R^2 was calculated using the method proposed by Jaeger *et al.* (2017) for LMMs.

To test whether age-14 P3 and theta predicted new onset/initiation of alcohol use behaviors in individuals with no reported alcohol use by age-14, a series of generalized LMMs (*glmer* function in lme4; logistic regressions; logit link function) were fit separately for three age-17 binary-dependent variables: ever used alcohol (without parental permission); ever been intoxicated; and ever engaged in binge drinking. Age-14 theta and P3 scores served as predictors alongside sex and parental AUD. The odds ratio (OR), reflecting change in the likelihood of developing the specified alcohol use behavior by age-17 per one-unit change in age-14 P3 or theta, was considered significant if the 95% confidence interval did not span one. We also assessed whether age-14 P3 and theta predicted the development of drinking index scores by age-17 among age-14 non-users.

To assess whether effects remained significant after accounting for other forms of substance initiation, significant findings were recomputed including tobacco or illicit drug initiation by age-14 as predictors ($n = 586$; eight participants had incomplete data).

Two sets of follow-up analyses were conducted. First, to determine if the EEG effects could be attributed to performance differences, models were fit for task-related behavioral measures [target mean RT and RT variability, target percent correct (arcsine transformed)]. Second, to evaluate whether the P3/theta effects were conditional on sex, significant models were recomputed adding an EEG (theta or P3) by sex (center effect coded for female) interaction term.

Results

Descriptive statistics

Descriptive statistics are provided in Table 1. Drinking index scores increased from age-11 to age-14 (β [95% CI] = 0.24 [0.18–0.31], $t_{(593)} = 7.27$, $p < 0.001$) and from age-14 to age-17 ($\beta = 0.32$ [0.28–0.36], $t_{(593)} = 14.65$, $p < 0.001$). Of note is the lack of use at age-11; only three individuals had non-zero index scores and no individual reported any history of intoxication. By age-14, only 121 individuals (20.4%) reported alcohol initiation. At age-17, 310 (52.2%) had initiated alcohol use. The mean drinking index score for those who initiated drinking by age-17 was 6.19 (S.D. = 4.30; range: 0–17). For those with age-17 scores of at least 6, their average past year use corresponded to drinking 1–3 times per month, 4–6 drinks each time, as many as 7–9 at one time, and having been intoxicated about once per month.

Age-14 parietal P3 amplitude was larger during target trials than standard trials (Fig. 1; $\beta = 0.77$ [0.75–0.80], $t_{(593)} = 54.31$, $p < 0.001$). Midfrontal theta was enhanced during rare target trials compared to standard trials (Fig. 2; $\beta = 0.51$ [0.47–0.54], $t_{(593)} =$

https://doi.org/10.1017/S0033291719003258 Published online by Cambridge University Press

Table 1. Descriptive statistics

Alcohol use	
Age-11	
Drinking Index	0.02 (0.24)
Quantity	0.01 (0.07)
Frequency	0.01 (0.10)
Intoxications	0.00 (0.00)
Maximum drinks	0.01 (0.07)
Ever used alcohol? (%)	7 (1.2%)
Ever intoxicated? (%)	0 (0%)
Ever binge drank? (%)	0 (0%)
Age-14	
Drinking Index	0.86 (2.35)
Quantity	0.25 (0.68)
Frequency	0.22 (0.59)
Intoxications	0.10 (0.46)
Maximum drinks	0.29 (0.80)
Ever used alcohol? (%)	121 (20.4%)
Ever intoxicated? (%)	51 (8.6%)
Ever binge drank? (%)	45 (7.6%)
Age-17	
Drinking Index	3.23 (4.39)
Quantity	0.84 (1.18)
Frequency	0.69 (0.94)
Intoxications	0.61 (1.11)
Maximum drinks	1.09 (1.48)
Ever used alcohol? (%)	310 (52.2%)
Ever intoxicated? (%)	220 (37.0%)
Ever binge drank? (%)	199 (33.5%)
Age-14 task-related EEG	
Target condition	
P3 amplitude (μV)	16.40 (6.53)
Theta power (dB)	2.42 (1.10)
Standard condition	
P3 amplitude (μV)	4.19 (2.75)
Theta power (dB)	1.30 (0.78)

μV, microvolt; dB, decibel.
Values given are mean (standard deviation) unless otherwise noted.

27.55, $p < 0.001$). Neither measure differed by sex [$|t|_{(330)} \leqslant 0.80$, $p \geqslant 0.425$].

Age-14 P3/theta predicting age-17 normative alcohol use

As shown in Table 2, reduced age-14 target P3 and theta prospectively predicted greater drinking index scores 3 years later. Theta and P3 explained unique variance in age-17 drinking scores, suggesting that these measures reflect distinct electrophysiological processes relevant to adolescent drinking (P3-theta zero-order correlation = 0.06). Notably, P3 and theta contributed incremental predictive power of age-17 drinking beyond relevant covariates, including parental AUD and age-11/14 drinking.

There was no significant effect for age-14 P3 or theta elicited by standard stimuli [$ps \geqslant 0.106$; change in model fit: $\Delta\chi^2_{(2)} = 2.96$, $p = 0.228$].

Predicting new-onset alcohol use by age-17 in age-14 non-drinkers

To determine if age-14 target P3 and theta predict the new onset of alcohol use behaviors at age-17, the following analyses were restricted to individuals with no alcohol use by age-14 ($n = 473$). Results are shown in Table 3 and Fig. 3. Smaller theta and P3 uniquely predicted greater likelihood of new-onset age-17 alcohol use initiation and binge drinking. Decreased theta predicted increased odds of new-onset alcohol intoxication; the P3 effect was in the expected direction but non-significant. Lower P3 and theta also significantly predicted the expression of normative alcohol use (i.e. drinking index scores) by age-17 (Table 3). Again, P3 and theta improved model fit/prediction.

Follow-up analyses

We tested whether the significant age-14 theta/P3 and age-17 drinking effects reported above (i.e. Tables 2 and 3) held after controlling for reported tobacco or illicit drug initiation by age-14. The pattern of results did not change (online Supplementary Tables S2 and S3), despite the fact that other substance initiation accounted for much of the variance in the alcohol outcome measures, indicating that the predictive utility of P3 and theta is robust to co-occurring substance initiation.

To determine if the observed EEG effects could be attributed to associations between task performance (see online Supplementary Materials for descriptives) and alcohol use outcomes, prospective mixed models were computed as above for task-related behavioral measures. No behavioral measure significantly predicted age-17 drinking index scores ($ps \geqslant 0.146$) or new-onset measures (all ORs spanned zero).

The approximately equal number of females and males in this sample allowed us to test whether the prospective relationships between age-14 target P3/theta and age-17 alcohol use varied by sex. The main results (i.e. Tables 2 and 3) were reanalyzed adding P3 × sex and theta × sex interaction terms. All interaction terms were non-significant ($ps \geqslant 0.465$ and ORs spanned zero) and did not improve model fit [$\Delta\chi^2_{(2)} \leqslant 2.03$, $p \geqslant 0.363$], indicating that the associations between attenuated age-14 P3/theta and age-17 alcohol use measures did not statistically differ as a function of sex and held for both males and females.

Conclusions

The current study tested the ability of parietal P3 amplitude and midfrontal theta to prospectively predict the development of normative drinking in a community-based representative sample of 594 adolescents. While past work has focused on using P3 to predict clinically problematic drinking, these results provide new evidence that reduced target-related P3 and theta at age-14 predict the range of alcohol use behavior and consumption arising 3 years later. Furthermore, among individuals with no reported alcohol use by age-14, attenuated P3 and theta increased the odds of new-onset alcohol behaviors by age-17, offering strong

https://doi.org/10.1017/S0033291719003258 Published online by Cambridge University Press

Table 2. Prospective prediction of normative alcohol use at age-17 using age-14 target-related midfrontal theta power and parietal P3 amplitude

	β (95% CI)	t (df)	p	R^2
Age-17 Drinking Index				0.14
Target P3	−0.12 (−0.19 to −0.04)	−3.05 (588)	0.002	
Target Theta	−0.11 (−0.18 to −0.03)	−2.91 (577)	0.004	
Age 11/14 Drink Index	0.28 (0.21–0.35)	7.26 (587)	<0.001	
Parental AUD	0.11 (0.02–0.20)	2.41 (329)	0.016	
Sex	−0.06 (−0.15 to 0.03)	−1.39 (329)	0.167	

CI, confidence interval; AUD, alcohol use disorder
Note: The model fit well [$F_{(5,\ 501)} = 16.83$, $p < 0.001$]. Including target-related theta and P3 improved model fit/prediction [$\Delta\chi^2_{(2)} = 18.96$, $p < 0.001$; $\Delta R^2 = 0.03$] beyond the covariate-only model (i.e. age 11/14 drink index, sex, parental AUD)

Table 3. Prospective analyses predicting new onset of alcohol use by age-17 using age-14 target parietal P3 and midfrontal theta

	New-onset alcohol use behaviors at age-17								
	Initiation		Intoxication		Binge drinking		Drinking Index		
	OR	95% CI	OR	95% CI	OR	95% CI	β (95% CI)	t (df)	p
Target P3	1.49	1.09–2.16	1.68	0.81–3.80	2.73	1.26–6.67	−0.15 (−0.24 to −0.06)	−3.32 (468)	0.001
Target Theta	1.48	1.08–2.16	2.82	1.32–7.11	2.50	1.20–5.88	−0.09 (−0.18 to −0.003)	2.01 (446)	0.045
Parental AUD	2.15	1.08–5.01	2.80	0.44–20.89	2.95	0.45–22.97	0.12 (0.01–0.22)	2.21 (283)	0.028
Sex	1.66	0.83–3.61	1.50	0.23–10.45	1.10	0.16–7.83	−0.03 (−0.13 to 0.07)	−0.56 (283)	0.566

OR, odds ratio; CI, confidence interval
Note: Analyses were restricted to individuals with no reported alcohol use by age-14 ($n = 473$). Significant odds ratios above one reflect the increased odds of developing the indicated alcohol use behavior by age-17 associated with a decrease in target-related parietal P3 or midfrontal theta at age-14 (theta and P3 were multiplied by −1 to produce the inverse relationship). Note that because theta (log decibel) and P3 (linear microvolt) are measured on different scales, these measures were standardized for the generalized linear mixed models (logistic regression) to facilitate direct comparison of the ORs. In all models, P3 and theta improved model fit/prediction beyond parental AUD status and sex [$\Delta\chi^2_{(2)} \geqslant 9.98$, $p \leqslant 0.007$]. R^2 for the drinking index model was 0.05 (ΔR^2 after adding theta and P3 = 0.03).

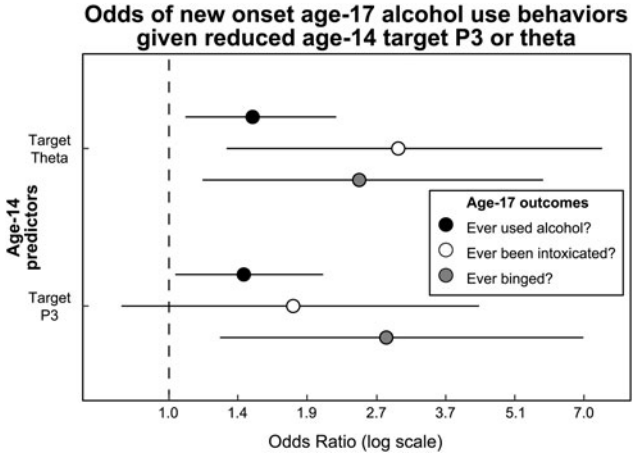


Fig. 3. Prospective odds of new-onset alcohol use behaviors at age-17 given age-14 P3 and theta among adolescents with no alcohol use by age-14 ($n = 473$). Separate generalized linear mixed models (logistic regression) were fit for the three alcohol initiation measures. Significant odds ratios (ORs) above one reflect the odds of developing the indicated alcohol use behavior by age-17 associated with a decrease in target-related parietal P3 or midfrontal theta at age-14 (theta and P3 were multiplied by −1 to produce the inverse relationship). ORs that do not cross one (dashed line) are significant (whiskers signify 95% confidence intervals). Note that because theta (log decibel) and P3 (linear microvolt) are measured on different scales, these measures were standardized for the logistic generalized linear mixed models to facilitate direct comparison of the ORs.

support for P3 and theta as candidate endophenotypes. The prospective P3 and theta effects were independent of each other and several prominent risk factors (prior alcohol use, tobacco/illicit drug initiation, parental alcohol use disorder), suggesting that they reflect distinct psychophysiological processes related to alcohol use development. In addition, an important novel finding is that theta and P3 scores provided significant incremental predictive power of future alcohol use beyond relevant risk factors. Overall, the current report is the first of our knowledge to demonstrate that deviations in parietal P3 and midfrontal theta are present prior to the initiation of alcohol use and prospectively predict the emergence of normative (full range)/non-pathological drinking in a large epidemiologically representative adolescent sample.

Results from the current study build upon prior research demonstrating that diminished P3 is a premorbid risk factor for the development of substance use disorders (Iacono *et al.*, 2002; Habeych *et al.*, 2005; Hill *et al.*, 2009; Iacono and Malone, 2011; Yoon *et al.*, 2015), and delinquent behaviors/substance use among adolescent males at high risk for alcoholism (Berman *et al.*, 1993). Increased alcohol use was predicted most strongly by P3 and theta during the cognitive demands of rare target detection. P3 elicited by the target condition is thought to index elaborative decisional processes to quickly and accurately determine the appropriate stimulus–response mapping (Polich, 2007; Verleger *et al.*, 2014; Barry *et al.*, 2016), whereas midfrontal theta likely reflects prefrontal attentional and control-related

https://doi.org/10.1017/S0033291719003258 Published online by Cambridge University Press

mechanisms to facilitate goal-directed behavior (Cavanagh *et al.*, 2012; Clayton *et al.*, 2015). Therefore, diminished P3 may confer vulnerability for suboptimal decision-making processes that influence the development/expression of inappropriate behaviors, while reduced attentional control-related midfrontal theta may contribute to a bias toward (or difficulty shifting attention from) alcohol/substance cues or immediate rewards. This interpretation is consistent with theoretical models implicating differences in adolescent motivational/decisional and regulatory-control systems as developmental risk factors for alcohol and substance use (Iacono *et al.*, 2008; Casey and Jones, 2010; Luciana and Collins, 2012; Squeglia and Gray, 2016). The current findings using psychophysiological measures align with work suggesting that variations in frontal brain structure/activity (Norman *et al.*, 2011; Wetherill *et al.*, 2013; Castellanos-Ryan *et al.*, 2014; Whelan *et al.*, 2014) and neuropsychological measures of executive functioning/cognitive control (Tarter *et al.*, 2003; Nigg *et al.*, 2006) reflect premorbid characteristics that predict future non-clinical alcohol involvement.

A valuable characteristic of endophenotypes is their ability to predict the development of the clinical phenotype, and demonstrating that endophenotypes account for significant unique additional variance in predicting an outcome is an important criterion to establish their potential utility and possible integration with clinical assessments (Patrick *et al.*, 2019). Despite its importance, this point has received little attention in the field of psychiatric endophenotypes (Iacono *et al.*, 2017). An important novel aspect of the current report is the demonstration that parietal P3 and midfrontal theta contributed unique incremental predictive value of age-17 alcohol use and new-onset cases over and above prominent risk factors (co-occurring/antecedent alcohol use; tobacco/illicit drug initiation; parental AUD). This indicates that the combination of self-report and EEG measures provided the strongest prediction of future alcohol use, which is consistent with a recent study that showed age-16 binge drinking was best predicted by the joint use of age-14 externalizing, personality, and structural/functional MRI variables (Whelan *et al.*, 2014). While endophenotype data collection is relatively costly and lab intensive, the current results suggest that P3 and theta supply valuable (neurocognitively relevant) variance unaccounted for by self-report risk factors that contribute to the development of adolescent alcohol engagement.

The current study represents an especially stringent and novel test for P3 and theta as candidate endophenotypes for two reasons. First, restricting the sample to alcohol-naive adolescents in the new-onset analyses likely removed those at highest genetic risk [e.g. those who initiated alcohol use by age-14 had higher rates of parental AUD than those who had not, $\chi^2_{(1)} = 8.23$, $p = 0.004$]. Second, we predicted the 3-year development of normative/ordinary adolescent use instead of exclusively pathological drinking, which might be expected to have the highest genetic loading. Nevertheless, P3 and theta remained significant predictors of normative drinking and new-onset alcohol behaviors 3 years later, attesting to their robustness as candidate endophenotypes.

These findings provide important evidence supporting the endophenotypic construct validity of midfrontal target-related theta (Iacono *et al.*, 2017). Theta is associated with normative and pathological alcohol use (Jones *et al.*, 2006; Andrew and Fein, 2010; Yoon *et al.*, 2013; Harper *et al.*, 2019); heritable (Harper *et al.*, 2019); diminished in first-degree relatives with AUD (Rangaswamy *et al.*, 2007); shares genetic variance with alcohol use (Harper *et al.*, 2019); and predicts alcohol use development (as shown here); all of which are important criterion for an endophenotype (Gottesman and Gould, 2003; Iacono *et al.*, 2017). Midfrontal theta elicited by other experimental tasks and cognitive processes, such as inhibitory control (Kamarajan *et al.*, 2006; however, see Harper *et al.*, 2018*b*), response conflict (Harper *et al.*, 2017*a*, 2018*a*), and feedback processing (Kamarajan *et al.*, 2015) may also reflect candidate endophenotypes for clinical and non-clinical drinking. This is consistent with the hypothesis that variations in midfrontal theta across varied cognitive demands reflect a generic and reactive processing mechanism to facilitate successful action monitoring and cognitive control (Cavanagh *et al.*, 2012; Cavanagh and Frank, 2014; Cohen, 2014*b*). As such, the general operation of midfrontal theta rhythms during various forms of action monitoring may account for the ubiquity of alcohol-related endophenotype findings for midfrontal theta. Further work is needed to understand the relationship between different 'expressions' of theta and alcohol use risk.

As noted elsewhere (Iacono and Malone, 2011), there has been a lack of work investigating potential sex differences in endophenotypes. An important contribution of the present work was comparing the prospective effects of age-14 P3 and theta between males and females to determine if effects held across sexes. There was no evidence of any statistically significant difference in the strength of effects between females and males for either P3 or theta. This is in contrast to some work suggesting that P3 is a more robust endophenotype for alcohol/substance use disorders in males (Gilmore *et al.*, 2010; Euser *et al.*, 2012). Given our findings, it may be that P3 has sex-specific effects for pathological substance use but not the full range of drinking behaviors. More work is needed to address this important gap in psychiatric endophenotype research.

This study is not without limitations. While reductions in parietal P3 and midfrontal theta appear to predate alcohol use, this does not mean that these endophenotypes may not also be affected by substance exposure, although the current study does not evaluate this possibility. Longer longitudinal studies are necessary to determine if adolescent theta, like P3, can predict alcohol use in adulthood. The scope of the study and multiple testing considerations led to a focus on predicting adolescent alcohol use; studying other forms of adolescent substance use would likely be informative. Finally, P3 and theta provided modest incremental prediction ($\Delta R^2 \sim 0.03$) of the various alcohol measures. This was not unexpected, as it is known that the association between cross-domain measures is expected to be lower than the correlation between within-domain measures (Campbell and Fiske, 1960). Correlations between psychophysiological and report-based measures are expected to be small in magnitude (Patrick *et al.*, 2013, 2019; Iacono, 2014), as has been reported for several recent large-scale studies on the brain-based correlates of substance use (Castellanos-Ryan *et al.*, 2014; Whelan *et al.*, 2014; Mackey *et al.*, 2018; Harper *et al.*, 2018*a*) and adolescent externalizing psychopathology (Hoogman *et al.*, 2019). Additionally, the version of the classic visual oddball task used in this report to elicit P3/theta is simpler than other tasks used to assess cognitive control (e.g. go/nogo; Wisconsin card-sorting test). While this may have yielded smaller effect sizes relative to more complex/cognitively demanding tasks, the simple design provides strength in that the interpretation of findings can be more straightforward compared to increasingly complex experimental designs. The reader is referred to (Iacono *et al.*, 2017;

https://doi.org/10.1017/S0033291719003258 Published online by Cambridge University Press

Funder and Ozer, 2019) for discussions on effect sizes in psychological and endophenotype research.

Reductions in age-14 target-related parietal P3 and midfrontal theta were predictive of greater drinking 3 years later, present in alcohol-naive adolescents who would later engage in alcohol use, and increased the odds of developing new-onset alcohol use behaviors (initiation, intoxication, binging) by age-17 in an epidemiologically representative sample. Results provide strong evidence that age-14 target-related parietal P3 and midfrontal theta reflect candidate endophenotypes that potentially influence the development and expression of adolescent drinking behaviors beyond salient risk factors. Identifying specific brain-based neurocognitive measures, such as P3 and theta, in early adolescence that prospectively predict future use may aid identification of high-risk youth and facilitate the developmental tracking of normative alcohol use behaviors across adolescence.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719003258.

Financial support. This work was supported by the National Institutes of Health grants DA013240 and DA036216. J.H. was supported by the National Science Foundation Graduate Research Fellowship under Grant No. 00039202 and the University of Minnesota Eva O. Miller Fellowship. Preliminary findings related to this manuscript appeared in a poster presentation at the 58th Annual Meeting of the Society for Psychophysiological Research (October 2018).

Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edn. Washington, DC: Author.

Andrew C and Fein G (2010) Event-related oscillations versus event-related potentials in a P300 task as biomarkers for alcoholism. *Alcoholism, Clinical and Experimental Research* **34**, 669–680.

Anokhin AP (2014) Genetic psychophysiology: advances, problems, and future directions. *International Journal of Psychophysiology* **93**, 173–197.

Bachman MD and Bernat EM (2018) Independent contributions of theta and delta time-frequency activity to visual oddball P300. *International Journal of Psychophysiology* **128**, 70–80.

Barry RJ, Steiner GZ and De Blasio FM (2016) Reinstating the Novelty P3. *Scientific Reports* **6**, 31200.

Barry RJ, Steiner GZ, De Blasio FM, Fogarty JS, Karamacoska D and MacDonald B (2019) Components in the P300: don't forget the Novelty P3!. *Psychophysiology*, e13371. https://doi.org/10.1111/psyp.13371

Başar-Eroglu C, Başar E, Demiralp T and Schürmann M (1992) P300-response: possible psychophysiological correlates in delta and theta frequency channels. A review. *International Journal of Psychophysiology* **13**, 161–179.

Bates D, Machler M, Bolker BM and Walker SC (2015) Fitting linear mixed-effects models using lme4. *Journal of Statistical Software* **67**, 1–48.

Begleiter H, Porjesz B, Bihari B and Kissin B (1984) Event-related brain potentials in boys at risk for alcoholism. *Science* **225**, 1493–1496.

Berman SM, Whipple SC, Fitch RJ and Noble EP (1993) P3 in young boys as a predictor of adolescent substance use. *Alcohol* **10**, 69–76.

Burwell SJ, Malone SM, Bernat EM and Iacono WG (2014) Does electroencephalogram phase variability account for reduced P3 brain potential in externalizing disorders? *Clinical Neurophysiology* **125**, 2007–2015.

Campbell DT and Fiske DW (1960) Convergent and discriminant validation by the multitrait-multimethod matrix. *Psychological Bulletin* **56**, 81.

Carlson SR, Iacono WG and McGue M (2004) P300 amplitude in nonalcoholic adolescent twin pairs who become discordant for alcoholism as adults. *Psychophysiology* **41**, 841–844.

Casey BJ and Jones RM (2010) Neurobiology of the adolescent brain and behavior: implications for substance use disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* **49**, 1189–1201; quiz 1285.

Castellanos-Ryan N, Struve M, Whelan R, Banaschewski T, Barker GJ, Bokde ALW, Bromberg U, Buchel C, Frouin V, Gallinat J, Gowland P, Heinz A, Lawrence C, Martinot JL, Nees F, Paus T, Pausova Z, Rietschel M, Robbins TW, Smolka MN, Schumann G, Garavan H and Conrod PJ and Imagen Consortium (2014) Neural and cognitive correlates of the common and specific variance across externalizing problems in young adolescence. *The American Journal of Psychiatry* **171**, 1310–1319.

Cavanagh JF and Frank MJ (2014) Frontal theta as a mechanism for cognitive control. *Trends in Cognitive Sciences* **18**, 414–421.

Cavanagh JF, Zambrano-Vazquez L and Allen JJB (2012) Theta lingua franca: a common mid-frontal substrate for action monitoring processes. *Psychophysiology* **49**, 220–238.

Clayton MS, Yeung N and Kadosh RC (2015) The roles of cortical oscillations in sustained attention. *Trends in Cognitive Sciences* **19**, 188–195.

Cohen MX (2014*a*) *Analyzing Neural Time Series Data: Theory and Practice*. Cambridge, MA: MIT Press.

Cohen MX (2014*b*) A neural microcircuit for cognitive conflict detection and signaling. *Trends in Neurosciences* **37**, 480–490.

Cohen MX and Cavanagh JF (2011) Single-trial regression elucidates the role of prefrontal theta oscillations in response conflict. *Frontiers in Psychology* **2**, 30.

Crews FT and Boettiger CA (2009) Impulsivity, frontal lobes and risk for addiction. *Pharmacology, Biochemistry, and Behavior* **93**, 237–247.

Delorme A, Westerfield M and Makeig S (2007) Medial prefrontal theta bursts precede rapid motor responses during visual selective attention. *The Journal of Neuroscience* **27**, 11949–11959.

Deutsch AR, Slutske WS, Richmond-Rakerd LS, Chernyavskiy P, Heath AC and Martin NG (2013) Causal influence of age at first drink on alcohol involvement in adulthood and its moderation by familial context. *Journal of Studies on Alcohol and Drugs* **74**, 703–713.

Euser AS, Arends LR, Evans BE, Greaves-Lord K, Huizink AC and Franken IHA (2012) The P300 event-related brain potential as a neurobiological endophenotype for substance use disorders: a meta-analytic investigation. *Neuroscience and Biobehavioral Reviews* **36**, 572–603.

Field M and Cox WM (2008) Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug and Alcohol Dependence* **97**, 1–20.

Flory K, Lynam D, Milich R, Leukefeld C and Clayton R (2004) Early adolescent through young adult alcohol and marijuana use trajectories: early predictors, young adult outcomes, and predictive utility. *Development and Psychopathology* **16**, 193–213.

Foster KT, Hicks BM, Iacono WG and McGue M (2014) Alcohol use disorder in women: risks and consequences of an adolescent onset and persistent course. *Psychology of Addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors* **28**, 322–335.

Funder DC and Ozer DJ (2019) Evaluating effect size in psychological research: sense and nonsense. *Advances in Methods and Practices in Psychological Science* **2**, 156–168.

Gilmore CS, Malone SM and Iacono WG (2010) Brain electrophysiological endophenotypes for externalizing psychopathology: a multivariate approach. *Behavior Genetics* **40**, 186–200.

Gottesman II and Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. *The American Journal of Psychiatry* **160**, 636–645.

Habeych ME, Charles PJ, Sclabassi RJ, Kirisci L and Tarter RE (2005) Direct and mediated associations between P300 amplitude in childhood and substance use disorders outcome in young adulthood. *Biological Psychiatry* **57**, 76–82.

Harper J, Malone SM and Iacono WG (2017*a*) Testing the effects of adolescent alcohol use on adult conflict-related theta dynamics. *Clinical Neurophysiology* **128**, 2358–2368.

https://doi.org/10.1017/S0033291719003258 Published online by Cambridge University Press

Harper J, Malone SM and Iacono WG (2017*b*) Theta-and delta-band EEG network dynamics during a novelty oddball task. *Psychophysiology* **54**, 1590–1605.

Harper J, Malone SM and Iacono WG (2018*a*) Conflict-related medial frontal theta as an endophenotype for alcohol use disorder. *Biological Psychology* **139**, 25–38.

Harper J, Malone SM and Iacono WG (2018*b*) Impact of alcohol use on EEG dynamics of response inhibition: a Cotwin control analysis. *Addiction Biology* **23**, 256–267.

Harper J, Malone SM and Iacono WG (2019) Target-related parietal P3 and medial frontal theta index the genetic risk for problematic substance use. *Psychophysiology* **56**, e13383.

Hicks BM, Iacono WG and McGue M (2010) Consequences of an adolescent onset and persistent course of alcohol dependence in men: adolescent risk factors and adult outcomes. *Alcoholism-Clinical and Experimental Research* **34**, 819–833.

Hill SY, Steinhauer S, Lowers L and Locke J (1995) Eight-year longitudinal follow-up of P300 and clinical outcome in children from high-risk for alcoholism families. *Biological Psychiatry* **37**, 823–827.

Hill SY, Steinhauer SR, Locke-Wellman J and Ulrich R (2009) Childhood risk factors for young adult substance dependence outcome in offspring from multiplex alcohol dependence families: a prospective study. *Biological Psychiatry* **66**, 750–757.

Hoogman M, Muetzel R, Guimaraes JP, Shumskaya E, Mennes M, Zwiers MP, Jahanshad N, Sudre G, Wolfers T, Earl EA, Soliva Vila JC, Vives-Gilabert Y, Khadka S, Novotny SE, Hartman CA, Heslenfeld DJ, Schweren LJS, Ambrosino S, Oranje B, de Zeeuw P, Chaim-Avancini TM, Rosa PGP, Zanetti MV, Malpas CB, Kohls G, von Polier GG, Seitz J, Biederman J, Doyle AE, Dale AM, van Erp TGM, Epstein JN, Jernigan TL, Baur-Streubel R, Ziegler GC, Zierhut KC, Schrantee A, Høvik MF, Lundervold AJ, Kelly C, McCarthy H, Skokauskas N, O'Gorman Tuura RL, Calvo A, Lera-Miguel S, Nicolau R, Chantiluke KC, Christakou A, Vance A, Cercignani M, Gabel MC, Asherson P, Baumeister S, Brandeis D, Hohmann S, Bramati IE, Tovar-Moll F, Fallgatter AJ, Kardatzki B, Schwarz L, Anikin A, Baranov A, Gogberashvili T, Kapilushniy D, Solovieva A, El Marroun H, White T, Karkashadze G, Namazova-Baranova L, Ethofer T, Mattos P, Banaschewski T, Coghill D, Plessen KJ, Kuntsi J, Mehta MA, Paloyelis Y, Harrison NA, Bellgrove MA, Silk TJ, Cubillo AI, Rubia K, Lazaro L, Brem S, Walitza S, Frodl T, Zentis M, Castellanos FX, Yoncheva YN, Haavik J, Reneman L, Conzelmann A, Lesch K-P, Pauli P, Reif A, Tamm L, Konrad K, Oberwelland Weiss E, Busatto GF, Louza MR, Durston S, Hoekstra PJ, Oosterlaan J, Stevens MC, Ramos-Quiroga JA, Vilarroya O, Fair DA, Nigg JT, Thompson PM, Buitelaar JK, Faraone SV, Shaw P, Tiemeier H, Bralten J and Franke B (2019) Brain imaging of the cortex in ADHD: a coordinated analysis of large-scale clinical and population-based samples. *The American Journal of Psychiatry* **176**, 531–542.

Iacono WG (2014) Neurobehavioral aspects of multidimensional psychopathology. *The American Journal of Psychiatry* **171**, 1236–1239.

Iacono WG and Malone SM (2011) Developmental endophenotypes: indexing genetic risk for substance abuse with the P300 brain event-related potential. *Child Development Perspectives* **5**, 239–247.

Iacono WG, Carlson SR, Malone SM and McGue M (2002) P3 event-related potential amplitude and the risk for disinhibitory disorders in adolescent boys. *Archives of General Psychiatry* **59**, 750–757.

Iacono WG, Malone SM and McGue M (2008) Behavioral disinhibition and the development of early-onset addiction: common and specific influences. *Annual Review of Clinical Psychology* **4**, 325–348.

Iacono WG, Malone SM and Vrieze SI (2017) Endophenotype best practices. *International Journal of Psychophysiology* **111**, 115–144.

Irons DE, Iacono WG and McGue M (2015) Tests of the effects of adolescent early alcohol exposures on adult outcomes. *Addiction* **110**, 269–278.

Jacobus J and Tapert SF (2013) Neurotoxic effects of alcohol in adolescence. *Annual Review of Clinical Psychology* **9**, 703–721.

Jaeger BC, Edwards LJ, Das K and Sen PK (2017) An R2 statistic for fixed effects in the generalized linear mixed model. *Journal of Applied Statistics* **44**, 1086–1105.

Johnston LD, Miech RA, O'Malley PM, Bachman JG, Schulenberg JE and Patrick ME (2019) *Monitoring the Future National Survey Results on Drug Use 1975–2018*: Overview, Key Findings on Adolescent Drug Use. Ann Arbor: Institute for Social Research, University of Michigan.

Jones KA, Porjesz B, Chorlian D, Rangaswamy M, Kamarajan C, Padmanabhapillai A, Stimus A and Begleiter H (2006) S-transform time-frequency analysis of P300 reveals deficits in individuals diagnosed with alcoholism. *Clinical Neurophysiology* **117**, 2128–2143.

Kamarajan C, Porjesz B, Jones K, Chorlian D, Padmanabhapillai A, Rangaswamy M, Stimus A and Begleiter H (2006) Event-related oscillations in offspring of alcoholics: neurocognitive disinhibition as a risk for alcoholism. *Biological Psychiatry* **59**, 625–634.

Kamarajan C, Pandey AK, Chorlian DB, Manz N, Stimus AT, Anokhin AP, Bauer LO, Kuperman S, Kramer J, Bucholz KK, Schuckit MA, Hesselbrock VM and Porjesz B (2015) Deficient event-related theta oscillations in individuals at risk for alcoholism: a study of reward processing and impulsivity features. *PLoS ONE* **10**, e0142659.

Keyes MA, Malone SM, Elkins IJ, Legrand LN, McGue M and Iacono WG (2009) The enrichment study of the Minnesota twin family study: increasing the yield of twin families at high risk for externalizing psychopathology. *Twin Research and Human Genetics* **12**, 489–501.

Koob GF and Volkow ND (2010) Neurocircuitry of addiction. *Neuropsychopharmacology* **35**, 1051–1051.

Kuznetsova A, Brockhoff PB and Christensen RHB (2017) Lmertest package: tests in linear mixed effects models. *Journal of Statistical Software* **82**, 1–26.

Luciana M and Collins PF (2012) Incentive motivation, cognitive control, and the adolescent brain: is It time for a paradigm shift? *Child Development Perspectives* **6**, 392–399.

Luciana M, Collins PF, Muetzel RL and Lim KO (2013) Effects of alcohol use initiation on brain structure in typically developing adolescents. *The American Journal of Drug and Alcohol Abuse* **39**, 345–355.

Lüdecke D (2019) *sjstats: Statistical Functions for Regression Models* (*Version 0.17.4*).

Mackey S, Allgaier N, Chaarani B, Spechler P, Orr C, Bunn J, Allen NB, Alia-Klein N, Batalla A, Blaine S, Brooks S, Caparelli E, Chye YY, Cousijn J, Dagher A, Desrivieres S, Feldstein-Ewing S, Foxe JJ, Goldstein RZ, Goudriaan AE, Heitzeg MM, Hester R, Hutchison K, Korucuoglu O, Li C-SR, London E, Lorenzetti V, Luijten M, Martin-Santos R, May A, Momenan R, Morales A, Paulus MP, Pearlson G, Rousseau M-E, Salmeron BJ, Schluter R, Schmaal L, Schumann G, Sjoerds Z, Stein DJ, Stein EA, Sinha R, Solowij N, Tapert S, Uhlmann A, Veltman D, van Holst R, Whittle S, Wright MJ, Yücel M, Zhang S, Yurgelun-Todd D, Hibar DP, Jahanshad N, Evans A, Thompson PM, Glahn DC, Conrod P, Garavan H and ENIGMA Addiction Working Group (2018) Mega-analysis of gray matter volume in substance dependence: general and substance-specific regional effects. *The American Journal of Psychiatry* **176**, 119–128.

Makeig S, Delorme A, Westerfield M, Jung TP, Townsend J, Courchesne E and Sejnowski TJ (2004) Electroencephalographic brain dynamics following manually responded visual targets. *PLoS Biology* **2**, 747–762.

Malone SM, Taylor J, Marmorstein NR, McGue M and Iacono WG (2004) Genetic and environmental influences on antisocial behavior and alcohol dependence from adolescence to early adulthood. *Development and Psychopathology* **16**, 943–966.

Malone SM, Luciana M, Wilson S, Sparks JC, Hunt RH, Thomas KM and Iacono WG (2014) Adolescent drinking and motivated decision-making: a Cotwin-control investigation with monozygotic twins. *Behavior Genetics* **44**, 407–418.

McGue M, Malone S, Keyes M and Iacono WG (2014) Parent-offspring similarity for drinking: a longitudinal adoption study. *Behavior Genetics* **44**, 620–628.

Nieuwenhuis S, Aston-Jones G and Cohen JD (2005) Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psychological Bulletin* **131**, 510–532.

Nigg JT, Wong MM, Martel MM, Jester JM, Puttler LI, Glass JM, Adams KM, Fitzgerald HE and Zucker RA (2006) Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents

https://doi.org/10.1017/S0033291719003258 Published online by Cambridge University Press

at risk for alcoholism and other substance use disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* **45**, 468–475.

Norman AL, Pulido C, Squeglia LM, Spadoni AD, Paulus MP and Tapert SF (2011) Neural activation during inhibition predicts initiation of substance use in adolescence. *Drug and Alcohol Dependence* **119**, 216–223.

Patrick CJ, Venables NC, Yancey JR, Hicks BM, Nelson LD and Kramer MD (2013) A construct-network approach to bridging diagnostic and physiological domains: application to assessment of externalizing psychopathology. *Journal of Abnormal Psychology* **122**, 902–916.

Patrick CJ, Iacono WG and Venables NC (2019) Incorporating neurophysiological measures into clinical assessments: fundamental challenges and a strategy for addressing them. *Psychological Assessment*.

Perlman G, Markin A and Iacono WG (2013) P300 amplitude reduction is associated with early-onset and late-onset pathological substance use in a prospectively studied cohort of 14-year-old adolescents. *Psychophysiology* **50**, 974–982.

Pfefferbaum A, Kwon D, Brumback T, Thompson WK, Cummins K, Tapert SF, Brown SA, Colrain IM, Baker FC, Prouty D, De Bellis MD, Clark DB, Nagel BJ, Chu W, Park SH, Pohl KM and Sullivan EV (2018) Altered brain developmental trajectories in adolescents after initiating drinking. *The American Journal of Psychiatry* **175**, 370–380.

Poikolainen K, Tuulio-Henriksson A, Aalto-Setälä T, Marttunen M and Lönnqvist J (2001) Predictors of alcohol intake and heavy drinking in early adulthood: a 5-year follow-up of 15–19-year-old Finnish adolescents. *Alcohol and Alcoholism* **36**, 85–88.

Polich J (2007) Updating P300: an integrative theory of P3a and P3b. *Clinical Neurophysiology* **118**, 2128–2148.

Rangaswamy M, Jones KA, Porjesz B, Chorlian DB, Padmanabhapillai A, Kamarajan C, Kuperman S, Rohrbaugh J, O'Connor SJ, Bauer LO, Schuckit MA and Begleiter H (2007) Delta and theta oscillations as risk markers in adolescent offspring of alcoholics. *International Journal of Psychophysiology* **63**, 3–15.

R Core Team (2018) *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.

Salvatore JE, Gottesman II and Dick DM (2015) Endophenotypes for alcohol use disorder: an update on the field. *Current Addiction Reports* **2**, 76–90.

Saunders GRB, McGue M, Iacono WG and Elkins IJ (2017) Parent-offspring resemblance for drinking behaviors in a longitudinal twin sample. *Journal of Studies on Alcohol and Drugs* **78**, 49–58.

Savage JE, Rose RJ, Pulkkinen L, Silventoinen K, Korhonen T, Kaprio J, Gillespie N and Dick DM (2018) Early maturation and substance use across adolescence and young adulthood: a longitudinal study of Finnish twins. *Development and Psychopathology* **30**, 79–92.

Squeglia LM and Gray KM (2016) Alcohol and drug use and the developing brain. *Current Psychiatry Reports* **18**, 46.

Squeglia LM, Tapert SF, Sullivan EV, Jacobus J, Meloy MJ, Rohlfing T and Pfefferbaum A (2015) Brain development in heavy-drinking adolescents. *The American Journal of Psychiatry* **172**, 531–542.

Substance Abuse and Mental Health Services Administration (2018) Key substance use and mental health indicators in the United States: results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/.

Tarter RE, Kirisci L, Mezzich A, Cornelius JR, Pajer K, Vanyukov M, Gardner W, Blackson T and Clark D (2003) Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *The American Journal of Psychiatry* **160**, 1078–1085.

Tessner KD and Hill SY (2010) Neural circuitry associated with risk for alcohol use disorders. *Neuropsychology Review* **20**, 1–20.

Verleger R and Śmigasiewicz K (2016) Do rare stimuli evoke large P3s by being unexpected? A comparison of oddball effects between standard-oddball and prediction-oddball tasks. *Advances in Cognitive Psychology/University of Finance and Management in Warsaw* **12**, 88–104.

Verleger R, Jaskowski P and Wascher E (2005) Evidence for an integrative role of P3b in linking reaction to perception. *Journal of Psychophysiology* **19**, 165–181.

Verleger R, Baur N, Metzner MF and Smigasiewicz K (2014) The hard oddball: effects of difficult response selection on stimulus-related P3 and on response-related negative potentials. *Psychophysiology* **51**, 1089–1100.

Wells JE, Horwood LJ and Fergusson DM (2004) Drinking patterns in mid-adolescence and psychosocial outcomes in late adolescence and early adulthood. *Addiction* **99**, 1529–1541.

Wetherill RR, Castro N, Squeglia LM and Tapert SF (2013) Atypical neural activity during inhibitory processing in substance-naïve youth who later experience alcohol-induced blackouts. *Drug and Alcohol Dependence* **128**, 243–249.

Whelan R, Watts R, Orr CA, Althoff RR, Artiges E, Banaschewski T, Barker GJ, Bokde ALW, Büchel C, Carvalho FM, Conrod PJ, Flor H, Fauth-Bühler M, Frouin V, Gallinat J, Gan G, Gowland P, Heinz A, Ittermann B, Lawrence C, Mann K, Martinot J-L, Nees F, Ortiz N, Paillère-Martinot M-L, Paus T, Pausova Z, Rietschel M, Robbins TW, Smolka MN, Ströhle A, Schumann G, Garavan H and IMAGEN Consortium (2014) Neuropsychosocial profiles of current and future adolescent alcohol misusers. *Nature* **512**, 185–189.

Wiers RW, Boelema SR, Nikolaou K and Gladwin TE (2015) On the development of implicit and control processes in relation to substance use in adolescence. *Current Addiction Reports* **2**, 141–155.

Wilson S, Malone SM, Thomas KM and Iacono WG (2015) Adolescent drinking and brain morphometry: a co-twin control analysis. *Developmental Cognitive Neuroscience* **16**, 130–138.

Yoon HH, Malone SM, Burwell SJ, Bernat EM and Iacono WG (2013) Association between P3 event-related potential amplitude and externalizing disorders: a time-domain and time-frequency investigation of 29-year-old adults. *Psychophysiology* **50**, 595–609.

Yoon HH, Malone SM and Iacono WG (2015) Longitudinal stability and predictive utility of the visual P3 response in adults with externalizing psychopathology. *Psychophysiology* **52**, 1632–1645.

Zucker RA, Heitzeg MM and Nigg JT (2011) Parsing the undercontrol-disinhibition pathway to substance use disorders: a multilevel developmental problem. *Child Development Perspectives* **5**, 248–255.

https://doi.org/10.1017/S0033291719003258 Published online by Cambridge University Press