

## Original Article

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

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**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-naïve 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; Tessler 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

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 Śmigajewicz, 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.*, 2017b; Bachman and Bernat, 2018) during action monitoring and behavioral control (Cavanagh *et al.*, 2012; Cohen, 2014b; 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.

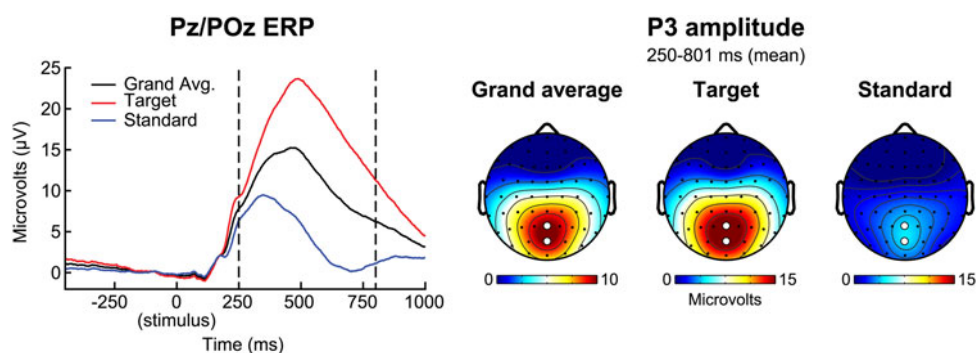
The current study was designed to test whether reductions in parietal P3 and midfrontal theta elicited during a visual oddball task predict the normative expression and initiation of alcohol use emerging in adolescence in a large epidemiological sample prospectively assessed throughout adolescence (ages 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-naïve 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  $\leq 50\%$ . 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.



**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.*, 2017a) 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  $\alpha$ : 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.*, 2017b, 2019) (see online Supplementary Material).

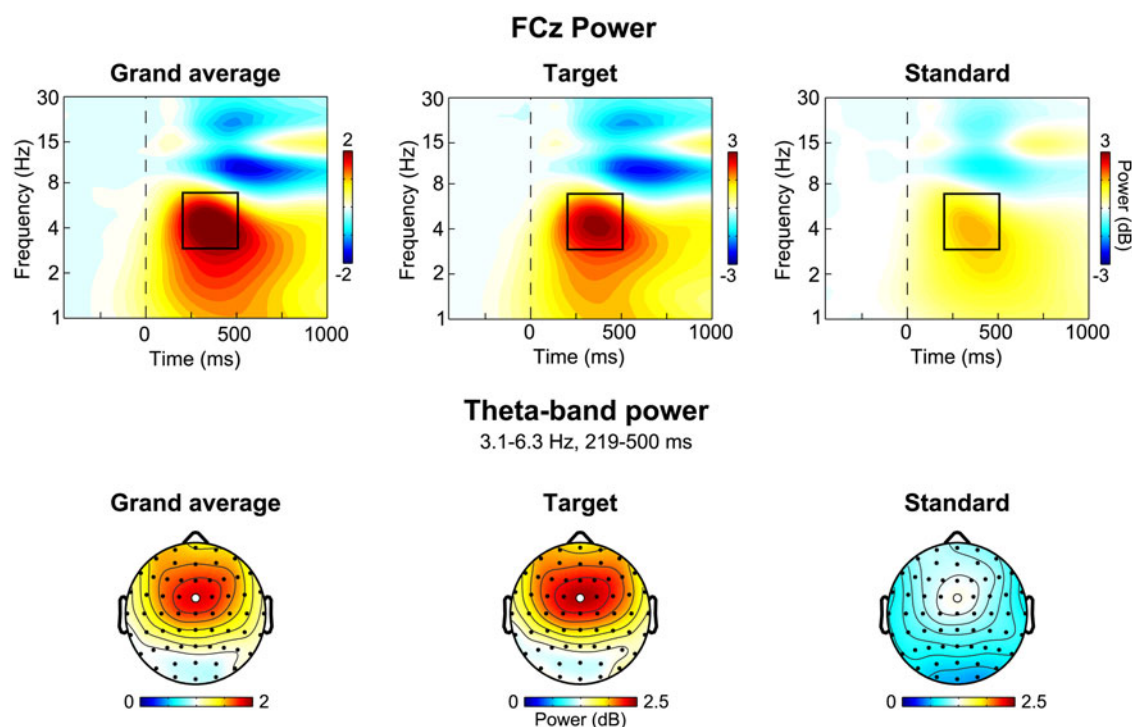
Trial-averaged ERPs were computed separately for target and standard trials/conditions (error trials were excluded from analyses). Based on the grand averaged ERP (Fig. 1), P3 amplitude was quantified as the mean amplitude between 250 and 801 ms (relative to a –450 to –250 ms average baseline) pooled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

Trial-level signals were transformed into time-frequency representations using complex Morlet wavelet convolution (Cohen, 2014a) (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.



**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 ( $\chi^2$  distribution approximation); a significant change provides evidence that P3 and theta improved model fit/prediction. Standardized regression coefficients ( $\beta$ ) with 95% confidence intervals (Lüdtke, 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 ( $\beta$  [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],  $t_{(593)} =$



**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 ( $\mu$ V)	16.40 (6.53)
Theta power (dB)	2.42 (1.10)
Standard condition	
P3 amplitude ( $\mu$ V)	4.19 (2.75)
Theta power (dB)	1.30 (0.78)

$\mu$ V, microvolt; dB, decibel.

Values given are mean (standard deviation) unless otherwise noted.

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

#### 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 [ $ps \geq 0.106$ ; 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 ( $ps \geq 0.146$ ) 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  $\times$  sex and theta  $\times$  sex interaction terms. All interaction terms were non-significant ( $ps \geq 0.465$  and ORs spanned zero) and did not improve model fit [ $\Delta\chi^2_{(2)} \leq 2.03$ ,  $p \geq 0.363$ ], 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

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

	$\beta$ (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

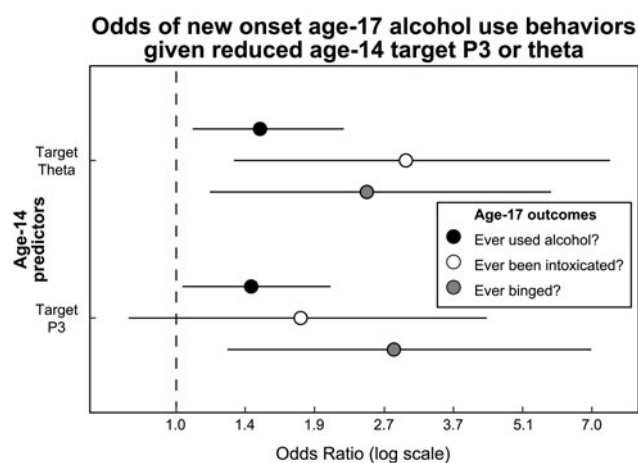
Note: The model fit well [ $F_{(5, 501)} = 16.83, p < 0.001$ ]. Including target-related theta and P3 improved model fit/prediction [ $\Delta\chi^2_{(2)} = 18.96, p < 0.001$ ;  $\Delta R^2 = 0.03$ ] beyond the covariate-only model (i.e. age 11/14 drink index, sex, parental AUD)

**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	$\beta$ (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 [ $\Delta\chi^2_{(2)} \geq 9.98, p \leq 0.007$ ].  $R^2$  for the drinking index model was 0.05 ( $\Delta R^2$  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

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-naïve 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.*, 2018b), response conflict (Harper *et al.*, 2017a, 2018a), 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, 2014b). 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.*, 2018a) 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;

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-naïve adolescents who would later engage in alcohol use, and increased the odds of developing new-onset alcohol use behaviors (initiation, intoxication, bingeing) 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 neuro-cognitive 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.

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**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.

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