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Does Electroencephalogram Phase Variability Account for Reduced P3 Brain Potential in Externalizing Disorders?

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Abstract

Objective—Amplitude deficits of the P3 event-related potential (ERP) are associated with externalizing psychopathology but little is known about the nature of underlying brain electrical activity that accounts for this amplitude reduction. We sought to understand if group differences in task-induced phase-locking in electroencephalographic (EEG) delta and theta frequencies may account for P3-externalizing associations.

Methods—Adult males ($N = 410$) completed a visual oddball task and frontal and parietal P3-related delta- and theta-band phase-invariant evoked energy and inter-trial phase-locking measures were investigated with respect to the externalizing spectrum, including substance dependence, adult antisociality, and childhood disruptive disorders. We hypothesized that P3-related phase-locking is weaker in externalizing-diagnosed individuals and this might mediate prior findings of reduced evoked P3energy.

Results—Reductions in both evoked energy and phase-locking, in both frequency bands, at both scalp sites, were associated with greater odds of externalizing diagnoses. Generally, adding phase-locking to evoked energy came with better prediction model fit. Moreover, reduced theta-band phase-locking partially mediated the effects of within-frequency evoked energy on externalizing prediction.

Conclusions—Inter-trial phase-locking underlying P3 appears to be an important distinction between externalizing and control subjects.

Significance—This cross-trial phase-variability for externalizing-diagnosed individuals might reflect deficient top-down “tuning” by neuromodulatory systems.

Keywords

event-related potential; externalizing; P3; phase-locking; substance use; theta

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Introduction

Amplitude reduction of the P3 event-related potential (ERP) is well-documented in cases of alcoholism (Euser et al., 2012). Recently, this deficit in P3 amplitude (P3AR) has been extended to a broader spectrum of “externalizing” psychopathology which includes substance use disorders (SUDs) and disorders that often co-occur with SUDs such as antisociality and attention-deficit hyperactivity disorder (Iacono et al., 2002). A common externalizing dimension is thought to unite these disorders (Kendler et al., 2003; Krueger, 1999) and accounts for their relationship with P3AR (Patrick et al., 2006). This association between P3AR and externalizing is heritable (Gilmore et al., 2010b; Yoon et al., 2006) and genetically mediated (Hicks et al., 2007) and has been posited as an endophenotype for such disorders (Iacono and Malone, 2011) whereby a biological measure (e.g., P3 amplitude) is thought to be closer to genetic influence than otherwise complex symptomatology (e.g., alcohol dependence). Although substantial clinical and epidemiological evidence exists demonstrating P3AR’s robust association with SUDs and other externalizing disorders, possible mechanisms underlying this difference in brain response has received considerably less attention. The current study asks whether reduced P3-related phase-locking (arrhythmic brain responding) could account for the externalizing and effect.

Neurobiological interpretation of P3AR associated with externalizing psychopathology is complicated. Target P3 (or “P3b”; see Polich, 2007) is commonly studied using a stimulus “oddball” task whereby participants are instructed to attend (e.g., button-press) to infrequent target stimuli and ignore frequent non-target stimuli. During the task, electroencephalogram (EEG) is recorded to measure the brain-generated electrical field at numerous locations on the scalp. Fluctuations in this electrical field are driven by the synchronized activation of post-synaptic currents of pyramidal neurons in the cortex (Buzsaki et al., 2012). Cross-trial averaging of stimulus-locked EEG produces a waveform characterized by three positive deflections; the third of these peaks (P3) occurs roughly 300 to 600 milliseconds following stimulus-onset. Augmentation of P3 is thought to reflect the focused activation of neurotransmitter systems to promote attentional gain, stimulus evaluation, and response selection; therefore, decrements in P3 amplitude might mark deficiencies in this process (Nieuwenhuis et al., 2005; Polich, 2007).

P3AR is classically studied in the time-domain by its trial-averaged amplitude or peak-latency (time-delay from stimulus). The convention of doing so adopts the “evoked” model of ERP generation which assumes that: 1) P3-voltage is fixed in polarity and latency relative to stimulus-onset (i.e. it is phase-locked), 2) there is an increase from post- relative to pre-stimulus EEG power, and 3) all non-phase-locked EEG is additive noise and suppressed by averaging (Shah et al., 2004). Indeed, evoked P3 has been tractable in the prediction of substance use and related disorders (Euser et al., 2012). Some have even extended time-domain evoked P3AR to the time-frequency domain which affords information about the ERP’s energy at specific times and frequencies. For instance, evoked P3 is comprised primarily of superimposed delta (1 – 3 Hz) and theta (4 – 8 Hz) frequency oscillations (Basar et al., 1999; Bernat et al., 2007; Karakas et al., 2000). Our group and others have shown that parietal evoked delta underlying the time-domain P3 peak explains a large portion of the variance in P3AR’s association with externalizing psychopathology (Gilmore

et al., 2010a; Jones et al., 2006; Rangaswamy et al., 2007). It is less clear how P3-related theta might contribute to this group difference. One study showed that theta-focused principal components derived from evoked ERPs are smaller for externalizing-relative to control-subjects (Yoon et al., 2013); however, others suggest that theta's contribution to P3 is more complex than what can be observed in the evoked ERP (Andrew and Fein, 2010; Jones et al., 2006; Rangaswamy et al., 2007). Because the vast majority of studies investigating P3AR focus exclusively on evoked P3, the effect is typically interpreted to indicate that externalizing individuals respond with smaller-voltage P3s to the stimulus on each trial.

An alternative explanation is that temporal shifts in P3-processes from trial-to-trial (i.e. "latency jitter" or more generally, a reduction in phase-locking) can also diminish trial-averaged (evoked) voltage (Makeig et al., 2002; Sauseng et al., 2007; Sayers et al., 1974). Specifically, if the same P3-related neuroelectrical activity occurs at the same time on each target trial of the ERP task, this activity should contribute prominently in the trial-averaged evoked target P3. Conversely, if the neuroelectric processes that underpin P3 are not consistent across trials, this would result in weak evoked P3. We posit that the temporal onset and offset of P3-related delta and theta components may be more variable across trials in externalizing-diagnosed individuals relative to controls and that this heightened "ERP arrhythmia" is partly responsible for the evoked P3-reductions seen in externalizing. This unexplored possibility would be characterized by a reduction in inter-trial phase-locking for externalizing individuals.

Extending an earlier report (Yoon et al., 2013), the present study examined the evoked energy and inter-trial phase-locking ERP components temporally-corresponding to the P3 peak in delta- and theta-frequencies to predict lifetime diagnoses of externalizing disorders. We hypothesized that reduced inter-trial phase-locking accounts at least in part for the P3-related voltage reductions associated with externalizing.

Methods

Participants

Participants were drawn from the older cohort of the Minnesota Twin Family Study, a longitudinal community-based sample studying twins and their parents (explained further in Iacono and McGue, 2002). This cohort was initially assessed when the twins were approximately 17 years of age and is almost entirely Caucasian (over 95%; consistent with the demographics for the state of Minnesota at the time the twins were born). At approximate ages of 17, 20, 24, and 29, participants underwent a battery of clinical interviews and psychophysiological measurements. The age-29 assessment included higher-density EEG recording than previous ones. Only participants who visited in-person and had EEG data at their age-29 visit were considered for the present study ($N = 434$, 199 twin pairs, 36 unmatched twins, mean age = 29.6, standard deviation = 0.6, age range = 28.5 – 31.9).

Diagnostic assessment/groups

At each assessment, each twin was interviewed individually by a trained clinical interviewer. Because P3AR has been shown to persist through adolescence and into adulthood (Iacono et al., 2002; Yoon et al., 2013) and we wanted to identify all cases of externalizing psychopathology, the present study constructed diagnostic groups based on *lifetime occurrence of an externalizing diagnosis* (Hamdi and Iacono, 2014). In other words, those who received a disorder diagnosis at any one of our four assessments were given a lifetime diagnosis for that disorder. Externalizing diagnoses of attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), adult antisocial behavior (AAB), nicotine dependence (NicD), alcohol dependence (AlcD), and illicit drug dependence (DrgD) were based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R; American Psychiatric Association, 1987), the diagnostic standard that was current at the time of participant intake assessment. To simplify grouping, DrgD was collapsed into one group that included a substance dependence diagnosis for any of the following psychoactive substance classes: amphetamines, cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidine, and sedatives. Childhood disruptive disorders (CDDs; ADHD, ODD, CD) were only assessed at the twins' intake assessment whereby twins and mothers (asked in pertinence to the twins' behavior) reported symptoms for these disorders in accordance with the Diagnostic Interview for Children and Adolescents (Reich, 2000; Welner et al., 1987) child- and parent-versions, respectively. To ensure diagnostic certainty, a "best-estimate" approach combining twin and mother reports was adopted (Kosten and Rounsaville, 1992; Leckman et al., 1982). All other disorders (AAB, NicD, AlcD, DrgD) were assessed at all four visits. AAB was diagnosed if an individual met *DSM-III-R* criteria for antisocial personality disorder but did not necessarily qualify the presence of childhood history of CD (cf. Elkins et al., 1997). The presence of SUDs (NicD, AlcD, DrgD) was assessed using the expanded substance abuse module (Robins et al., 1988) as they pertained to lifetime (intake and second visits) and since-last-visit (third and fourth visits) experience. Clinical reports were independently reviewed by at least two individuals with advanced clinical training (Cohen's κ 's > 0.7) (Iacono et al., 1999) who whenever they did not score a symptom identically, reviewed the symptom together to achieve consensus. The comparison group for the present study consisted of those who met criteria for none of the above disorders at any of the four assessments. In addition, they did not meet criteria for *DSM-III-R* substance abuse.

ERP task

The rotated-heads oddball paradigm (Begleiter et al., 1984) used in the current study is a complex visuospatial task which has been repeatedly shown to differentiate externalizing subjects and non-externalizing controls (Iacono et al., 2002; Polich et al., 1994). Stimuli consisted of four infrequently occurring target stimuli ($n = 80$) interspersed with one frequently occurring non-target stimulus ($n = 160$) presented in pseudo-random order. Target stimuli resembling "heads" were presented as an oval with one triangular "nose" appearing on either the top (oriented up) or bottom (oriented down) of the oval and one "ear" appearing on either the left or right side of the same oval. The non-target stimulus was a simple oval of the same size and shape without nose or ear. Sitting in a sound-attenuated

dimly-lit room, subjects were instructed to press a button on the left or right armrest of a chair (indicating which side of the stimulus “head” the “ear” appears on) to target stimuli and ignore non-target stimuli. For half of target stimuli, the head was oriented towards the top of the screen (response-hand is congruent with ear-position). For the other half of target stimuli, the head was rotated 180° (response-hand is incongruent with ear-position). These two stimulus manipulations are regarded as “easy” and “difficult” trial-conditions, respectively. The current study focused solely on ERP data from the target condition, as consistent with prior research.

EEG data acquisition

Continuously recorded EEG (61 sensors, 10/20 placement) data were digitized at 1024 Hz with a passband of DC to 205 Hz using the BioSemi ActiveTwo recording system (BioSemi, Amsterdam, Netherlands). Two additional reference electrodes were placed on either earlobe. Vertical and horizontal ocular movements were monitored by two electrodes placed superior and inferior to the right eye and two electrodes placed on left and right temple, respectively.

EEG processing

Data for 12 subjects could not be used because equipment failure resulted in the loss of event triggers. The 422 remaining EEGs were processed offline in MATLAB (version 7.8, Mathworks Inc.) using the EEGLAB toolbox (Delorme and Makeig, 2004) and an automatic routine developed by the first two authors that integrates artifact-pruning elements from published data pipelines (Junghofer et al., 2000; Mognon et al., 2011; Nolan et al., 2010). We adopted the same general approach to Nolan et al. (2010) in that we identified artifact at a progressively finer scale, successively pruning artifact-contaminated data by examining, in order, 1) electrode, 2) time segment, 3) temporal and spatially stereotyped ocular activity (cf. Mognon et al., 2011), and finally 4) electrode/time segments. As in existing EEG processing pipelines, artifact was identified as data segments that exceeded some threshold value (e.g., 3 standard deviations) of the empirical distribution of descriptive properties (e.g., temporal deviation, maximum difference between two time-points) derived for contiguous 1-second segments of multiple-electrode EEG. The threshold was based on a robust measure of spread, the normalized median absolute deviations (Rousseeuw and Croux, 1993) to minimize the influence of outliers on the thresholds used to identify them.

For each subject, continuous EEG was downsampled to 256 Hz and highpass-filtered with a windowed sinc filter (0.1 Hz cutoff, Kaiser window, order of 1286). Gross artifacts, defined as electrode segments in which more than 75% of the samples were contaminated or time segments in which more than 15% of the electrodes were contaminated, were deleted before data were re-referenced to the averaged potential of the earlobe electrodes and lowpass-filtered to remove high-frequency noise (30 Hz cutoff, Kaiser window, order of 644). Artifact-pruned and re-referenced EEG was decomposed with Infomax independent component analysis (Bell and Sejnowski, 1995) for the purpose of correcting blinks and ocular artifacts. Each component's time course and topographic distribution (inverse-weights) were correlated with the time course of a criterion channel (bipolar vertical electrooculogram, or EOG) and a spatial template (typical inverse-weights of a blink

component), respectively. Components with squared correlation-coefficients exceeding threshold derived empirically using an expectation maximization algorithm (Mognon et al., 2011) were considered to represent blink activity and subtracted from the data. Horizontal eye movement artifacts were corrected in a similar manner but with a bipolar horizontal EOG as the signal. Epochs spanning -2 to 2 seconds relative to stimulus-onset were assessed for artifact using similar criteria as in our initial step. Artifact-contaminated electrodes or electrode/epochs were interpolated using a spherical-spline method (Perrin et al., 1989). Trials on which $>15\%$ of electrodes required interpolation were dropped.

A total of seven cases (1.6%) were dropped as a result of automatic processing. Five additional cases (1.2%) were dropped because visual inspection (by a trained psychophysicologist) of averaged ERPs indicated irreparable drift in the vast majority of trial-epochs. This resulted in 410 (94.5 %) cases of analyzable EEGs with an average of 69.6 ($SD = 10.4$) artifact-free trials per subject.

ERP component extraction

Trial-averaged evoked ERPs for each subject-electrode were decomposed into real-valued time-frequency energy surfaces $E(t, f)$ to evaluate the evoked ERP's intensity at specific times ($t = 512, -2$ to 2 seconds) and frequencies ($f = 129, DC$ to 64 at $.5$ Hz steps). Also, each subject-electrode's degree of phase-locking to the stimulus across trials was quantified by computing "phase-locking factor" (PLF, also called inter-trial phase coherence; Delorme and Makeig, 2004; Tallon-Baudry et al., 1996) from the complex-valued (containing phase-information) $C(t, f)$ surface. For each set of N (number of trials) C s extracted from each

subject-electrode, i , we computed $PLF_i(t, f)$ as $\frac{1}{N} \sum_{j=1}^N \exp(\phi_{ij}(t, f))$ where ϕ_{ij} represents the energy-normalized phase-angles from C for that electrode on trial j . PLF ranges from zero, indicating randomness of phases across trials, to one, indicating perfect phase-locking across trials. Most commonly, time-frequency energy and PLF have been computed using wavelet transforms (Delorme and Makeig, 2004; Ford et al., 2008; Roach and Mathalon, 2008; Tallon-Baudry et al., 1996), but to circumvent characteristic time-smearing (low time-frequency resolution) associated with wavelets, we used reduced interference distribution (RID) transforms belonging to Cohen's class to compute energy (real-valued RID-binomial) and PLF (complex-valued RID-Rihaczek). The time-frequency transforms used here provide uniform resolution whereas wavelets do not (Aviyente et al., 2011; Aviyente and Mutlu, 2011; Bernat et al., 2005).

Once evoked energy (hereinafter denoted with "EVK") and PLF ("PLF") were computed for each subject-electrode, measures were baseline corrected within frequency-band by subtracting the pre-stimulus mean (Aviyente et al., 2011; Spencer et al., 2004) within a -1000 and -1 millisecond window to adequately baseline-correct frequencies as low as one hertz (Roach and Mathalon, 2008). Component scores were extracted as mean values within delta ($1 - 3.5$ Hz) and theta ($3.5 - 8$ Hz) bands spanning the window of 300 to 600 milliseconds (encapsulating the P3 peak in these data) following stimulus-onset. We chose only these frequencies because delta and theta are most prominent in P3 (Basar et al., 1999; Bernat et al., 2007; Karakas et al., 2000); their boundary was chosen by "splitting the difference" between commonly-used cutoffs ranging between three and four hertz.

Statistical analyses

Generalized estimating equations (GEEs) were computed in R (version 2.13.1) using the function *geeglm* from the “geepack” package, modeling within-family correlation as exchangeable to account for the lack of independence within twin pairs. Externalizing diagnoses (1 = disorder present, 0 = control) were first regressed onto $\text{delta}_{\text{EVK}}$, $\text{theta}_{\text{EVK}}$, $\text{delta}_{\text{PLF}}$, and $\text{theta}_{\text{PLF}}$ as separate predictors and then again with within-band (e.g., $\text{theta}_{\text{EVK}}$ and $\text{theta}_{\text{PLF}}$) components in the same model as predictors, which permitted us to assess the degree to which PLF within a frequency band might mediate any associations between reduced EVK in that band and externalizing diagnoses. For all models, a form of the Quasi-likelihood under the Independence model Criterion (QIC; Pan, 2001) was computed using the R package “MESS.” Designed as a goodness of fit statistic for GEE models, the QICu used here is appropriate for comparing models with the same correlation structure. When comparing QICu values from two models, it can be inferred that the model with a smaller QICu accounts more adequately for the relationship between predictor(s) and outcome. Moreover, in comparing models with different numbers of predictors, the QICu for the more complex model is penalized for added predictors; this balances the trade-off between goodness of fit and model-complexity. For instance, when we add PLF to EVK in our models, a smaller value of QICu relative to the simpler EVK-only model would indicate that adding PLF to the model effectively offsets the penalty incurred by having added a second parameter, leading one to infer that the more complex model accounts for the data better than the simpler one.

Most research showing P3AR with externalizing-diagnoses is based on the evoked ERP, which is equivalent to the phase-locked energy associated with all the frequencies comprising P3. In a mediation framework this can be thought of as the “total effect” of EVK on externalizing, corresponding to path c in Figure 1A. Theoretically, a high-degree of PLF is necessary for large values of EVK, but large values of EVK are not necessary for a high-degree of PLF. Hence, we tested the mediation model proposed in Figure 1B where the “total effect” has been partitioned into “direct” (path c') and “indirect” (paths a and b) effects. Path c' is computed as the difference between the total effect of EVK (as in Figure 1A) and its indirect effect through PLF, which is the product of a and b . PLF is considered to partially mediate the relationship between EVK and externalizing if a significant reduction in the magnitude of c to c' occurs; or equivalently, if the indirect effect ab is significantly different from zero.

PLF was considered to have partially mediated the relationship between EVK and externalizing if shrinkage in the value of c to c' was significantly different than zero. The difference between c and c' can be approximated by calculating the product of paths a and b . Therefore, the size of this reduction was evaluated with a bootstrapping approach (for review, see Shrout and Bolger, 2002) where 5,000 indirect effects (ab , equivalent to the change in c to c') were simulated from the sample with replacement, keeping the proportion of matched- to unmatched-twin-pairs constant. Confidence intervals were estimated from this distribution of simulated ab effects to evaluate statistical significance.

Results

Analytic ERP/diagnostic data

Six participants were excluded for admitted current drug use or having a positive breathalyzer test. The final diagnostic groups for analysis resulting from EEG processing and diagnostic inclusion/exclusion criteria were as follows: ADHD ($n = 25$), ODD ($n = 41$), CD ($n = 115$), AAB ($n = 60$), AlcD ($n = 154$), NicD ($n = 153$), DrgD ($n = 70$), and externalizing diagnosis-free controls ($n = 93$). Composite variables were also made based on the presence of any childhood disruptive disorder (Any-CDD; $n = 133$), any substance use disorder (Any-SUD; $n = 220$), or any of the seven disorders studied here (Any-EXT; $n = 245$). Sixty-six individuals with usable ERP data did not meet inclusion criteria for either diagnostic or control groups (e.g., those without history of definite externalizing disorder but with a diagnosis of substance abuse). However, a recent paper by Yoon et al. (2013) using the same sample and assessment with identical exclusion criteria has shown that included and excluded individuals did not differ based on P3 amplitude or externalizing psychopathology at their original (age-17) assessment.

Task performance

No significant task performance measures (errors of commission, reaction time) differences existed between diagnostic and control groups ($F_s < 1$, p 's $> .3$).

Evoked energy and phase-locking factor associations with P3 amplitude

Figure 2A displays group-averaged time-domain voltage waveforms at the parietal site for all externalizing-diagnosis groups and controls. The adjacent head-plot displays the topographical distribution of grand-average P3 scores (mean voltage between 300 and 600 milliseconds) for all subjects. The grand-average EVK distribution (i.e. average time-frequency representation of time-domain ERPs) is presented alongside topographical distributions for corresponding delta and theta scores in Figure 2B windows for scores (denoted by dotted boxes). Pixels with the largest values ("hottest" colors) are consistent with times and frequencies where the voltage in Figure 2A is greatest. Likewise, Figure 2C shows the grand-average PLF loadings and topographical distributions for delta and theta scores. Here, pixels that are "hottest" reflect times and frequencies relative to the stimulus where cross-trial ERP phase is most consistent; similar to the EVK grand-average, PLF pixels of the largest value line-up with the P3-peak. Generally, grand means for delta were larger than those for theta, as reflected by the less intense heat-maps for theta relative to delta (which were plotted using the same color scale). Most extant literature has focused on electrode site PZ over temporal/parietal cortex (Euser et al., 2012; Iacono et al., 2002), but cortical generators for P3 are also thought to exist in the frontal lobe (Polich, 2007). Therefore, we selected scores for subsequent analyses from midline-frontal (sites AFZ, FZ, F1, F2, and FCZ) and midline-parietal (CPZ, PZ, P1, P2, and POZ) regions.

Predicting externalizing diagnoses with EVK and PLF

Figures 2D, 2E, and 2F display group differences between the Any-EXT and control groups on measures shown in Figures 2A, 2B, and 2C, respectively. Here, "cooler" colors indicate

topographical regions where reductions in externalizing groups' amplitude, EVK, and PLF scores relative to controls are greatest. It can be seen that for all head-plots in Figure 2D, 2E, and 2F, the Any-EXT group shows a reduction in voltage, EVK, or PLF in delta- and theta-bands in comparison to controls and these reductions are generally greatest in the parietal region. This relationship between externalizing and reduced EVK and PLF is further reflected by the negative regression coefficients and odds ratios (ORs) >1 in each of the logistic models displayed in Table 1.

The left side of Table 1 indicates that for the frontal region, with one exception (DrgD), $\text{delta}_{\text{EVK}}$ was always associated with smaller values of QICu than $\text{delta}_{\text{PLF}}$, indicating that frontal EVK better accounts for the relationship between P3-related delta and externalizing diagnoses than frontal PLF. However, the obverse was true for P3-related frontal theta: with the exception of ADHD and ODD, PLF accounted for more variance in externalizing disorders than EVK. Several effects were statistically significant. One standard deviation decrease in $\text{delta}_{\text{EVK}}$ was associated with a twofold increase in the odds for ADHD as well as increased odds for the Any-EXT composite. No $\text{delta}_{\text{PLF}}$ effects were significant, but $\text{theta}_{\text{PLF}}$ was significantly associated with all individual SUDs, as well as Any-CDD, Any-SUD, and Any-EXT composites.

The same analyses were carried out for scores at the midline-parietal region (Table 1, right). Comparing delta components, for disinhibitory disorders (ADHD, ODD, CD, AAB), EVK was always associated with smaller QICu than PLF, indicating that EVK was the better predictor of these disorders. The opposite relationship was evident for SUDs (NicD, AlcD, DrgD, Any-SUD) and Any-EXT; PLF accounted for more variance in diagnoses than did EVK. Turning to theta at the parietal site, across the board, $\text{theta}_{\text{PLF}}$ prediction models were associated with better model-fit than $\text{theta}_{\text{EVK}}$, suggesting that $\text{theta}_{\text{PLF}}$ more strongly predicts all of the externalizing disorders. Additionally, the ORs for PLF were significant for all of the individual disorders and composite diagnostic groups, while EVK ORs was significant in nearly all cases. One standard deviation decrease on $\text{delta}_{\text{EVK}}$, $\text{delta}_{\text{PLF}}$, $\text{theta}_{\text{EVK}}$, or $\text{theta}_{\text{PLF}}$ was associated with a 34% to 44% increase in odds for having an externalizing diagnosis (Any-EXT).

Does adding PLF to EVK improve goodness of fit in predicting externalizing disorders?

An important consideration is whether PLF adds sufficiently to the prediction of externalizing beyond EVK to justify increasing model complexity by adding another predictor. When frontal PLF and EVK were entered as dual predictors for externalizing diagnoses, QICu values for the dual predictor model were smaller than those for single predictor EVK models in most cases (see Table 2 for change in QICu values), despite many single predictor PLF models having no significant regression coefficients in Table 1. With one exception (predicting AAB using delta), the dual predictor model at the parietal site resulted in an improvement in fit over the EVK-only model. To summarize, 40 model fitting tests were carried out to see if a model that included both PLF and EVK predicted externalizing better than one using EVK alone, and in 85% (34/40) of the comparisons, the dual predictor model fit was better, pointing to the importance of PLF over and above EVK alone to the prediction of externalizing.

Does PLF mediate the effects of EVK?

Also of interest was whether the association between reduced energy and externalizing disorders was mediated by a reduction in the phase-locking of EEG activity. To simplify this analysis, we carried out these mediation analyses using the model in Figure 1 at the parietal site (which produced stronger effects than the frontal site) for the three composite disorders. We first examined results for delta and found that path c' was not significantly smaller than path c and no indirect effect (path ab , Figure 1B) was detected, thus failing to provide evidence that for delta, the EVK effect was mediated by PLF. As illustrated in Figure 3, mediation effects were observed for theta. The total effect of θ_{EVK} (path c) became non-significant (path c') while the effect of θ_{PLF} (path b) remained substantial in models predicting Any-SUD ($p = .04$) and Any-EXT ($p = .05$). A mediating role of θ_{EVK} by θ_{PLF} (path ab) was significant for these two models, suggesting that a reduction in P3-related theta phase-locking at the parietal site may partially explain the total effect of reduced theta energy on externalizing diagnoses, particularly those involving SUDs.

Discussion

The present study examined how inter-trial phase-locking on target trials relates to externalizing disorders and tested the hypothesis that reduced inter-trial phase-locking contributes to the association between reduced P3-related evoked energy and externalizing psychopathology. Energy and phase-locking scores in delta and theta frequencies corresponding to P3 peak-latency were smaller for externalizing-diagnosed individuals in comparison to controls. To the best of our knowledge, this is the first report demonstrating that reduced phase-locking was a significant predictor of antisocial behavior, CDDs, and SUDs. Additionally, by using both evoked energy and inter-trial phase-locking in the same model to predict externalizing diagnoses (rather than evoked energy by itself), we accounted for more variance in externalizing diagnoses. In some cases (e.g., frontal delta) this improvement in fit was small whereas in others (e.g., theta), it was larger (see Table 2). Moreover, theta-band associations between evoked energy and externalizing composites (Any-SUD and Any-EXT) were significantly mediated by theta phase-locking. This was not the case for delta-band evoked energy and phase-locking.

The association between externalizing disorders and highly variable EEG phase (trial-to-trial “arrhythmia”) during the P3 time-window might provide insight into several differences in neurotransmission that have been implicated in the etiology of alcoholism and ADHD. Relative to non-preferring mice, the alcohol-preferring inbred mouse strain C57BL/6 also shows decrements in P3-related phase-locking in delta- and theta-frequencies (Criado and Ehlers, 2009). This mouse model of alcoholism exhibits decreased hippocampal acetylcholine concentrations (Imperato et al., 1996), decreased sensitivity to glutamate agonists (Kosobud and Crabbe, 1990), and has been suggested to have deficits in γ -aminobutyric-acid (GABA) receptor function (Metten and Crabbe, 2005). Such associations between EEG and human alcoholism have also been supported by linkage to genes with cholinergic, glutamatergic, and GABAergic functions (for review, see Rangaswamy and Porjesz, 2008). Reduced theta-band phase-locking in the time-window between stimulus and button-response has also been observed in ADHD (McLoughlin et al., 2014). Several

candidate gene studies suggest abnormal neurotransmission in ADHD (particularly genes related to catecholamine function; Faraone et al., 2005), but what these mean for P3-related delta and theta expression remains unclear. Because differences in evoked energy are thought to reflect changes in the number of neurons directly activated by sensory stimulation and differences in phase-locking are thought to be influenced by “top down” neuromodulatory mechanisms (Sauseng et al., 2007), perhaps decrements in phase-locking for externalizing individuals is at least partly due to dysfunctional “tuning” of ongoing EEG rhythms by GABAergic interneurons, particularly in the theta-band (Cobb et al., 1995).

It is not known whether phase-locking differences between externalizing- and control-groups reflected preexisting differences between the groups (e.g., genes) or neurotoxic effects of chronic/heavy substance use. Indeed, significant effects and better model-fit values were associated with phase-locking for SUDs. Substance use, particularly alcoholism, has been posited to interfere with GABAergic and glutamatergic neurotransmission, which may be in part responsible for some phase-locking difference reported here. However, P3 deficits in SUDs appear to be strongly familial (Euser et al., 2012) and mouse strains liable to develop an alcohol preference show phase-locking deficits before ever being administered alcohol (Criado and Ehlers, 2009). Given extant literature, we do not conclude that phase-locking effects are a consequence of substance use, although future research should examine this notion more fully. We do conclude that phase-locking may contribute to the P3 amplitude differences between heavy substance users and controls. Although there is no widely-accepted method to determine the significance of changes in QICu values, adding phase-locking measures clearly better-accounted for externalizing prediction because QICu values were smaller when phase-locking was used as a predictor of SUDs either alone (Table 1; 5/8 instances for delta, 8/8 for theta) or in conjunction with evoked energy (Table 2; 6/8 for delta, 8/8 for theta).

These findings were limited to externalizing disorders and do not rule out the possibility that similar effects might also be observed with other clinical diagnoses where P3 amplitude is abnormally low such as schizophrenia (Jeon and Polich, 2003). For instance, Ford et al. (1994) found that the latencies of trial level P3 peaks were more variable for schizophrenia patients relative to controls. When these findings were revisited (Ford et al., 2008), they found that patients exhibited less intertrial delta and theta phase-locking and weaker trial level delta energy (irrespective of phase) during P3. Unlike our study, Ford et al.’s (2008) results indicated that delta measures accounted for evoked P3 amplitude reductions seen in patients. Nonetheless, the present report and the Ford et al. findings converge by showing reduced delta and theta phase-locking for schizophrenia and externalizing groups, a potentially interesting neurobiological similarity that could help explain comorbidity shared across these disorders. Viewing P3 in terms of its time-frequency energy and phase-locking dynamics may prove to be an important tool for future research to compare and contrast pathophysiological factors for a number of psychiatric disorders. By combinative use of multiple P3-related measures (“multivariate endophenotype”; cf. Gilmore et al., 2010b; Iacono et al., 2000), perhaps greater specificity and statistical power in prediction of certain diagnoses can be achieved.

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References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed.. Washington, DC: American Psychiatric Press; 1987. rev.
- Andrew C, Fein G. Event-related oscillations versus event-related potentials in a P300 task as biomarkers for alcoholism. *Alc Clin Exp Res*. 2010; 34:669–680.
- Aviyente S, Bernat EM, Evans WS, Sponheim SR. A phase synchrony measure for quantifying dynamic functional integration in the brain. *Hum Br Mapp*. 2011; 32:80–93.
- Aviyente S, Mutlu AY. A Time-Frequency-Based Approach to Phase and Phase Synchrony Estimation. *IEEE Trans Sig Proc*. 2011; 59:12.
- Basar E, Basar-Eroglu C, Karakas S, Schurmann M. Are cognitive processes manifested in event-related gamma, alpha, theta and delta oscillations in the EEG? *Neurosci Lett*. 1999; 259:165–168. [PubMed: 10025584]
- Begleiter H, Porjesz B, Bihari B, Kissin B. Event-related brain potentials in boys at risk for alcoholism. *Science*. 1984; 225:1493–1496. [PubMed: 6474187]
- Bell AJ, Sejnowski TJ. An information-maximization approach to blind separation and blind deconvolution. *Neural computation*. 1995; 7:1129–1159. [PubMed: 7584893]
- Bernat EM, Malone SM, Williams WJ, Patrick CJ, Iacono WG. Decomposing delta, theta, and alpha time-frequency ERP activity from a visual oddball task using PCA. *Int J Psychophys*. 2007; 64:62–74.
- Bernat EM, Williams WJ, Gehring WJ. Decomposing ERP time-frequency energy using PCA. *Clin Neurophysiol*. 2005; 116:1314–1334. [PubMed: 15978494]
- Buzsaki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents--EEG, ECoG, LFP and spikes. *Nat Rev Neurosci*. 2012; 13:407–420. [PubMed: 22595786]
- Cobb SR, Buhl EH, Halasy K, Paulsen O, Somogyi P. Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature*. 1995; 378:75–78. [PubMed: 7477292]
- Criado JR, Ehlers CL. Event-related oscillations as risk markers in genetic mouse models of high alcohol preference. *Neuroscience*. 2009; 163:506–523. [PubMed: 19540906]
- Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Meth*. 2004; 134:9–21.
- Elkins IJ, Iacono WG, Doyle AE, McGue M. Characteristics associated with the persistence of antisocial behavior: Results from recent longitudinal research. *Aggress Viol Behav*. 1997; 2:101–124.
- Euser AS, Arends LR, Evans BE, Greaves-Lord K, Huizink AC, Franken IH. The P300 event-related brain potential as a neurobiological endophenotype for substance use disorders: a meta-analytic investigation. *Neurosci Biobehav Revs*. 2012; 36:572–603. [PubMed: 21964481]
- Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005; 57:1313–1323. [PubMed: 15950004]
- Ford JM, Roach BJ, Hoffman RS, Mathalon DH. The dependence of P300 amplitude on gamma synchrony breaks down in schizophrenia. *Brain Res*. 2008; 1235:133–142. [PubMed: 18621027]
- Ford JM, White P, Lim KO, Pfefferbaum A. Schizophrenics have fewer and smaller P300s: a single-trial analysis. *Biol Psychiatry*. 1994; 35:96–103. [PubMed: 8167215]
- Gilmore CS, Malone SM, Bernat EM, Iacono WG. Relationship between the P3 event-related potential, its associated time-frequency components, and externalizing psychopathology. *Psychophysiology*. 2010a; 47:123–132. [PubMed: 19674392]

- Gilmore CS, Malone SM, Iacono WG. Brain electrophysiological endophenotypes for externalizing psychopathology: a multivariate approach. *Behavior genetics*. 2010b; 40:186–200. [PubMed: 20155392]
- Hamdi NR, Iacono WG. Lifetime prevalence and co-morbidity of externalizing disorders and depression in prospective assessment. *Psychological medicine*. 2014; 44:315–324. [PubMed: 23590946]
- Hicks BM, Bernat E, Malone SM, Iacono WG, Patrick CJ, Krueger RF, et al. Genes mediate the association between P3 amplitude and externalizing disorders. *Psychophysiology*. 2007; 44:98–105. [PubMed: 17241145]
- Iacono WG, Carlson SR, Malone SM. Identifying a multivariate endophenotype for substance use disorders using psychophysiological measures. *Int J Psychophys*. 2000; 38:81–96.
- Iacono WG, Carlson SR, Malone SM, McGue M. P3 event-related potential amplitude and the risk for disinhibitory disorders in adolescent boys. *Arch Gen Psychiatry*. 2002; 59:750–757. [PubMed: 12150652]
- Iacono WG, Carlson SR, Taylor J, Elkins IJ, McGue M. Behavioral disinhibition and the development of substance-use disorders: findings from the Minnesota Twin Family Study. *Development Psychopathology*. 1999; 11:869–900. [PubMed: 10624730]
- Iacono WG, Malone SM. Developmental Endophenotypes: Indexing Genetic Risk for Substance Abuse with the P300 Brain Event-Related Potential. *Child development perspectives*. 2011; 5:239–247. [PubMed: 22247735]
- Iacono WG, McGue M. Minnesota Twin Family Study. *Twin Res*. 2002; 5:482–487. [PubMed: 12537881]
- Imperato A, Obinu MC, Mascia MS, Casu MA, Zocchi A, Cabib S, et al. Strain-dependent effects of dopamine agonists on acetylcholine release in the hippocampus: an in vivo study in mice. *Neuroscience*. 1996; 70:653–660. [PubMed: 9045078]
- Jeon YW, Polich J. Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. *Psychophysiology*. 2003; 40:684–701. [PubMed: 14696723]
- Jones KA, Porjesz B, Chorlian D, Rangaswamy M, Kamarajan C, Padmanabhapillai A, et al. S-transform time-frequency analysis of P300 reveals deficits in individuals diagnosed with alcoholism. *Clin Neurophysiol*. 2006; 117:2128–2143. [PubMed: 16926113]
- Junghofer M, Elbert T, Tucker DM, Rockstroh B. Statistical control of artifacts in dense array EEG/MEG studies. *Psychophysiology*. 2000; 37:523–532. [PubMed: 10934911]
- Karakas S, Erzengin OU, Basar E. The genesis of human event-related responses explained through the theory of oscillatory neural assemblies. *Neurosci Lett*. 2000; 285:45–48. [PubMed: 10788704]
- Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry*. 2003; 60:929–937. [PubMed: 12963675]
- Kosobud AE, Crabbe JC. Genetic correlations among inbred strain sensitivities to convulsions induced by 9 convulsant drugs. *Brain Res*. 1990; 526:8–16. [PubMed: 2078820]
- Kosten TA, Rounsaville BJ. Sensitivity of psychiatric diagnosis based on the best estimate procedure. *Am J Psychiatry*. 1992; 149:1225–1227. [PubMed: 1503136]
- Krueger RF. The structure of common mental disorders. *Arch Gen Psychiatry*. 1999; 56:921–926. [PubMed: 10530634]
- Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM. Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch Gen Psychiatry*. 1982; 39:879–883. [PubMed: 7103676]
- Makeig S, Westerfield M, Jung TP, Enghoff S, Townsend J, Courchesne E, et al. Dynamic brain sources of visual evoked responses. *Science*. 2002; 295:690–694. [PubMed: 11809976]
- McLoughlin G, Palmer JA, Rijdsdijk F, Makeig S. Genetic overlap between evoked frontocentral theta-band phase variability, reaction time variability, and attention-deficit/hyperactivity disorder symptoms in a twin study. *Biol Psychiatry*. 2014; 75:238–247. [PubMed: 24001472]
- Metten P, Crabbe JC. Alcohol withdrawal severity in inbred mouse (*Mus musculus*) strains. *Behav Neurosci*. 2005; 119:911–925. [PubMed: 16187819]

- Mognon A, Jovicich J, Bruzzone L, Buiatti M. ADJUST: An automatic EEG artifact detector based on the joint use of spatial and temporal features. *Psychophysiology*. 2011; 48:229–240.
- Nieuwenhuis S, Aston-Jones G, Cohen JD. Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psych Bull*. 2005; 131:510–532.
- Nolan H, Whelan R, Reilly RB. FASTER: Fully Automated Statistical Thresholding for EEG artifact Rejection. *J Neurosci Meth*. 2010; 192:152–162.
- Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics*. 2001; 57:120–125. [PubMed: 11252586]
- Patrick CJ, Bernat EM, Malone SM, Iacono WG, Krueger RF, McGue M. P300 amplitude as an indicator of externalizing in adolescent males. *Psychophysiology*. 2006; 43:84–92. [PubMed: 16629688]
- Perrin F, Pernier J, Bertrand O, Echallier JF. Spherical splines for scalp potential and current density mapping. *Electroenceph Clin Neurophysiol*. 1989; 72:184–187. [PubMed: 2464490]
- Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol*. 2007; 118:2128–2148. [PubMed: 17573239]
- Polich J, Pollock VE, Bloom FE. Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psych Bull*. 1994; 115:55–73.
- Rangaswamy M, Jones KA, Porjesz B, Chorlian DB, Padmanabhapillai A, Kamarajan C, et al. Delta and theta oscillations as risk markers in adolescent offspring of alcoholics. *Int J Psychophys*. 2007; 63:3–15.
- Rangaswamy M, Porjesz B. Uncovering genes for cognitive (dys)function and predisposition for alcoholism spectrum disorders: a review of human brain oscillations as effective endophenotypes. *Brain Res*. 2008; 1235:153–171. [PubMed: 18634760]
- Reich W. Diagnostic interview for children and adolescents (DICA). *J Am Acad Child Adolesc Psychiatry*. 2000; 39:59–66. [PubMed: 10638068]
- Roach BJ, Mathalon DH. Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. *Schiz Bull*. 2008; 34:907–926.
- Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, et al. The Composite International Diagnostic Interview. An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Arch Gen Psychiatry*. 1988; 45:1069–1077. [PubMed: 2848472]
- Rousseeuw PJ, Croux C. Alternatives to the Median Absolute Deviation. *J Am Stat Assoc*. 1993; 88:1273–1283.
- Sauseng P, Klimesch W, Gruber WR, Hanslmayr S, Freunberger R, Doppelmayr M. Are event-related potential components generated by phase resetting of brain oscillations? A critical discussion. *Neuroscience*. 2007; 146:1435–1444. [PubMed: 17459593]
- Sayers BM, Beagley HA, Henshall WR. The mechanism of auditory evoked EEG responses. *Nature*. 1974; 247:481–483. [PubMed: 4818547]
- Shah AS, Bressler SL, Knuth KH, Ding M, Mehta AD, Ulbert I, et al. Neural dynamics and the fundamental mechanisms of event-related brain potentials. *Cereb Cortex*. 2004; 14:476–483. [PubMed: 15054063]
- Shrout PE, Bolger N. Mediation in experimental and nonexperimental studies: new procedures and recommendations. *Psych Meth*. 2002; 7:422–445.
- Spencer KM, Nestor PG, Perlmuter R, Niznikiewicz MA, Klump MC, Frumin M, et al. Neural synchrony indexes disordered perception and cognition in schizophrenia. *PNAS*. 2004; 101:17288–17293. [PubMed: 15546988]
- Tallon-Baudry C, Bertrand O, Delpuech C, Pernier J. Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. *J Neurosci*. 1996; 16:4240–4249. [PubMed: 8753885]
- Welner Z, Reich W, Herjanic B, Jung KG, Amado H. Reliability, validity, and parent-child agreement studies of the Diagnostic Interview for Children and Adolescents (DICA). *J Am Acad Child Adolesc Psychiatry*. 1987; 26:649–653. [PubMed: 3667494]

- Yoon HH, Iacono WG, Malone SM, McGue M. Using the brain P300 response to identify novel phenotypes reflecting genetic vulnerability for adolescent substance misuse. *Addict Behav.* 2006; 31:1067–1087. [PubMed: 16644137]
- Yoon HH, Malone SM, Burwell SJ, Bernat EM, Iacono WG. Association between P3 event-related potential amplitude and externalizing disorders: A time-domain and time-frequency investigation of 29-year-old adults. *Psychophysiology.* 2013; 50:595–609. [PubMed: 23614581]

Highlights

1) Trial to trial variation in P3-related delta and theta EEG phase predicts externalizing disorders (antisocial behavior, ADHD, substance dependence). 2) Time-frequency energy and phase-locking are better predictors of externalizing disorders together than either alone. 3) These novel findings suggest weakened neuromodulation during cognitive processes in externalizing individuals.

Figure 1. Does reduced intertrial phase-locking mediate energy deficits in evoked P3 energy?

Most research showing P3-amplitude reductions with externalizing-diagnoses (EXT) uses the evoked event-related potential, which is composed of phase-locked energy (EVK). In a mediation framework, the contribution attributable to P3 amplitude can be thought of as the "total effect" of EVK on EXT, corresponding to path c in model **A**. Theoretically, a high-degree of phase-locking factor (PLF, phase-locking independent of energy) is necessary for large values of EVK, but large values of EVK are not necessary for a high-degree of PLF. This is reflected in the mediation model **B** where the total effect, has been partitioned into "direct" (path c') and "indirect" (paths a and b , or ab) effects. Path c' is the difference between the total effect of EVK and the indirect effect through PLF, which is the product of

a and b . Partial mediation is inferred when a reduction in the magnitude of c to c' has occurred; or equivalently, an indirect effect ab is significantly different from zero.

Figure 2. Grand averages, topographical distributions and group-differences

A) Time-domain group-averaged voltage waveforms at the parietal site for attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), adult antisocial behavior (AAB), nicotine dependence (NicD), alcohol dependence (AlcD), illicit substance dependence (DrgD), and externalizing diagnosis-free controls (Con). The adjacent head-plot displays the topographical distribution of grand-average P3 scores for all subjects. **B)** Grand-average time-frequency evoked energy (phase-invariant stimulus-locked energy, EVK; in Joules, or J) transform of the time-domain voltage waveforms and topographical distributions for mean P3-corresponding delta and theta scores (windows for time-frequency scores denoted by dotted boxes). **C)** Grand-average phase-locking factor (the degree to which intertrial EEG phases are consistent, PLF) loadings and topographical distributions of delta and theta scores. Figures **D**, **E**, and **F** display group differences between externalizing (any of the above disorders) and control groups on measures displayed in **A**, **B**, and **C**, respectively; “cooler” colors indicate topographical regions where reductions in externalizing groups relative to controls are greatest.

Figure 3. Theta phase-locking partially mediates the pathway between evoked energy and externalizing prediction

Mediation models with parietal theta-frequency evoked energy (EVK) and phase-locking factor (PLF) as dual predictors of externalizing composites for any childhood disruptive disorder (Any-CDD), any substance use disorder (Any-SUD), and any externalizing disorder (Any-EXT). The total effect of EVK on diagnostic composites (path c) became non-significant (path c') while the effect of PLF remained significant in models predicting Any-SUD and Any-EXT. This mediating role of EVK by PLF (i.e. the indirect path ab) was also

significant for these two models, suggesting that a reduction in P3-related theta phase-locking partially explains the total effect of reduced theta energy on externalizing diagnoses.

*** $p < .001$, ** $p < .01$, * $p < .05$ for path coefficients.

Table 1

Externalizing diagnoses regressed onto single predictors of energy or phase-locking

Diagnosis	Frontal site					Parietal site						
	Delta _{EVK}			Delta _{apF}		Delta _{EVK}			Delta _{apF}			
	B (SE)	OR	QICu	B (SE)	OR	QICu	B (SE)	OR	QICu	B (SE)	OR	QICu
ADHD	-4.2 (1.5)	2.13 **	348.5	-6.6 (3.8)	1.48	353.8	-3.2 (1.3)	2.25 *	349.5	-6.1 (3.0)	1.62 *	354.0
ODD	-1.5 (0.8)	1.31	429.2	-1.5 (2.0)	1.09	432.1	-2.4 (0.8)	1.80 **	421.1	-6.7 (2.0)	1.68 **	422.8
CD	-1.0 (0.8)	1.20	697.6	-2.6 (1.8)	1.17	698.4	-1.5 (0.7)	1.49 *	694.6	-5.0 (1.8)	1.49 **	695.1
AAB	-0.7 (0.8)	1.15	509.8	-2.3 (2.3)	1.16	510.2	-2.5 (0.8)	1.82 **	500.3	-7.4 (2.2)	1.79 **	503.1
NicD	-0.8 (0.6)	1.15	815.8	-0.6 (1.9)	1.03	817.8	-1.8 (0.6)	1.54 **	805.2	-5.2 (1.8)	1.50 **	804.7
AlcD	-1.0 (0.7)	1.20	818.4	-1.8 (2.1)	1.11	820.1	-0.9 (0.5)	1.27	817.7	-4.0 (1.8)	1.36 *	816.6
DrgD	-1.0 (0.7)	1.21	548.0	-4.3 (2.5)	1.31	547.6	-0.5 (0.6)	1.16	548.0	-4.3 (1.8)	1.41 *	544.7
Any-CDD	-1.1 (0.7)	1.21	753.8	-2.4 (1.8)	1.16	754.6	-1.5 (0.6)	1.47 *	749.9	-5.1 (1.8)	1.50 **	750.2
Any-SUD	-1.1 (0.6)	1.21	1003.0	-2.9 (2.0)	1.18	1004.4	-1.3 (0.5)	1.38 **	999.5	-4.5 (1.6)	1.42 **	999.0
Any-EXT	-1.3 (0.6)	1.25 *	1069.1	-3.0 (2.0)	1.19	1070.6	-1.3 (0.5)	1.38 **	1066.2	-4.5 (1.6)	1.42 **	1065.7
Diagnosis	Theta _{EVK}			Theta _{apF}		Theta _{EVK}			Theta _{apF}			
	B (SE)	OR	QICu	B (SE)	OR	QICu	B (SE)	OR	QICu	B (SE)	OR	QICu
ADHD	-10.0 (5.5)	1.64	353.3	-8.5 (6.3)	1.40	354.8	-17.1 (7.0)	2.27 *	348.3	-14.7 (4.0)	2.24 **	344.9
ODD	-7.8 (5.1)	1.47	426.1	-6.1 (3.7)	1.27	430.3	-10.8 (4.4)	1.66 *	423.0	-10.2 (2.5)	1.74 **	417.0
CD	-2.3 (1.9)	1.15	701.1	-4.8 (2.9)	1.21	698.7	-7.3 (3.1)	1.40 *	694.6	-5.5 (2.1)	1.35 *	694.1
AAB	-4.5 (3.1)	1.26	509.8	-7.1 (3.9)	1.32	509.4	-10.0 (4.3)	1.59 *	505.3	-7.9 (2.9)	1.54 **	504.4
NicD	-5.7 (2.3)	1.30 *	810.8	-7.9 (3.1)	1.33 *	810.7	-9.6 (3.1)	1.49 **	805.5	-8.1 (2.3)	1.53 **	800.9
AlcD	-4.8 (2.7)	1.25	815.4	-8.9 (3.6)	1.40 *	814.9	-6.8 (2.9)	1.35 *	813.9	-6.8 (2.4)	1.44 **	811.5
DrgD	-4.6 (2.9)	1.24	546.2	-9.1 (3.8)	1.43 *	542.9	-6.3 (3.6)	1.34	545.3	-6.1 (2.8)	1.41 *	543.2
Any-CDD	-3.4 (2.2)	1.22	756.4	-6.4 (3.0)	1.29 *	752.8	-8.5 (3.2)	1.47 **	748.5	-6.5 (2.3)	1.42 **	747.4

	Frontal site					Parietal site						
Any-SUD	-3.9 (2.2)	1.20	1001.6	-8.1 (3.1)	1.35 **	999.5	-6.8 (2.6)	1.33 *	998.4	-6.8 (2.2)	1.44 **	994.9
Any-EXT	-3.1 (2.1)	1.18	1070.6	-7.2 (3.0)	1.31 *	1067.2	-6.6 (2.6)	1.34 *	1066.3	-6.6 (2.1)	1.42 **	1062.4

Logistic regressions for delta (1 – 3.5 Hz) and theta (3.5 – 8 Hz) evoked energy (EVK) and phase-locking factor (PLF) at frontal and parietal electrode sites in prediction of attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), adult antisocial behavior (AAB), nicotine dependence (NicD), alcohol dependence (AlcD), and illicit drug dependence (DrgD) diagnoses and composites of any childhood disruptive disorder (Any-CDD), any substance use disorder (Any-SUD), and any externalizing disorder (Any-EXT). Negative regression coefficients (Bs) reflect smaller EVK or PLF values for externalizing groups. Odds ratios (ORs) reflect *increased odds* of disorder *per one standard deviation decrease* on the predictor; this was done by inverting the exponentiated product between the standard deviation of the predictor and its corresponding B. The Quasi-likelihood under the Independence model Criterion (QICu) can be compared across rows within the same quadrant of the table (e.g., ADHD for frontal deltaEVK versus deltaPLF); smaller values of QICu (bolded) indicate better model-fit between EVK and PLF predictors.

* $p < .05$,
** $p < .01$

Table 2

Change in model fit by adding phase-locking factor to evoked energy.

Diagnosis	Frontal site (QICu)		Parietal site (QICu)	
	Delta	Theta	Delta	Theta
ADHD	−0.3	−0.5	−0.3	−5.0
ODD	−0.4	0	−0.4	−7.1
CD	−0.3	−2.2	−0.7	−2.1
AAB	0.2	−0.8	0.4	−2.2
NicD	0	−2.5	−2.4	−6.8
AlcD	−0.1	−2.2	−1.4	−3.2
DrgD	−0.3	−3.4	−4.1	−2.4
Any-CDD	−0.1	−3.3	−0.9	−3.0
Any-SUD	0	−3.1	−1.6	−4.4
Any-EXT	0	−3.7	−1.5	−4.5

Difference in Quasi-likelihood under the Independence model Criterion (QICu) between prediction of externalizing diagnoses using evoked energy (EVK) on its own and using EVK in combination with phase-locking factor (PLF) to predict externalizing diagnoses. Negative values of

QICu indicate that using both within-frequency EVK and PLF as dual predictors of externalizing disorders provides improved model-fit (i.e. less information loss) over solely using EVK.