RESEARCH

Electrophysiological indices of reward anticipation as ADHD risk and prognostic biomarkers

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Abstract

The attention-deficit/hyperactivity disorder (ADHD) clinical phenotype has limitations for deciphering ADHD etiology and predicting prognosis. Although relative to the clinical phenotype, intermediate phenotypes may have better explanatory and prognostic power, the extent to which ADHD intermediate phenotypes are associated with ADHD risk and prognosis is unknown. The aim of this study was to evaluate evidence for event-related potential (ERP) measures of reward anticipation as ADHD risk and prognostic biomarkers. We examined, whether (1) in a sample of adolescents ($N = 304$; $M_{age} = 15.78$ years, $SD = 1.08$; 39.5% female), accounting for the effects of age, sex, ADHD severity and depression, ERPs are associated with ADHD polygenic risk scores (PRSs) (ADHD risk) and (2) in a sample of adolescents at-risk for ADHD ($n = 99$; $M_{age} = 15.78$ years, $SD = 1.08$; 39.5% female), accounting for the effects of age, sex, ADHD severity, depression, and baseline outcome values, ERPs are associated, prospectively, with alcohol misuse (ADHD prognosis). In adolescents, greater ADHD PRSs were associated with lower electrophysiological anticipatory attention to motivationally relevant feedback ($b = -0.115$, $p = .046$ 95%CI [-0.228; -0.002]). The predictors accounted for 5% of the variance in the outcome. In adolescents at-risk for ADHD, at 18-month follow-up, lower electrophysiological anticipatory attention to motivationally relevant feedback was associated with greater alcohol consumption ($b = -7.454$, $p = .007$, 95%CI [-12.873; -2.034]). The predictors accounted for 31% of the variance in this outcome. These findings were replicated in sensitivity analyses with behavioral performance variables added as covariates. The current findings support the hypothesis that ERP amplitudes of reward anticipation may be ADHD risk and prognostic biomarkers and suggest that intermediate phenotypes may confer advantages over the ADHD clinical phenotype in delineating etiology and predicting prognosis.

Keywords ADHD · Biomarker · Event-related potential · Polygenic risk score · Adolescent

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is an early-onset, functionally impairing and prevalent disorder that is associated with greater risk for a host of negative and impairing outcomes [1], including alcohol problems [2]. Adolescents and adults with ADHD are at greater risk for developing alcohol use disorders and problems, and in individuals with ADHD, the lifetime prevalence of alcohol dependence is ~3–11% and of any alcohol use disorder, it is ~43% [2]. The comorbidity of ADHD with alcohol use disorder is associated with additional comorbidities and worse response to treatment [2]. Adolescent alcohol use is associated with attenuated grey matter and deficits in cognitive processes affected by ADHD, including attentional and executive functions, leading to worse cognitive and developmental outcomes for adolescents with ADHD who

frequently consume alcohol. In turn, worse adolescent cognitive outcomes are associated with greater risk for adulthood alcohol binge drinking and, over time, worse health and socioeconomic status [2]. Better understanding the causes of ADHD and identifying predictors in adolescence of prognosis in young adulthood is key to advancing the effectiveness of early identification of at-risk individuals and to the individualization of prevention and treatment, i.e. precision psychiatry.

A clinical phenotype is the clinically observable and relevant characteristics of a disorder, i.e. manifest symptoms. Data indicate efforts to determine etiology and predict prognosis relying on the clinical phenotype have been largely unsuccessful, arguably because the ADHD clinical phenotype is heterogeneous in terms of causes, manifestation, and course [3, 4]. Specifically, a multitude of developmental pathways can lead to a clinical phenotype that is multifaceted both with regard to core symptoms (i.e., difficulties with regulating activity, attention, and impulses [1]), and with regard to associated features (e.g. emotional features [5], executive functioning [6], and reward processing [7]). This multifaceted clinical phenotype, in turn, leads to diverse outcomes.

Intermediate phenotypes are biological markers that are heritable and, considering an etiological framework, located between genetic predisposition and manifest symptoms [8, 9]. Relative to the clinical phenotype, intermediate phenotypes, by virtue of their homogeneity, are hypothesized to have better explanatory and prognostic power [7]. Evidence indicates reward processing may be an ADHD intermediate phenotype, as findings show associations between differences in reward processing and ADHD [3, 4, 7]. Research on biomarkers of reward processing in ADHD is comprised almost exclusively of case–control and diagnostic biomarker studies. A *diagnostic biomarker* (1) confirms or detects the absence/presence of a condition and/or (2) differentiates across presentations (subtypes) of that disorder [10]. In many cases, between-group differences across ADHD and control groups were not detectable/ replicated [11–14], or biomarkers did not differentiate diagnostic groups [7], leading to the conclusion that the biomarker is clinically irrelevant or uninformative. Yet, findings of case–control studies may be misleading as even in the absence of between-group differences in the biomarker, there may be a difference in the extent to which (or whether) the biomarker is associated with functional outcomes. In case of reward processing, even in the absence of between-group differences in neural reward response, there is a between-groups difference in how neural reward response is associated with affective and alcohol outcomes. For example, in adolescents at-risk for ADHD, a negative association was observed between neural reward response and depression and a positive

association was observed between neural reward response and hazardous alcohol use. In adolescents not at-risk for ADHD, neural reward response was not associated with depression and it was negatively associated with hazardous alcohol use [14]. By definition, diagnostic biomarker studies assess the extent to which a given biomarker of an intermediate phenotype converges with the categorical clinical phenotype even though the very utility of the biomarker lies in being an improvement upon and thus nonredundant with the clinical phenotype. Both case–control and diagnostic biomarker studies, albeit informative about differences at the group level, are by nature uninformative about causes and course.

Taken together, the test of clinical utility of a biomarker of an intermediate phenotype is not whether it differs or differentiates between groups, i.e. whether it is a diagnostic biomarker. Rather, the apt test of such utility is whether it explains the causes of or the course of the disorder, i.e. whether it is a risk or a prognostic biomarker [7]. A biomarker that indicates the potential for developing a disorder or medical condition in an individual who does not currently have clinically apparent disorder or the medical condition is classified as a *susceptibility/risk* biomarker. The concept is similar to prognostic biomarkers, except that the key issue is the association with the development of a disease rather than prognosis after one already has the diagnosis [10]. *A prognostic biomarker* indicates the likelihood of a clinical event or outcome, or the progression or recurrence of the disorder in individuals with the condition [10].

Event-related potentials (ERPs) are changes in the electroencephalogram (EEG) as a result of specific events (i.e. stimuli) that reflect, physiologically, the synchronous activity of neuronal populations and psychologically, different cognitive functions, e.g. affective, cognitive, motor, of perceptual processes that are experimentally probed by stimuli or a task [15]. ERPs are appropriate and ideal for assessing aspects of reward processing defined and differentiated based on their occurrence in time [16]. Moreover, given their acceptance by participants, cost effectiveness, and relatively high movement tolerance, ERPs are also suitable for collecting data from large clinical samples longitudinally [17, 18]. Case–control studies indicate between-group differences in ERPs to reward across ADHD and control groups, e.g. adolescents and children with ADHD exhibited enhanced ERPs to escaping delay [19] and to salience of reward [20] as well as greater improvements in behavioral inhibition as a result of social rewards [21].

In some cases, between-group differences in ERPs to reward across ADHD and control groups were not detected, e.g. between adults and children with and without ADHD to error and to inhibition [22–24], to probabilistic reward learning [25], or with regard to improved performance as a result of reward [26]. Diagnostic biomarker studies indicate

in adolescents, ERPs of reward do not differentiate adolescents with and without ADHD [7].

Here, we examine whether electrophysiological indices of reward processing are ADHD risk and prognostic biomarkers. We index ADHD risk by ADHD polygenic risk scores (PRS), which reflect the cumulative effect of frequent genetic variants [5], and index ADHD prognosis via alcohol use. Specifically, our aims were to examine whether (Aim 1) in a sample of adolescents, ERP measures of reward anticipation are associated with ADHD PRSs, and whether (Aim 2) in a sample of adolescents with the ADHD clinical phenotype, ERPs of reward anticipation are associated, longitudinally, with alcohol use. We hypothesized that ERP measures of reward anticipation are associated with ADHD PRSs and longitudinally, with alcohol use.

Across analyses, we account for the effects of age, sex and depression, given an established link between reward processing and these variables [27, 28]. We also account for the effects of ADHD severity; first, to ensure that its shared variance with ADHD PRSs does not account for findings and second, to ensure that any findings obtained reflect effects of the intermediate phenotype beyond the clinical phenotype.

Methods

General procedure

Data analyzed in the current study were collected at the first two assessment sessions of the second (Wave 1) and fourth (18-month follow-up, i.e. Wave 2) years of a longitudinal study, the Budapest Longitudinal Study of ADHD and Externalizing Disorders.

Participants were excluded if they exhibited cognitive ability at or below the percentile rank that corresponds to a full-scale IQ score of 80 on the Wechsler intelligence scale for children–Fourth Edition (WISC-IV) or the Wechsler adult intelligence scale–Fourth Edition (WAIS–IV) [29, 30]; met diagnostic criteria for bipolar, obsessive–compulsive or psychotic disorder on the Structured Clinical Interview for DSM-5 Disorders, Clinical Version (SCID-5-CV); had a prior autism spectrum disorder (severity ≥ 2) diagnosis; reported a neurological illness; and had visual impairment (uncorrected, impaired vision < 50 cm).

Following written informed assent (adolescents) and written informed assent (parents), adolescents completed a series of tests. At Wave 1, the first assessment session comprised clinical interview and cognitive testing, genetic sampling, and completion of questionnaires. The second assessment session comprised an EEG measurement and completion of questionnaires. At Wave 2, the first assessment session comprised completion of questionnaires. The second assessment session comprised an EEG measurement. Questionnaires were completed by parents via Psytoolkit [31, 32] and

Qualtrics (Version June 2020–May 2023) (Qualtrics, Provo, UT). The longitudinal study was approved by the National Institute of Pharmacy and Nutrition (OGYÉI/17089-8/2019). The study has been performed in adherence to the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

ADHD classification was determined using parent-report on the ADHD Rating Scale-5 (ARS-5) [33]. To be classified as at-risk for ADHD, adolescents had to meet a total of ≥ 4 of the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5) ADHD symptoms (from either domain). To be classified as diagnosed with ADHD (for purposes of research), adolescents had to meet a total of ≥ 6 (youth < 17 years old) or 5 (youth ≥ 17 years old) of the DSM-5 ADHD inattentive (IA) or hyperactive/impulsive (H/I) symptoms and exhibit impairment (i.e., rating of ≥ 2 = moderate impairment) in ≥ 3 areas of functioning.

Addressing different questions, findings with samples drawn from the larger longitudinal study, have been previously published [7, 14, 34–36].

Participants

Participants were $N = 304$ adolescents oversampled for ADHD, i.e. recruited from the community and hospitals, as detailed in previous publications [34, 35]; at baseline, adolescents were between 14 and 17 years ($M_{age} = 15.78$ years, $SD = 1.08$; 39.5% female); $n = 132$ (43.4%) met criteria for at-risk for ADHD. At Wave 2, data were available for $n = 233$ adolescents (23% attrition), of whom $n = 99$ (42.5%) were classified at baseline as at-risk for ADHD. At Wave 2, adolescents at-risk for ADHD were between 15 and 19 years ($M_{age} = 17.08$ years, $SD = 1.07$; 29.3% female).

Participants' average cognitive ability was in the 61st percentile ($SD = 20.86$). Based on net household income per person, compared to the 2020 Hungarian average of ~ 147 000 HUF [37], with a sample average of 156 374 HUF ($SD = 77 685$), participating adolescents and their families were from a somewhat above-average socioeconomic background $t(303) = 2.104$, $p = 0.036$, Cohen's $d = 0.121$ (95% CI[0.008, 0.233]). For details on medication washout, see Supplement.

Measures

Rating scale measures

Items from the self-reported European School Survey Project on Alcohol and Other Drugs (ESPAD) master questionnaire [38] were used to assess alcohol consumption, binge drinking, and drunkenness across lifetime, during the last 12 months, and during the last 30 days. The parent-reported ARS 5 [33] was used to assess ADHD. Prior findings

indicate acceptable psychometric properties for both the ESPAD [34, 38–41] and the ARS 5 [7, 14, 33]. In the current sample, the Binge Drinking ($\omega_{baseline} = 0.940$; $\omega_{T2} = 0.938$), the Consumption ($\omega_{baseline} = 0.916$; $\omega_{T2} = 0.934$), and the Drunkenness ($\omega_{baseline} = 0.944$; $\omega_{T2} = 0.938$) subscales of the ESPAD and the ARS-5 Total ($\omega_{baseline} = 0.954$) exhibited acceptable internal consistency and were used in analyses. For details, see Supplement.

Monetary incentive delay (MID) task

The MID task [42, 43] is the recommended task for probing reward anticipation [44] and its electrophysiological version, the e-MID task is appropriate for differentiating electrophysiological response to anticipation and receipt of reward [45]. Evidence indicates reliability of e-MID ERPs [16] as well as convergent validity between e-MID ERPs and self-report reward processing [46]. For description of the employed MID parameters and version, see Supplement. For analyzed ERP variables, see *Analytic Plan*.

EEG data acquisition and processing

Details and procedures for EEG data recording and processing have been described previously [7]. Electrodes and time windows were selected based on the literature [7, 16, 27, 45, 47] based on when and where ERPs were maximal during our pilot studies: Cue P3 at Pz, POz, P1, and P2, for the 450–650 ms time window; Target P3 at CPz, Pz, P1, and P2, for the 200–375 ms time window; SPN at CPz, Pz, CP1, CP2, P1, and P2, for the -200–0 ms time window; and RewP at CPz, Cz, FCz, CP1, CP2, FC1, and FC2, for the 225–325 ms time window [7].

Genotyping

Genomic DNA was isolated from saliva samples. Samples were processed following manufacturer guidelines and recommendations [48] and genotyped using the Illumina Infinium Global Screening Array-24 v3.0 BeadChip by LIFE & BRAIN GmbH (Bonn, Germany).

Analytic plan

All analyses were conducted in RStudio (version 2023.09.1. Build 494, R version 4.3.2.). For packages used, see Table S1.

Data preparation involved imputation of missing data. Missing alcohol use data were substituted using multiple imputation with a state-of-the-art deep learning method, for details see [49]. One of five generated datasets was used.

PRS

ADHD PRSs were calculated based on a discovery dataset involving 38,691 individuals with ADHD and 186,843 controls [50]. Using SNP cutoff of $p < 0.50$, the number of ADHD PRS SNPs was 99,330 with an associated R^2 of $\approx 3.7\%$. For details, see Supplement.

Statistical analyses

Exploratory factor analysis (EFA) EFA was conducted with the aim of dimension reduction, on 48 ERP variables: indices of amplitude and latency for Cue P3, Target P3, SPN, and RewP to conditions of win, lose, neutral win and neutral lose; indices of amplitude for Cue P3, Target P3, SPN, and RewP to win-lose, win-neutral win, lose-neutral lose difference scores.

EFA was conducted applying promax rotation (based on correlations between ERP variables) and 15 factors (based on parallel analysis). Items were first eliminated if they loaded poorly (< 0.40 on any factor) [51, 52] and then if they loaded on more than one factor (> 0.40 on $\geq$ two factors) [51, 52]. Dual loading items were eliminated starting with the item whose second highest loading (absolute value) was the highest. After each elimination, parallel analysis was rerun until no additional items were indicated for removal.

Considering eigenvalues > 1 [53] and factors with $>$ two variables [51, 52], two factors were retained (factor-item loadings ≥ 0.820). The first factor (ERPf1$_{TargetP3}$) included Target P3 amplitude variables, to win (0.939), lose (0.919), neutral win (0.911), and neutral lose (0.912). The second factor (ERPf2$_{SPN}$) included SPN amplitude variables to win (0.823), lose (0.899), neutral win 0.850), and neutral lose (0.820). Target P3 to win and to lose trials achieved acceptable internal consistency by the ~ tenth trial, MID SPN to win and to lose trials by the ~ 20th trial, Target P3 to neutral win and to neutral lose by the ~ 14th trial, and SPN to neutral win and to neutral lose by the ~ 26th trial (Figure S1).

Regression analysis Across Aim 1 and 2 models, linear regression analyses were conducted. Across Aim 1 and Aim 2 models, covariates were baseline age, sex, ADHD severity, and Depressive Problems T scores. For Aim 1 models, independent variables were ADHD PRSs; dependent variables were ERPf1$_{TargetP3}$ and ERPf2$_{SPN}$. For Aim 2 models, independent variables were ERPf1$_{TargetP3}$ and ERPf2$_{SPN}$; dependent variables were Wave 2 values of alcohol use (ESPAD binge drinking, consumption, and drunkenness subscales). For Aim 1 models, additional covariates were the first four genetic principal components and for Aim 2 models, additional covariates were baseline values of the outcome variable. p-values corresponding to the effect of interest were adjusted for false discovery rate (FDR) [54].

Across models, distribution of residuals was checked using normality tests (Anderson–Darling, Lilliefors-corrected Kolmogorov–Smirnov as well as visual inspection of diagnostic plots (histograms, density and Q-Q plots); homoscedasticity using the studentized Breusch-Pagan test, and multicollinearity using variance inflation factors. If the assumption of normal distribution of residuals was violated, robust linear regression analysis was conducted applying SMDM estimation with the psi function set to LQQ. Heteroscedasticity ($ps > 0.05$) and multicollinearity (VIFs < 1.24) were never observed.

To determine whether findings held accounting for behavioral performance variables, indices of reaction time (RT) to target were added as covariates to each model in sensitivity analyses conducted following identical steps as main analyses (see Supplement).

To determine whether attrition was at random, binary logistic regression analyses were conducted with age, sex, ADHD risk status, cognitive ability, socioeconomic status and Wave 1 ESPAD scores as independent variables entered simultaneously and whether an adolescent had Wave 2 data as the dependent variable.

Results

Attrition and basic descriptives

The model for attrition analysis was nonsignificant: $\chi^2(9) = 9.266$, $p = 0.413$. For descriptive statistics of and correlations across main study variables, see Tables S2 and S3.

ERPs

For scalp distributions and ERP grand average waveforms for Aim 1 and 2 analyses, see Figs. 1 and 2.

Aim 1

The robust regression model did not predict ERPf1$_{TargetP3}$ ($\chi^2(9) = 6.552$, $p = 0.684$). The linear regression model predicted ERPf2$_{SPN}$, ($F(9, 272) = 2.600$, $p = 0.007$; adj. $R^2 = 0.049$) (Table 1), with a negative association of standardized ADHD PRSs ($b = -0.115$, $SE = 0.057$, $p = 0.046$) and a positive association of baseline Depressive Problems scores ($b = 0.017$, $SE = 0.007$, $p = 0.019$) with ERPf2$_{SPN}$ scores (Fig. 3). In sensitivity analyses, alternative models with behavioral performance variables as additional covariates were comparable to main models (see Supplement).

Aim 2

The robust regression model with ERPf1$_{TargetP3}$ predicted Wave 2 alcohol consumption ($\chi^2(6) = 48.053$, $p < 0.001$, adj. $R^2 = 0.295$) (Table 2), with (no association of ERPf1$_{TargetP3}$ $p_{FDR} = 0.120$, but) a positive association of baseline alcohol consumption scores ($b = 0.814$, $SE = 0.152$, $p < 0.001$) with Wave 2 alcohol consumption scores. The robust regression model with ERPf2$_{SPN}$ predicted Wave 2 alcohol consumption ($\chi^2(6) = 51.807$, $p < 0.001$, adj. $R^2 = 0.316$), with a negative association of ERPf2$_{SPN}$ ($b = -7.454$, $SE = 2.728$, $p_{FDR} = 0.042$) and of baseline alcohol consumption scores ($b = 0.891$, $SE = 0.146$, $p < 0.001$) with Wave 2 alcohol consumption scores (Fig. 4). In sensitivity analyses, alternative models with behavioral performance variables as additional covariates were comparable to main models (see Supplement).

The Wave 2 binge drinking robust regression models with ERPf1$_{TargetP3}$ ($\chi^2(6) = 48.292$, $p < 0.001$, adj. $R^2 = 0.301$) and with ERPf2$_{SPN}$ ($\chi^2(6) = 48.385$, $p < 0.001$, adj. $R^2 = 0.301$) were significant, with (no association of ERPf1$_{TargetP3}$ $p_{FDR} = 0.480$ or ERPf2$_{SPN}$ $p_{FDR} = 0.480$, but) a positive association of age (ERPf1$_{TargetP3}$ model: $b = 1.581$, $SE = 0.698$, $p = 0.026$ and ERPf2$_{SPN}$ model: $b = 1.792$, $SE = 0.693$, $p = 0.011$) and of baseline binge drinking (ERPf1$_{TargetP3}$ model: $b = 0.729$, $SE = 0.127$, $p < 0.001$ and ERPf2$_{SPN}$ model: $b = 0.767$, $SE = 0.127$, $p < 0.001$) with Wave 2 binge drinking scores. In sensitivity analyses, alternative models with behavioral performance variables as additional covariates were comparable to main models (see Supplement).

The Wave 2 drunkenness robust regression models with ERPf1$_{TargetP3}$ ($\chi^2(6) = 49.469$, $p < 0.001$, adj. $R^2 = 0.444$) and with ERPf2$_{SPN}$ ($\chi^2(6) = 49.261$, $p < 0.001$, adj. $R^2 = 0.447$) were significant, with (no association of ERPf1$_{TargetP3}$ $p_{FDR} = 0.819$ or ERPf2$_{SPN}$ $p_{FDR} = 0.819$, but) a positive association of baseline drunkenness (ERPf1$_{TargetP3}$ model: $b = 0.856$, $SE = 0.102$, $p < 0.001$ and ERPf2$_{SPN}$ model: $b = 0.889$, $SE = 0.106$, $p < 0.001$) with Wave 2 drunkenness scores. In sensitivity analyses, alternative models with behavioral performance variables as additional covariates were comparable to main models (see Supplement).

Discussion

Earlier we argued that despite its advantages in clinical practice, the ADHD clinical phenotype has limitations with regard to determining etiology and explaining prognosis. We hypothesized that intermediate phenotypes may confer advantages over the clinical phenotype in these regards. To evaluate this hypothesis, we evaluated evidence for electrophysiological reward anticipation as an ADHD risk and prognostic biomarker. To this end, rather than evaluating
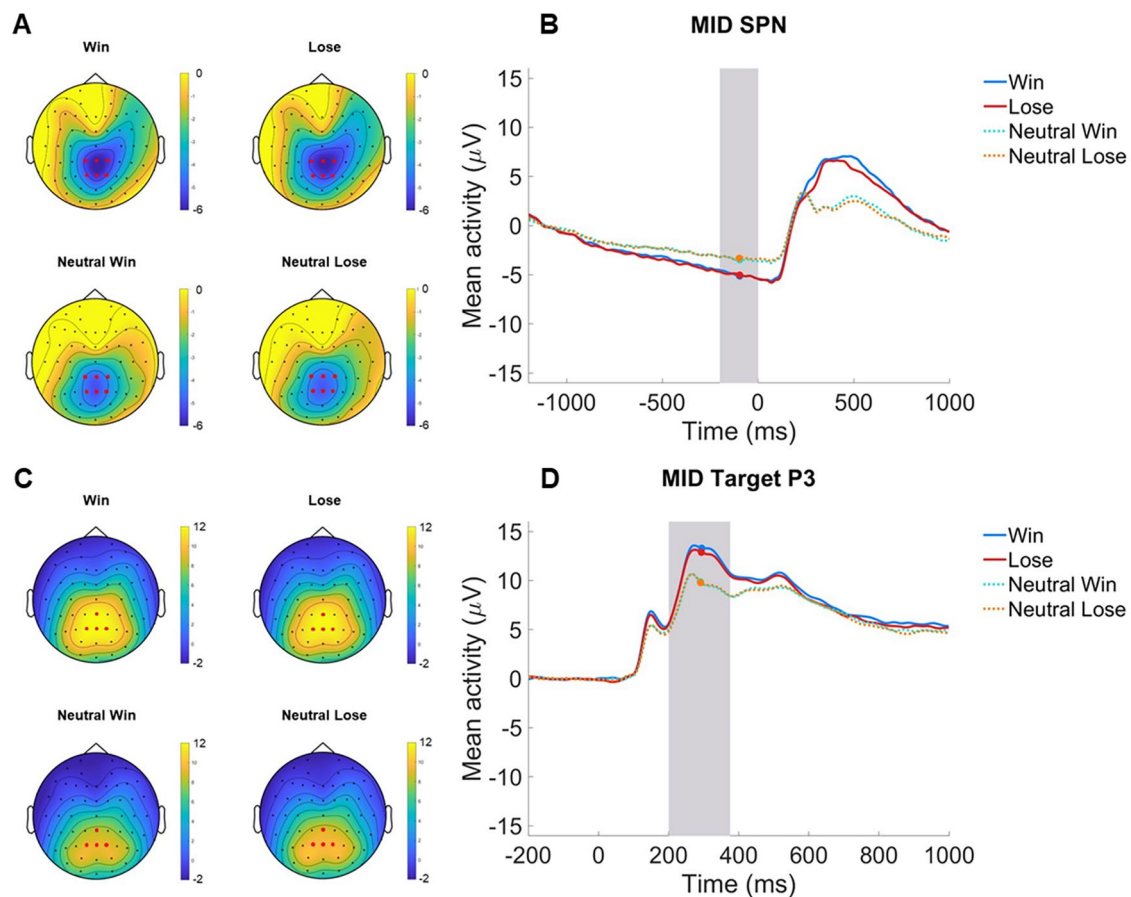
Fig. 1 MID SPN and Target P3 in the Aim 1 analysis sample. **A** Scalp distributions depicting activation before feedback in win (SPN win), lose (SPN lose), neutral win (SPN neutral win), and neutral lose (SPN neutral lose) in the -200–0 ms time window, with electrodes selected for scoring the SPN (CPz, Pz, CP1, CP2, P1, and P2) in red. **B** ERP grand average waveforms (negative up) of the win (blue), lose (red), neutral win (cian, dotted), and neutral lose (range, dotted) condition cues. Feedback stimuli were presented at 0 ms and ERPs scored in the -200–0 ms time window indicated by grey shad-ing. **C** Scalp distributions depicting activation to target stimuli sign-aling win (Target P3 win), lose (Target P3 loss), neutral win (Target P3 neutral win), and neutral lose (Target P3 neutral lose) in the 200–375 ms time window, with electrodes selected for scoring the Target P3 (CPz, Pz, P1, and P2) in red. **D** ERP grand average waveforms (negative up) of the win (blue), lose (red), neutral win (cian, dotted), and neutral lose (range, dotted) condition cues. Target stimuli were presented at 0 ms and ERPs were scored in the 200–375 ms time window indicated by grey shading. N = 282

evidence for electrophysiological reward anticipation as a biomarker of the clinical phenotype, we examined whether electrophysiological reward anticipation is associated with ADHD polygenic risk and, in individuals with the ADHD clinical phenotype, with ADHD prognosis.

Data indicate ERPs of reward anticipation and initial response to reward attainment may not be ADHD diagnostic biomarkers [7]. We have argued, however, that differentiat-ing between groups that are defined based on clinical phe-notype (i.e., with and without ADHD) by definition neces-sitates considerable overlap between the biomarker and the clinical phenotype. If an intermediate phenotype confers an advantage over the clinical phenotype in determining etiol-ogy and in predicting prognosis, then the intermediate phe-notype will not overlap with the clinical phenotype, rather

it will be associated with indices of etiology and prognosis above and beyond the clinical phenotype [7, 55].

Regarding etiology or risk, the current findings evince that ERPs of reward anticipation may be ADHD risk bio-markers insofar as ERPs of reward anticipation were associ-ated with ADHD PRSs, above and beyond ADHD severity. These results suggest that there is an association between the biomarker and an index of ADHD etiology. Next steps for validating ERPs of reward anticipation as ADHD risk biomarkers include examining the extent to which ERPs of reward anticipation predict development of ADHD in children before the observable emergence of the clinical phenotype.

Regarding prognosis, the current findings evince that ERPs of reward anticipation may be ADHD prognostic
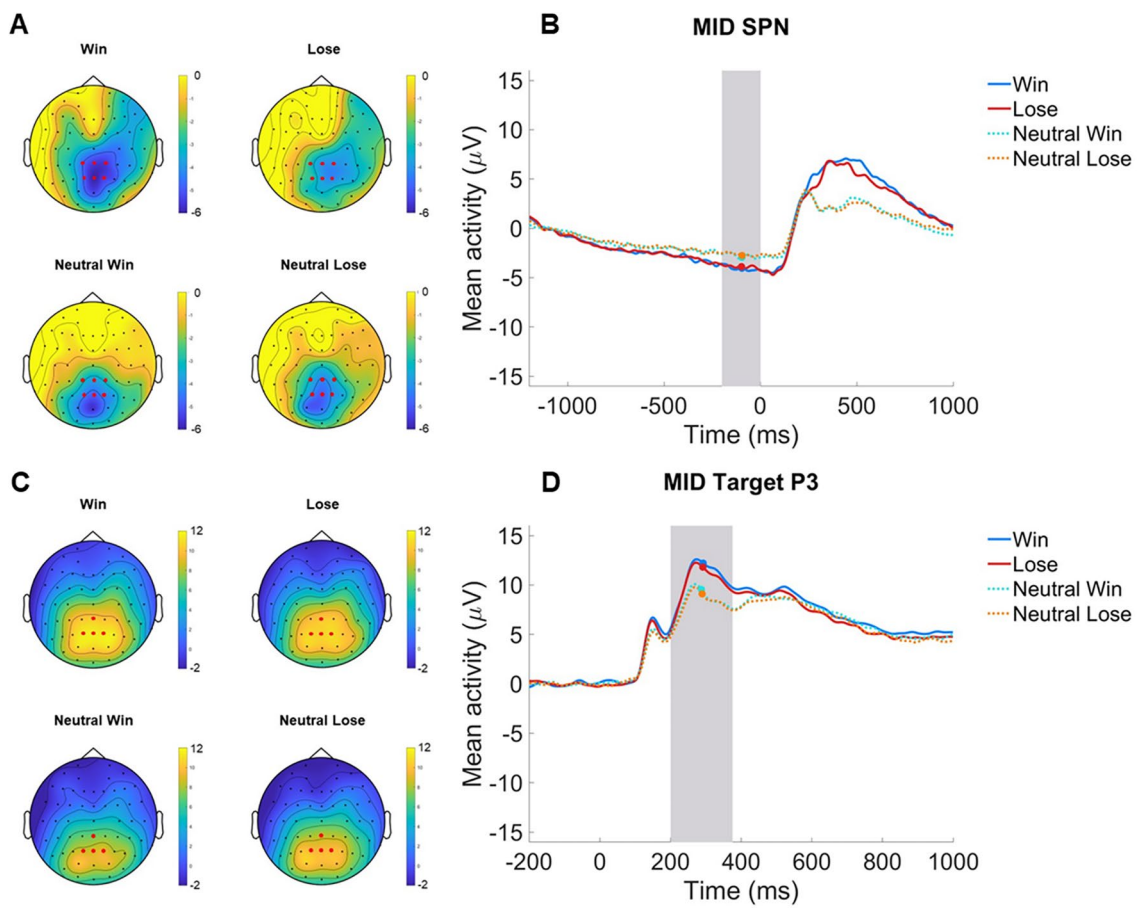
Fig. 2 MID SPN and Target P3 in the Aim 2 analysis sample. **A** Scalp distributions depicting activation before feedback in win (SPN win), lose (SPN lose), neutral win (SPN neutral win), and neutral lose (SPN neutral lose) in the -200–0 ms time window, with electrodes selected for scoring the SPN (CPz, Pz, CP1, CP2, P1, and P2) in red. **B** ERP grand average waveforms (negative up) of the win (blue), lose (red), neutral win (cian, dotted), and neutral lose (range, dotted) condition cues. Feedback stimuli were presented at 0 ms and ERPs scored in the -200–0 ms time window indicated by grey shad-

ing. **C** Scalp distributions depicting activation to target stimuli signaling win (Target P3 win), lose (Target P3 loss), neutral win (Target P3 neutral win), and neutral lose (Target P3 neutral lose) in the 200–375 ms time window, with electrodes selected for scoring the Target P3 (CPz, Pz, P1, and P2) in red. **D** ERP grand average waveforms (negative up) of the win (blue), lose (red), neutral win (cian, dotted), and neutral lose (range, dotted) condition cues. Target stimuli were presented at 0 ms and ERPs were scored in the 200–375 ms time window indicated by grey shading. n = 98

biomarkers insofar as they are associated, longitudinally, with alcohol use as an index of ADHD prognosis, above and beyond baseline alcohol and attitude values and ADHD severity. Alcohol misuse is one of many domains of outcomes that are prognostically relevant in ADHD and current findings pertain to prognosis over 18 months. Next steps for validating ERPs of reward anticipation as prognostic biomarkers include evaluating outcomes beyond those examined here and prognosis over longer periods. Finally, to be applicable in clinical practice, neuromarkers will ultimately have to predict prognosis—based on models developed with a given group—for new individuals. The current findings reflect within-sample prospective associations and justify next steps of developing models for evaluating out-of-sample predictions.
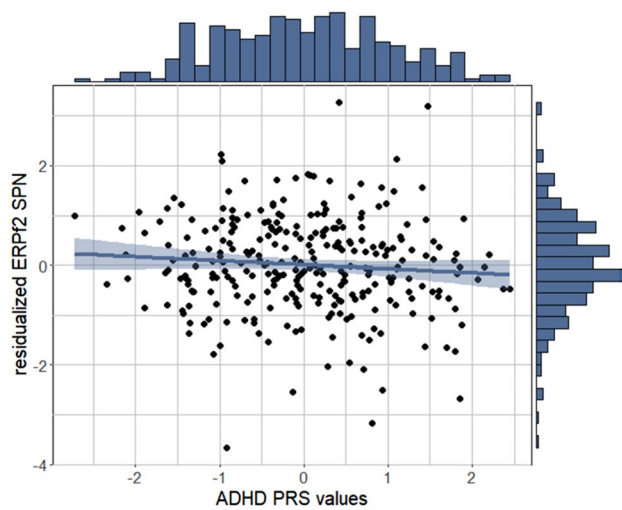
Of note, because behavioral performance may affect the obtained results, to determine whether findings held accounting for behavioral performance variables, we conducted sensitivity analyses with RT to target added as additional covariates to each model. The findings of the original and sensitivity tests were comparable, though in case of the association between ERPs of reward anticipation and ADHD PRSs, whereas the association was significant in the original model, it minimally surpassed significance threshold (0.053) in the sensitivity model, arguably due to the addition of extra variables attenuating power.

Across aims and analyses, the SPN factor – comprising SPN amplitude to lose, to win, to neutral lose, and to neutral win and indexing anticipatory attention to, or anticipation of, informational (correct or incorrect response) and

Table 1 Parameter estimates for linear regression model predicting ERP SPN values
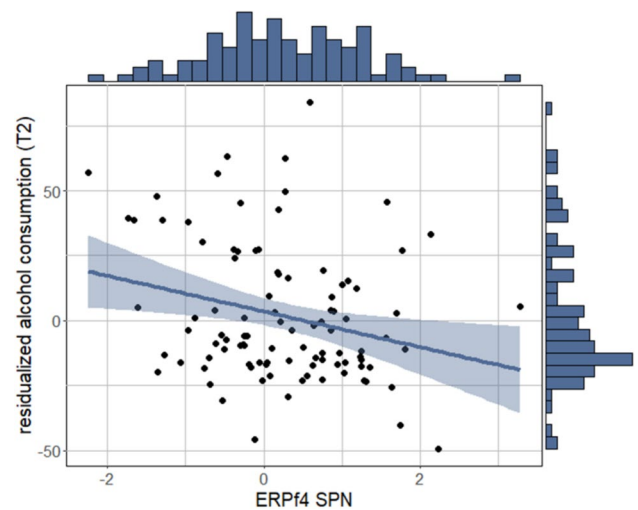
	b	SE	t	p
(Intercept)	−2.363	0.867	−2.726	0.007
standardized ADHD PRSs	−0.115	0.057	−2.008	0.046
Genetic PC1	−0.392	0.998	−0.393	0.695
Genetic PC2	0.601	0.955	0.630	0.529
Genetic PC3	1.397	1.028	1.358	0.175
Genetic PC4	−0.898	0.983	−0.913	0.362
Age	0.073	0.056	1.318	0.189
Sex	0.235	0.123	1.915	0.056
ADHD severity	0.006	0.005	1.297	0.196
Depressive problems	0.017	0.007	2.363	0.019

ADHD attention-deficit/hyperactivity disorder, *PRS* polygenic risk score, *PC* principal component

Fig. 4 In adolescents with ADHD, electrophysiological anticipation of reward is associated with alcohol use at 18-month follow-up. Anticipation of reward is indexed by SPN factor scores. Residualized alcohol use scores are created by regressing baseline alcohol use, age, sex, ADHD severity, and depression scores onto follow-up alcohol use scores

Fig. 3 In adolescents, ADHD PRS values are associated with electrophysiological anticipation of reward. Anticipation of reward is indexed by SPN factor scores. Residualized ERPf2 SPN scores are created by regressing Genetic PC1-4, age, sex, ADHD severity, and depression scores onto standardized ADHD PRS values

Table 2 Parameter estimates for robust linear regression model predicting alcohol use at 18-month follow-up with an effect of ERPs

	b	SE	t	p
(Intercept)	−41.222	42.806	−0.963	0.338
ERPf2$_{SPN}$	−7.454	2.728	−2.732	0.008
Age	4.173	2.645	1.578	0.118
Sex	1.377	6.054	0.227	0.821
ADHD severity	−0.229	0.313	−0.731	0.466
Depressive problems	0.021	0.326	0.064	0.949
Alcohol consumption at baseline	0.891	0.146	6.101	<.001

ERP event-related potential, *ADHD* attention-deficit/hyperactivity disorder

motivational (loss or win) aspects of feedback [16]—was a consistent marker of ADHD risk and prognosis. Regarding the physiological sources of the SPN, findings from spatiotemporal dipole modeling suggested the insula as a source [56]. Results from positron emission tomography (PET) [57] and functional magnetic resonance imaging (fMRI) confirmed activation in the anterior insula [58–60] and detected activation in eight additional regions [58] during paradigms probing the SPN. The anterior insula is implicated in affective-motivational processing [61], attention [62], and error-processing [63], and the additionally identified regions are implicated in anticipation (left inferior occipital gyrus and the left superior parietal lobule); arousal (right inferior parietal lobule); expectation of reward (anterior cingulate cortex, midcingulate cortex, left precentral gyrus); and processing salience (right middle frontal gyrus, bilateral insula) [58]. Greater ADHD PRS was associated with lower SPN. Lower SPN was associated with greater alcohol consumption. Accordingly, ADHD polygenic risk is associated with attenuated anticipatory attention to informational and motivational aspects of feedback and, in adolescents with the ADHD clinical phenotype, this attenuated anticipatory attention is associated with greater alcohol consumption.

Regarding ADHD risk, arguably, attenuated attention to aspects of feedback reduces the extent to which behavior is impacted and shaped by such feedback, i.e. it reduces the extent to which learning results from feedback. Consistent with this, conceptually, the ADHD clinical phenotype may be partly explained by diminished dopamine signal in anticipation of (or following) a reinforcer [64]. Empirically,

ADHD in some children is associated, for example, with deficits in conditional discrimination learning [65] and perseverative responding under extinction and reversal [66]. Related to ADHD prognosis, data indicate attenuated BOLD [67] and electrophysiological [68] response to reward anticipation in individuals with alcohol dependence [67], high-risk use [68], and with a family history of alcohol dependence but low levels of use [69]. Further, attenuated BOLD response to reward anticipation predicts greater increases in alcohol use in adolescent females [70]. Finally, in the single SPN study, findings show the SPN is sensitive to craving induction in individuals with alcohol dependence [71]. Taken together, ADHD genetic risk may be associated with attenuated anticipation of aspects of feedback and this attenuated anticipation, in individuals who manifest the clinical phenotype, may confer risk for alcohol consumption.

Current findings and subsequent work may be translated into clinical practice either directly—by applying ERPs to predict ADHD prognosis or risk in clinical settings, or indirectly—by applying ERPs to inform about the biological mechanisms of behavior and impairments and through this understanding of mechanisms, to inform about targets for intervention.

Regarding direct translation, applying ERPs as predictors of ADHD risk or prognosis in clinical settings is nontrivial. Assessing ERPs is arguably more complex and time-consuming than employing certain clinical (e.g. interview, rating scale) measures. Yet, data indicate neuromarkers are concurrently and prospectively associated with education, learning, and performance as well as responses to behavioral or pharmacological treatments in children and adults; further, neuromarkers either enhance or outperform traditional measures of individual variability (e.g. educational or neuropsychological tests, interview, rating scale) [55]. By yielding unique information on individual differences in brain function and structure that influence the diversity of educational and clinical outcomes, neuromarkers appear to carry the humanitarian and practical possibility of optimizing educational and clinical practices [55]. Yet, concerns persist about availability and cost of neurophysiological measures. Validity of these concerns is questionable as the cost of a neuropsychological assessment and report often exceeds that of an fMRI [55]. Also, of neurophysiological measures, EEG is relatively cost efficient, tolerable and transportable. Finally, any economic analysis of a battery involving neurophysiological measures relative to a battery not involving those has to account for the costs associated with current practices where, e.g., children have to exhibit academic impairment before they are deemed eligible for educational treatments or where patients are prescribed treatments that may not be the most effective for them. Combination of ERPs and clinical measures may enhance clinical precision while maintaining economic efficiency and a combined approach may be clinically applicable and is promising.

Regarding indirect translation, advancing understanding of the biological correlates of ADHD risk and prognosis is informative for identifying and personalizing targets for prevention and both pharmacotherapy and psychotherapy, as deficient reinforcement learning may partly account for poor response to traditional behavioral management treatments in some youth with ADHD [72, 73].

Limitations and strengths

We note key limitations. PRSs do not directly evince causality; PRSs are especially vulnerable to pleiotropic effects [74] and, as with all correlations, apparent associations between PRSs and ERPs may be explained by unmeasured variables or reflect indirect pathways including assortative mating, dynastic effects, or population stratification [75]. Adolescents may have underreported their alcohol use and adolescent report may be combined with objective measures or parent report in subsequent studies.

Regarding generalizability, the extent to which these findings generalize to adolescents with more severe alcohol use, to adolescents with more severe depression, or to adolescents from lower income, rural communities, is unclear. Beyond depression, other characteristics and disorders, including callous-unemotional traits and conduct disorder are also relevant for the association of ADHD with differences in reward processing [76] and these were not modeled here, but in larger samples, should be modeled.

Finally, in the current study, the "money" that was won during the task was virtual (and exchangeable for snacks as in [7, 14, 16, 34]) unlike in certain other studies where the money was given to participants as cash money at the end of the task. This difference may be also reflected in the extent to which adolescents were engaged in the task and thus magnitude of neural response to the task.

We also note strengths of the current study. We carefully characterized the sample, applied a measure of genetic risk derived from a genome-wide association study, an established and validated task to assess anticipation of reward (MID), and measures spanning different modalities (genetic, electrophysiological, rating scale). We accounted for ADHD and depression severity to ensure findings are not driven by overlap between ADHD PRSs and ADHD severity or are explainable by depression.

Conclusion

Converging evidence across models indicates electrophysiological indices of anticipation of reward are associated, principally, with ADHD genetic risk and prognosis, but

not depression severity. Specifically, amplitude values of ERPs reflecting anticipatory attention to, or anticipation of, informational (correct or incorrect response) and motivational (loss or win) aspects of feedback are associated, in adolescents, with ADHD PRSs and in adolescents at-risk for ADHD, with alcohol use. These electrophysiological indices of anticipation of reward may thus be biomarkers of ADHD risk and prognosis.

Data availability Datasets generated for this study are available at: https://osf.io/2p9hc/

Declarations

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