Effects of family history of substance use disorder on reward processing in adolescents with and without attention-deficit/hyperactivity disorder

Maria Paraskevopoulou1 | Daan van Rooij2 | Aart H. Schene1 | Albert Batalla3 | Roselyne J. Chauvin2 | Jan K. Buitelaar4,5 | Arnt F. A. Schellekens1,6

1Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands
2Donders Centre for Cognitive Neuroimaging, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands
3Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
4Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Centre, Nijmegen, The Netherlands
5Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, The Netherlands
6Nijmegen Institute for Scientist Practitioners in Addiction, Nijmegen, The Netherlands

Correspondence
Maria Paraskevopoulou MSc, Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Kapittelweg 29, Nijmegen 6525 EN, The Netherlands.
Email: maria.paraskevopoulou@radboudumc.nl

Funding information
Shire Pharmaceuticals, Grant/Award Number: unrestricted grant; Horizon2020 Programme of the European Union, Grant/Award Number: 667302; VU University Amsterdam; Accare: University Medical Center Groningen; ZonMW, Grant/Award Number: 60-66600-97-193; National Institute of Health, Grant/Award Number: R01MH62873; Radboud University Nijmegen Medical Center; Netherlands Organisation for Scientific Research, Grant/Award Numbers: 1750102007010, 916.15.101

Abstract
Patients with attention-deficit/hyperactivity disorder (ADHD) often develop early onset substance use disorder (SUD) and show poor treatment outcomes. Both disorders show similar reward-processing alterations, but it is unclear whether these are associated with familial vulnerability to SUD. Our aim was to investigate effects of family history of SUD (FH) on reward processing in individuals with and without ADHD, without substance misuse. Behavioural and functional magnetic resonance imaging (fMRI) data from a modified monetary incentive delay task were compared between participants with and without FH (FH positive [FH+]: n = 76 and FH negative [FH−]: n = 69; 76 with ADHD, aged 16.74 ± 3.14, 82 males), while accounting for continuous ADHD scores. The main analysis showed distinct positive association between ADHD scores and reaction times during neutral versus reward condition. ADHD scores were also positively associated with anticipatory responses of dorsolateral prefrontal cortex, independent of FH. There were no main FH effects on brain activation. Yet, FH+ participants showed distinct neural alterations in ventrolateral prefrontal cortex (VLPFC), dependent on ADHD. This was driven by positive association between ADHD scores and VLPFC activation during reward outcome, only in FH+. Sensitivity analysis with stricter SUD index showed hyperactivation of anterior cingulate cortex for FH+, independent of ADHD, during reward anticipation. There were no FH or ADHD effects on activation of ventral striatum in any analysis. Findings suggest both FH and ADHD effects in circuits of reward and attention/memory during reward processing. Future studies should examine whether these relate to early substance use initiation in ADHD and explore the need for adjusted SUD prevention strategies.

KEYWORDS
ADHD, attention-deficit/hyperactivity disorder, reward processing, substance misuse, substance use disorder
1 | INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neuropsychiatric disorder characterized by symptoms of inattention and hyperactivity–impulsivity.1 Patients with ADHD are at increased risk for developing substance use disorder (SUD).2,3 with two to three times higher prevalence rates of alcohol, drug or nicotine use disorder compared with non-ADHD individuals.4 ADHD patients with comorbid SUD are also characterized by an earlier SUD onset, more severe substance abuse and decreased treatment effectiveness compared with SUD-only patients.5 The frequent co-occurrence between ADHD and SUD suggests that these conditions share neurobiological mechanisms.

Genome-wide association studies (GWAS) have shown shared genetic liability between ADHD and substance use.6,7 Recent Mendelian randomization studies have also revealed a causal pathway from liability for ADHD to tobacco and cannabis use, but evidence for causal effects on SUD is not conclusive.8–12 ADHD and SUD patients also show many similarities at (endo)phenotypic level. For instance, high sensation seeking is a core feature in both disorders.3 This is thought to express deficits in reward processing, resulting in a desire for novel and stimulating experiences.13 At the neural level, reward processing takes place at the cortico-basal ganglia circuit, especially at the ventral striatum (VS). Increased VS responses to reward outcome during a number-guessing paradigm were found to have a mediating role in the causal pathway from polygenic risk for ADHD to problematic alcohol use.14 Reward-processing deficits might thus contribute to SUD development in the presence of higher genetic liability to ADHD.

Considering the research domain criteria (RDoC) neuropsychological constructs,15 reward expectancy and reward prediction errors—often measured with the monetary incentive delay (MID) task—were suggested to be among the primary constructs for the understanding of addictive behaviours.16 Indeed, meta-analysis of functional magnetic resonance imaging (fMRI) studies showed deficits in reward processing in patients with SUD, with decreased VS activation during reward anticipation, followed by increased VS activation during reward outcome in a MID task.17

Similarly, meta-analysis of fMRI studies in patients with ADHD suggested decreased VS activation during reward anticipation in a MID task.18 Whereas a subsequent study replicated this finding,19 others found non-significant increased VS activation for ADHD patients compared with controls.20,21 Studies that also examined reward outcome reported increased activation in reward circuitry (including VS) for patients compared with controls21,22 or no differences.23 Although available ADHD literature shows some inconsistencies, overall results show overlapping deficits in reward processing in both ADHD and SUD. However, it is unclear to what extent overlapping findings might be associated with familial vulnerability to or consequences of substance (mis)use in subsets of individuals with ADHD. Knowledge on neurobiological endophenotypes for SUD in ADHD could help identify more homogeneous ADHD subpopulations and direct personalized ADHD treatment, as well as SUD prevention strategies for subsets of patients.

Some studies investigated familial vulnerability as indexed by family history of SUD (FH) on reward processing. Individuals with FH positive (FH+) for SUD without drinking habits (or ADHD) have previously shown decreased VS activation during reward anticipation in a MID task, compared with FH negative (FH−) individuals.24 Others reported increased activation in dorso-lateral prefrontal cortex (DLPFC) and dorsal striatum (DS) and decreased activation in temporal areas25 or no differences between FH+/− (without ADHD) individuals during reward anticipation.26 These studies also showed no differences during outcome in a MID task.25,26 Moreover, compared with ADHD FH− and controls, ADHD FH+ showed increased activation in reward circuitry (including DS and orbitofrontal cortex [OFC]) and decreased in DLPFC during reward anticipation and increased activation in DLPFC, DS and temporal areas during outcome in an anticipatory–conflict–reward (ACR) paradigm.27,28 Interestingly, coordinate-based meta-analysis found that adolescent substance use vulnerability was more reliably associated with increased DS activation that was driven by reward/motivational tasks and was more common in samples with comorbid externalizing disorders.29

Available literature does not present conclusive evidence for SUD familial trait effects (i.e., vulnerability) related to reward processing. Moreover, to the best of our knowledge, there are no published studies comparing FH effects on reward processing in individuals with and without ADHD. Our study aims to address this question, comparing whole-brain responses to reward anticipation and outcome in a MID task between FH+ and FH− individuals without substance misuse with high and low ADHD scores (compatible with the dimensional RDoC approach). We hypothesized (1) increased activation in reward circuitry in FH+ individuals compared with FH− during reward anticipation and outcome and (2) decreased activation in reward circuitry for those with high ADHD scores during reward anticipation and increased activation for those with high ADHD scores during reward outcome, regardless of FH. We also explored interaction effects between ADHD scores and FH.

2 | METHODS AND MATERIALS

2.1 | Participants

The sample of the current study is part of the NeuroIMAGE cohort,30 which recruited ADHD and control families as part of the Dutch follow-up of the International Multicenter ADHD Genetics (IMAGE) study. Data on substance use were collected during NeuroIMAGE and the intermediate follow-up. IMAGE participants had to be between 5 and 30 years old, of European Caucasian descent, to have IQ ≥ 70 and no diagnosis of autism spectrum disorder (ASD), epilepsy, general learning difficulties, brain or known genetic disorders. During NeuroIMAGE, participants were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-
Present and Lifetime Version (K-SADS)\textsuperscript{21} for presence/absence of other affective, anxiety, behavioural and tic disorders that were not accounted for in the present study. Detailed description of the NeuroIMAGE cohort, including the recruitment procedure, exclusion criteria and the diagnostic procedure, can be found in the Supporting Information and/or the main design paper of the NeuroIMAGE cohort.\textsuperscript{30}

The present study included offspring with ADHD from ADHD families and offspring without ADHD from control families. Additional exclusion criteria applied here were not having stopped medication or alcohol/drug use 48 and 24 h before testing, respectively, incidental MRI findings, insufficient task performance, technical problems, excessive movement during testing, missing data on substance use for participants or their parents, and substance misuse in participants (see the Supporting Information and Substance Use section). The final sample consisted of 69 participants with FH\textsuperscript{–} (35 with ADHD) and 76 with FH\textsuperscript{+} (41 with ADHD), without substance misuse, aged 10.2–24.5 years (Table 1).

2.2 | Instruments/measurements

2.2.1 | ADHD

ADHD diagnosis was based on an algorithm that included assessment with the K-SADS\textsuperscript{21} and the Conners' ADHD questionnaires completed by parents (CPRS) and teachers or the participants (CTRS/CAARS).\textsuperscript{32,33} The detailed diagnostic algorithm can be found in the Supporting Information.

| TABLE 1  | Sample characteristics |
|-----------|-------------------------|
|           | FH\textsuperscript{–} (n = 69) | FH\textsuperscript{+} (n = 76) |
|           | ADHD FH\textsuperscript{–} (n = 35) | Control FH\textsuperscript{–} (n = 34) | ADHD FH\textsuperscript{+} (n = 41) | Control FH\textsuperscript{+} (n = 35) | FH differences\textsuperscript{c} |
| Age (M ± SD) | 16.63 ± 3.15 | 16.79 ± 3.34 | 16.81 ± 3.52 | 16.73 ± 2.57 | p = 0.901 |
| Gender (male–female) | 27–8 | 14–20 | 29–12 | 12–23 | p = 0.507 |
| IQ\textsuperscript{a} (M ± SD) | 104.77 ± 14.33 | 111.26 ± 11.86 | 97.15 ± 13.45 | 108.37 ± 14.67 | p = 0.019 |
| Scan site (Nijmegen–Amsterdam) | 20–15 | 16–18 | 22–19 | 18–17 | p = 0.956 |
| DBD (yes–no) | 9–26 | 0–34 | 9–32 | 0–35 | p = 0.827 |
| ADHD medication (yes–no) | 17–18 | 0–34 | 21–20 | 0–35 | p = 0.682 |
| Conners' Rating Scales\textsuperscript{b}  |
| Inattention (M ± SD) | 65.39 ± 9.71 | 45.56 ± 5.16 | 64.07 ± 9.88 | 47.91 ± 5.68 | p = 0.613 |
| Hyperactivity–impulsivity (M ± SD) | 64.03 ± 12.53 | 45.60 ± 4.54 | 63.43 ± 11.89 | 46.31 ± 5.09 | p = 0.782 |
| Total (M ± SD) | 67.14 ± 11.13 | 44.93 ± 4.69 | 65.67 ± 11.08 | 46.59 ± 5.13 | p = 0.761 |

Abbreviations: ADHD FH\textsuperscript{–}, ADHD with negative family history of SUD; ADHD FH\textsuperscript{+}, ADHD with positive family history of SUD; Control FH\textsuperscript{–}, controls with negative family history of SUD; Control FH\textsuperscript{+}, controls with positive family history of SUD; DBD, disruptive behavioural disorder (i.e., oppositional defiant disorder [ODD] or conduct disorder [CD]); FH, family history of SUD; FH\textsuperscript{–}, negative family history of SUD; FH\textsuperscript{+}, positive family history of SUD.

\textsuperscript{a}IQ level was estimated with cognitive performance in Block Design and Vocabulary tasks of Wechsler Intelligence Scale for Children (WISC) and Wechsler Adult Intelligence Scale (WAIS).

\textsuperscript{b}Conners' Rating Scale = average scores on Conners' Parents Rating Scale (CPRS) and Conners' Teacher Rating Scale (CTRS)/Adult ADHD Rating Scale (CAARS).

\textsuperscript{c}Differences between FH\textsuperscript{–} and FH\textsuperscript{+} groups were examined with t tests for independent samples for age, IQ and Conners' rating scales and with chi-square tests for gender, scan site, DBD and ADHD medication.

2.2.2 | Substance use

Assessment of parental substance use included data from the intermediate follow-up collected with the Alcohol Use Disorders Identification Test (AUDIT),\textsuperscript{36} the Drug Abuse Screening Test (DAST),\textsuperscript{35} the Fagerström Test for Nicotine Dependence (FTND)\textsuperscript{36} and the Timeline Follow Back (TLFB)\textsuperscript{37,38} that recorded the daily number of drinks and cigarettes in the last month. Alcohol dependence was defined for scores ≥8 for females and ≥9 for males\textsuperscript{39} or on average ≥7 drinks for females and ≥14 drinks for males per week based on TLFB, which was compatible with validated recommendations of the National Institute on Alcoholism and Alcohol Abuse (NIAAA).\textsuperscript{40}

Combined use of AUDIT and screener for heavy drinking was in line with previous recommendations due to high specificity, but wide range of sensitivity levels for standard AUDIT thresholds.\textsuperscript{41} Drug dependence was defined for scores ≥6 in DAST\textsuperscript{35} and nicotine dependence for scores ≥5 in FTND\textsuperscript{36} or on average ≥10 cigarettes per day based on TLFB.\textsuperscript{38} Alcohol, drug or nicotine dependence in at least one of the parents indicated FH\textsuperscript{+}, whereas absence of alcohol, drug and nicotine dependence in both parents indicated FH\textsuperscript{–}. Participants were excluded for missing data for at least one parent unless the data of the other parent indicated SUD and thus FH\textsuperscript{+}.

Substance use in participants was examined with data from NeuroIMAGE collected with the Dutch version of the revised Self-Reported Delinquency Scale (SRD).\textsuperscript{42,43} Daily alcohol or tobacco use or (at least) weekly drug use within the past 6 months was regarded as indicative of substance misuse in line with the Dutch Measurement of Addiction for Triage and Evaluation (MATE).\textsuperscript{44} Due to the young
age of the sample, substance use problems that met criteria for substance misuse, instead of full-blown SUD, were considered clinically relevant for participants. Participants were excluded for missing data in SRD or for substance misuse to avoid interference with effects resulting from substance misuse.

2.3 Modified MID task

Reward processing was assessed with a modified version of the MID task. The task contained 25 reward and 25 neutral trials interleaved with 25 trials without events. Reward and neutral trials were introduced with the presentation of the cue (jittered interval 3.5–8.5 s) that indicated the trial type (i.e., reward or neutral). That was followed by the target (270–500 ms), and participants were asked to press the button as fast as possible responding to this stimulus. Each trial ended with the feedback screen that indicated the outcome of the trial (1650 ms). The response window that marked a correct trial was adapted in the following trial according to participants’ performance (i.e., 33% hit rate). The feedback screen in reward trials indicated the gain of the monetary reward (i.e., 20 cents) if participants responded to the target within the given response window or no reward gain if the response was not fast enough. Neutral trials resulted in no reward gain, regardless of the response to the target. Time interval between trials was fixed at 500 ms. Participants performed a practice block before the experimental block, and the duration of the experiment was 12 min. At the end of the experiment, participants received the total amount they gained during the task (Figure S1). The modified MID task (i.e., lower reward magnitude and hit probability) was used to increase task demands and induce stronger engagement and to meet practical constraints of NeuroIMAGE. Further details concerning task description and rationale can be found in von Rhein et al.

2.4 Analyses

2.4.1 Behavioural data analysis

Greater reaction time (RT) and intra-individual coefficient of variation (ICV) have been repeatedly seen in ADHD probably due to inattention and lower processing speed. Thus, compatible with ADHD and FH studies using the MID task, behavioural variables consisted of RT and ICV during reward and neutral trials. Trials with no or premature responses (i.e., RT < 100 ms or button press prior target onset) or trials with more than one button press were excluded from the calculation of the mean. For the calculation of the ICV, the standard deviation of RTs was divided by the mean RT. The variables were transferred to normality with the reciprocal transformation. We then performed mixed-effects models for repeated measures in R (R version 3.6.2; Rstudio version 1.2.5033) for RT and ICV separately. FH (two levels: FH− and FH+) and ADHD scores (i.e., average of CPRS and CTRS/CAARS scores) and condition (two levels: reward and neutral) were included as independent variables, while accounting for subject’s random effect. Age, gender and scan site were also included as covariates. When homogeneity of regression slopes was not met, interactions between these covariates and the independent factor(s) were included in the models. Significant interactions led to follow-up models to further explore these effects.

2.4.2 fMRI data analysis

MRI data acquisition and preprocessing can be found in the Supporting Information. More information on scanning protocol can be found in the design paper of NeuroIMAGE. Statistical parametric maps of the first-level analysis were estimated with a general linear model (GLM) in FSL FEAT with six regressors of interest (i.e., onset times for cues and onset times for hits and misses in reward and neutral trials), five regressors of no interest (i.e., onset times for cues in reward and neutral trials and cue, target and outcome for trials with no, premature or multiple responses) and the temporal derivatives of the regressors. The regressors and their temporal derivatives were convolved with a canonical hemodynamic response function (HRF). Regressors of interest included reward anticipation (i.e., reward−neutral anticipation; onset time for cues in reward trials minus onset time for cues in neutral trials) and reward outcome (i.e., reward−neutral outcome; onset times for reward hits-onset times for reward misses minus onset times for neutral hits-onset times for neutral misses). Functional images were transformed to MNI152 standard space, with registration to their structural images, which were registered to MNI152 standard space with linear registration with FSL FLIRT and were refined with non-linear registration with FSL FNIRT. Due to the age range of NeuroIMAGE sample, all participants’ brains were registered to a custom template generated by averaging all structural images of NeuroIMAGE after non-linear transformation to MNI152 space with FSL FNIRT. This resulted into a non-linear warp-field for normalization to the custom template.

2.4.3 Whole-brain analysis

Group-level analysis was conducted with separate mixed-effects models with FSL flame and outlier de-weighting for reward (i.e., reward−neutral anticipation and outcome separately. We included t-test contrasts for positive and negative effects of FH, ADHD scores and their interaction. Mean-centred age, gender, IQ and scan site were added as covariates. Z statistical images were thresholded with a cluster forming threshold of Z > 2.6 and a family-wise corrected cluster significance threshold of p < 0.05. Individual mean activation parameters (beta values) were extracted from the significant clusters and were used in follow-up tests in R (R version 3.6.2; Rstudio version 1.2.5033) to further explore interaction effects.
2.4.4 | ROI analysis

Based on a priori interest in VS activity, we created a region of interest (ROI) mask in nucleus accumbens (NAcc) using the Harvard–Oxford subcortical structural atlas in FSL. Individual beta values were extracted from the masked first-level statistical parametric maps for reward (i.e., reward-minus-neutral) anticipation and outcome and were used in separate two-way analyses of variance (ANCOVAs) with FH and ADHD scores as independent variables and age, gender, IQ and scan site as covariates.

2.4.5 | Sensitivity analysis

To make sure our findings were not confounded by other covariates, we performed separate mixed-effects models for each behavioural variable and significant cluster, adding family ID as random factor and ADHD medication use and comorbid disruptive behavioural disorder (DBD; i.e., oppositional defiant disorder [ODD] or conduct disorder [CD]) that is believed to be a strong SUD risk factor (Model 1). Moreover, to account for the possibility of differential gender effects across groups, we performed separate two-way ANCOVAs for each significant cluster of the whole-brain analysis, adding gender interaction effects (Model 2).

Considering previous GWAS results that showed shared, but also distinct genetic loci for heavy drinking and alcohol use disorder (AUD) diagnosis, we performed additional whole-brain and ROI analyses to explore neural correlates linked to different (familial) AUD indices (Model 3). In this, heavy drinking (here indexed by TLFB data) was not indicative of SUD. Groups consisted of 82 FH− (41 with ADHD) and 55 FH+ individuals (33 with ADHD). Eight participants were excluded from this analysis due to missing data either in AUDIT or in the other parent. Covariates were the same as in the main analysis.

3 | RESULTS

3.1 | Sample description

We identified 69 FH− participants without substance misuse over the past 6 months (age: 16.71 ± 3.22, IQ: 107.97 ± 13.48, 41 males, 36 scanned in Nijmegen, inattention scores: 55.62 ± 12.64, hyperactivity–impulsivity scores: 54.95 ± 13.22, total ADHD scores: 56.19 ± 14.06, 17 medicated ADHD, 9 with DBD) and 76 FH+ individuals (41 with ADHD). Characteristics of separate FH−/FH+ subgroups with and without ADHD are summarized in Table 1.

3.2 | Behavioural results

We found condition effects on both RT (p < 0.001) and ICV (p = 0.002). For RT, there were no significant effects of FH (p = 0.215), ADHD (p = 0.278), FH * ADHD (p = 0.078), but there were ADHD * condition effects (p = 0.017). Follow-up analysis for each condition showed a trend for positive association between ADHD scores and RT during neutral (p = 0.064), but not reward condition (p = 0.999). For ICV, there were no significant effects of FH (p = 0.566), ADHD (p = 0.741), FH * ADHD (p = 0.256), FH * condition (p = 0.061), ADHD * condition (p = 0.251) or FH * ADHD * condition effects (p = 0.121; Table 2). There were significant effects of FH * condition * gender (p = 0.002) and FH * ADHD * condition * gender (p = 0.026) on ICV. Follow-up analysis showed condition effect on ICV in FH− group (p = 0.001) and in FH− females (p < 0.001), but not FH− males (p = 0.317), and a trend for negative association between ADHD scores and ICV in FH− females during reward (p = 0.055), but not neutral condition (p = 0.338). Small number of FH− females with high ADHD scores (i.e., with ADHD; n = 8) limits interpretation of this result.

3.3 | fMRI results

3.3.1 | Whole-brain analysis

Group activation during reward (reward-minus-neutral) anticipation and outcome can be found in Table S2 and Figures S2 and S3. During reward (reward-minus-neutral) anticipation, ADHD scores were positively associated with neural activation in right dorsal frontal pole, regardless of FH (p = 0.020; Figure S4). No clusters were significantly associated with FH or ADHD * FH interaction during this contrast. During reward (reward-minus-neutral) outcome, ADHD * FH interaction was related to activation in right ventral frontal pole (p = 0.004). Follow-up analysis showed activation in ventral frontal pole was positively associated with ADHD scores in FH+ (p < 0.001, B = 65.6), but not in FH− individuals (p = 0.203, B = −22.5; Figure 1). We found no clusters significantly related to main effects of FH or ADHD scores during this contrast (Table 3).

3.3.2 | ROI analysis

In the ROI analysis, we did not find significant effects of FH, ADHD scores or FH * ADHD scores interaction on bilateral NAcc activation during reward anticipation (i.e., reward-minus-neutral; FH: F_{1,137} = 0.09, p = 0.764; ADHD: F_{1,137} = 1.00, p = 0.318; FH * ADHD: F_{1,137} = 0.71, p = 0.399) or outcome (FH: F_{1,137} = 0.02, p = 0.878; ADHD: F_{1,137} = 0.03, p = 0.861; FH * ADHD: F_{1,137} = 0.23, p = 0.628; Figure S5).
TABLE 2  Behavioural data analysis

|               | ADHD FH− (n = 35) | Control FH− (n = 34) | ADHD FH+ (n = 41) | Control FH+ (n = 35) | Group differences |
|---------------|-------------------|----------------------|-------------------|----------------------|-------------------|
| Reaction times (M ± SD) |                   |                      |                   |                      |                   |
| Reward condition | 301.11 ± 36.44    | 301.96 ± 27.61       | 307.19 ± 40.86    | 286.93 ± 35.07       | F_{1,138} = 1.55, p = 0.215 (η^2 = 0.01)^a |
| Neutral condition | 338.42 ± 53.99    | 335.65 ± 47.01       | 342.66 ± 54.91    | 310.18 ± 42.38       | F_{1,138} = 1.18, p = 0.278 (η^2 < 0.01)^b |
| Intra-individual coefficient of variation (M ± SD) |                   |                      |                   |                      |                   |
| Reward condition | 0.201 ± 0.120     | 0.177 ± 0.066        | 0.183 ± 0.075     | 0.172 ± 0.064        | F_{1,135} = 0.33, p = 0.566 (η^2 < 0.01)^a |
| Neutral condition | 0.272 ± 0.208     | 0.225 ± 0.168        | 0.254 ± 0.169     | 0.209 ± 0.159        | F_{1,135} = 0.11, p = 0.741 (η^2 < 0.01) ^b |

Abbreviations: ADHD FH−, ADHD with negative family history of SUD; ADHD FH+, ADHD with positive family history of SUD; Control FH−, controls with negative family history of SUD; Control FH+, controls with positive family history of SUD; FH, family history of SUD; FH−, negative family history of SUD; FH+, positive family history of SUD.

*Effect of FH.
^aEffect of ADHD scores.
^bADHD scores * FH interaction effects.
^cFH * condition interaction effects.
^dADHD scores * condition interaction effects.
^eFH * ADHD scores * condition interaction effects.

3.3.3  | Sensitivity analysis

Results of the main analysis remained after inclusion of additional potential confounders (Model 1) and after inclusion of gender interaction effects (Model 2; Supporting Information). Model 3 showed that, during reward (reward-minus-neutral) anticipation, FH was associated with increased activation of anterior cingulate cortex (ACC), regardless of ADHD scores (p < 0.001; Figure 2; Table 3). There were no FH or ADHD effects on NAcc during anticipation (FH: F_{1,129} = 1.05, p = 0.307; ADHD: F_{1,129} = 0.51, p = 0.474; ADHD * FH: F_{1,129} = 0.29, p = 0.723) or outcome (FH: F_{1,129} = 0.90, p = 0.396; ADHD * FH: F_{1,129} = 0.03, p = 0.855).

4  | DISCUSSION

The present study provides new insights into FH effects on reward processing in individuals with and without ADHD, using a sample of adolescents and young adults without any substance misuse. We found distinct positive association between ADHD scores and RT during neutral versus reward condition. The whole-brain analysis showed no significant clusters associated with FH, independent of ADHD symptom levels, during reward anticipation or outcome. We observed increased neural activation in right DLPFC for high ADHD symptom levels, regardless of FH, during reward anticipation, but no association during outcome. Moreover, in those with FH+, high ADHD symptom levels were associated with increased neural activation in right ventrolateral prefrontal cortex (VLPFC) during reward outcome. In contrast to our hypothesis, ROI analysis showed no FH or ADHD effects on bilateral VS, during reward anticipation or outcome.

Our results showed altered neural responses for high ADHD symptom levels, independent of FH, in DLPFC, which is thought to be responsible for attention/memory and other cognitive processes.51 There was no association between ADHD scores and neural responses in reward circuitry. This is in contrast to our hypothesis and the meta-analysis in ADHD that reported decreased striatal activation during reward anticipation.18 It is possible that decreased striatal anticipatory responses previously seen in ADHD are associated with other traits that are often present in these patients, for example, internalizing/externalizing traits. We also must note that our sample was part of that in von Rhein et al. that found non-significant increased VS responses, but did not exclude those with substance misuse.21

In contrast to our hypothesis, the main analysis did not show FH effects, regardless of ADHD, in the reward or other circuitries. However, we observed ADHD * FH effects on VLPFC activation, with greater activation for higher ADHD symptom levels in FH+. Closer look at this finding showed that it was driven by presence of distinct alterations in FH+ individuals with high versus low ADHD symptom levels (Figure 1C). VLPFC is thought to be involved in processes related to memory and attention.51 Interestingly, it was previously suggested that working memory deficits in FH+ might contribute to poor decision-making skills and subsequently to SUD vulnerability.52
Furthermore, converging evidence suggests that frontal regions might be associated with the degree of SUD risk. In detail, DLPFC connectivity with posterior cingulate cortex (PCC) during resting state and DLPFC activation during a response inhibition task in FH+ predicted substance use in adolescence and early adulthood, respectively. Moreover, increased frontal responses in a reward-related decision-making task were associated with follow-up increase in cannabis use in a group of heavy users. It would be interesting for future studies to investigate the role of these deficits in early SUD onset and high severity in FH+ individuals with comorbid ADHD.

There were no ADHD * FH effects in reward circuity. Of note, we cannot rule out long-lasting ADHD medication effects, as a substantial portion of the study population received ADHD medication. Yet, ADHD medication in sensitivity analyses did not affect main findings. Future studies with longitudinal designs should examine whether stimulant medication interacts with SUD trait effects in the reward circuity. Lack of differences in striatal activation here is in line with previous FH studies. In fact, previous review on FH+ indicated altered responses in frontal regions during executive functioning tasks, but uncertainty about premorbid reward-processing deficits. Altered frontal activation observed here was in relation to reward (i.e., in reward versus neutral contrasts). Together these findings suggest premorbid reward-processing deficits in FH+ individuals beyond the primary reward circuity. However, this speculation is in contrast with the recent meta-analysis that found putamen hyperactivation (driven by reward/motivational tasks) to be more reliably associated with adolescent vulnerability to substance use. It seems plausible that altered reward circuity is only seen in those at risk for substance use initiation in adolescence, a large portion of whom were excluded here. Alternatively, it was previously hypothesized that as reward circuity is under development until early adulthood, FH effects might only be present at later developmental stages.
It is also possible that use of various indices for parental SUD accounts for mixed results in high-risk literature. Importantly, both shared and unique genetic loci were previously found for AUD and heavy drinking (i.e., TLFB data here). AUD, but not heavy drinking, was also genetically correlated with various psychiatric disorders, including ADHD.50 Considering these, we performed sensitivity analysis with a more specific index for parental AUD (based on AUDIT). We found increased anticipatory responses of ACC to reward for FH+ individuals, independent of ADHD symptom levels. ACC has been repeatedly implicated in both reward and cognitive processes.57

Interestingly, its ventral division is thought to encode one's perception on strategy reliability. Increased responses in patients with SUD were suggested to reflect decreased consideration of alternative strategies, leading to impulsive behaviour.57 Results here suggest that although alterations of VLPFC are shared in those with either parental AUD or heavy drinking, ACC alterations are present only in those with parental AUD.

Moreover, altered activation in these areas as a function of reward might indicate altered connections between reward and attention/memory networks in FH+ without substance misuse. Indeed,

**TABLE 3** Functional magnetic resonance imaging (fMRI) data analysis

| Significant clusters                  | N voxel | Hemisphere | MNI coordinates | t test       |
|---------------------------------------|---------|------------|-----------------|--------------|
| Reward anticipation                   |         |            |                 |              |
| ADHD scores                           |         |            |                 |              |
| Dorsal frontal pole                   | 264     | R          | 22 46 38        | t137 = 3.06; p = 0.020 |
| Reward outcome                        |         |            |                 |              |
| FH * ADHD scores                      | 359     | R          | 44 44 0         | t137 = 3.22; p = 0.004 |
| Sensitivity analysis (n = 137)        |         |            |                 |              |
| Reward anticipation                   |         |            |                 |              |
| Family history of SUD                 |         |            |                 |              |
| Anterior cingulate cortex             | 543     | L          | –6 58 2         | t130 = 3.00; p < 0.001 |
| ADHD scores                           |         |            |                 |              |
| Dorsal frontal pole                   | 267     | R          | 22 46 38        | t130 = 3.07; p = 0.020 |

Note: Reward = reward–neutral; each t value represents average t value across the cluster; MNI coordinates (mm) represent the location of the peak voxel.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FH, family history of SUD; SUD, substance use disorder.

**FIGURE 2** Increased activation of anterior cingulate cortex (ACC) in positive family history of substance use disorder (SUD) (FH+) compared with negative family history of SUD (FH−) individuals (regardless of attention-deficit/hyperactivity disorder [ADHD] scores) during reward anticipation resulted from the t test for effects of family history of SUD (FH) in the sensitivity analysis (Model 3); error bars = standard error of the mean; *p < 0.05, **p < 0.01, ***p < 0.001
Welland et al. found altered functional connectivity between NAcc and attention (and motor) networks during reward anticipation in FH + young adults (primarily without substance abuse). It was then hypothesized that FH+ might be characterized by altered interactions between NAcc and other brain regions, rather than altered NAcc responses per se. Another study found altered NAcc connectivity with cognitive control areas during resting state in FH+ adolescents without heavy substance use. Together with similar deficits reported in different tasks, this might imply altered baseline activity/connectivity between these networks that subsequently affects task contrasts (e.g., reward vs. neutral, no-go vs. go).

5 | STRENGTHS AND LIMITATIONS

The main strength of the present study is the design that disentangled preceding familial trait effects of SUD from effects resulting from substance misuse in participants. This innovative design contributes to the exploration of trait biomarkers that aim at improving prognosis and early intervention strategies. Moreover, with our sample, we were able to examine shared and distinct endophenotypes for SUD with and without comorbid ADHD. With the current design, however, we were not able to account for the potential confounding effect of ADHD subtypes. Future FH studies should examine effects of inattentive and hyperactivity–impulsivity scores separately and might explore other potential subtypes of ADHD patients, for example, with/without other psychiatric comorbidities such as anxiety or mood disorders and personality disorders. Another limitation of our study lies in the absence of formal SUD diagnosis in the parents. However, the instruments used to screen for SUD in parents (i.e., AUDIT, DAST, FTND and TLFB) have previously shown sufficient reliability and validity. Another limitation lies in the use of a modified MID task. Compared with previous ADHD and SUD/FH+ studies, the task had a lower reward magnitude and hit probability, with lower number of successful outcome trials. Higher reward magnitudes are linked to more robust striatal responses, compared with lower magnitudes. Similarly, low hit probability might have influenced the perceived difficulty of the task, leading to frustration and surprise, instead of reward anticipation and outcome. Nevertheless, both reward value and hit probability are coded relatively, depending on the context. Because the task did not combine multiple reward levels or blocks with varying hit probabilities, we believe that the modified MID task did not significantly affect our findings. More on this limitation can be seen in von Rhein et al. Future studies should examine whether lack of differences in VS activation across FH+ participants with high or low ADHD symptoms are confirmed in MID tasks with higher reward magnitude and hit probability. Because the current dataset was part of a larger study, and participant selection was based on the availability of substance use data for both parents and participants, no a priori power analysis was performed. Hence, we cannot exclude the possibility that potentially low power here might have influenced findings.

6 | CONCLUSION

To conclude, we found no evidence for premorbid striatal deficits in FH+ adolescents and young adults with high and low ADHD symptom levels. However, we observed altered activation of frontal areas during reward processing in this population. Results provide direction for future investigation of connections between the reward circuitry and networks involved in attention and memory processes in those with FH+. Moreover, FH+ participants with high and low ADHD symptom levels showed both similar and distinct alterations during reward-processing. Future studies should examine whether distinct deficits in brain function of FH+ individuals with comorbid ADHD contribute to earlier substance use initiation and can direct development of distinct prevention strategies in this population.

ACKNOWLEDGEMENTS

This work was supported by VENI Grant 916.15.101 (to AFAS) from the Netherlands Organisation for Scientific Research (NWO) and grants from Radboud University Nijmegen Medical Center. The NeurolIMAGE project was supported by NIH Grant R01MH62873, NWO Large Investment Grant 1750102007010 and ZonMw Grant 60-60600-97-193 (to JKB), grants from Radboud University Nijmegen Medical Center, University Medical Center Groningen and Accare, and VU University Amsterdam and an unrestricted grant from Shire Pharmaceuticals. The work is further supported by the Horizon2020 Programme of the European Union (grant number 667302 for the Comorbid Conditions of Attention-deficit/Hyperactivity Disorder [CoCA] consortium).

CONFLICTS OF INTEREST

JKB has been a consultant to/member of advisory board of and/or speaker for Janssen Cilag BV, Eli Lilly, Roche, Medice, Takeda/Shire, Novartis and Servier. He is not an employee or a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents and royalties. The other authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

AFAS was responsible for the study concept. MP, DvR, AHS, JKB and AFAS were responsible for the study design. MP and RJC performed the analysis. DvR, AB and AFAS assisted with data analysis. DvR, AHS, JKB and AFAS assisted with interpretation of findings. MP drafted the manuscript. DvR, AHS, RJC, AB, JKB and AFAS provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the authors upon reasonable request (https://www.ru.nl/donders/vm-site/collaborations/projects/neuroimage/).
REFERENCES

1. Polanczyk G, Rohde LA. Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. Curr Opin Psychiatry. 2007;20(4):386-392. doi:10.1097/YCO.0b013e3281568d7a

2. Molina BSG, Pelham WE. Attention-deficit/hyperactivity disorder and risk of substance use disorder: developmental considerations, potential pathways, and opportunities for research. Annu Rev Clin Psychol. 2014;10:607-639. doi:10.1146/annurev-clinpsych-032813-153722

3. Adisetiyo V, Gray KM. Neuroimaging the neural correlates of increased risk for substance use disorders in attention-deficit/hyperactivity disorder—a systematic review. Am J Addict. 2017;26(2):99-111. doi:10.1111/ajad.12500

4. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association study Meta-Analysis of the Alcohol Use Disorders Identification Test (AUDIT) in two population-based cohorts. Am J Psychiatry. 2019;176(2):107-118. doi:10.1176/appi.ajp.2018.18040369

5. Wilens TE. Impact of ADHD and its treatment on substance abuse in adults. J Clin Psychiatry. 2004;65:38-45.

6. Sanchez-Roige S, Palmer AA, Fontanillas P, et al. Genome-Wide Association Study Meta-Analysis of the Alcohol Use Disorders Identification Test (AUDIT) in two population-based cohorts. Am J Psychiatry. 2019;176(2):107-118. doi:10.1176/appi.ajp.2018.18040369

7. Pasman JA, Verweij KJH, Gerring Z, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. Nat Neurosci. 2018;21(9):1161-1170. doi:10.1038/s41593-018-0206-1

8. Treur JL, Demontis D, Smith GD, et al. Investigating causality between liability to ADHD and substance use, and liability to substance use and ADHD risk, using Mendelian randomization. Addict Biol. 2019;24(1):e12849. doi:10.1111/adb.12849

9. Soler Artigas M, Sánchez-Mora C, Rovira P, et al. Attention-deficit/hyperactivity disorder and lifetime cannabis use: genetic overlap and causality. Mol Psychiatry. 2019;25(10):2493-2503. doi:10.1038/s41380-018-0339-3

10. Vilar-Ribó L, Sánchez-Mora C, Rovira P, et al. Genetic overlap and causality between substance use disorder and attention-deficit and hyperactivity disorder. Am J Med Genet Part B Neuropsychiatr Genet. 2021;186(3):140-150. doi:10.1002/ajmg.b.32827

11. Fluharty ME, Sallis H, Munafò MR. Investigating possible causal effects of externalizing behaviors on tobacco initiation: a Mendelian randomization analysis. Drug Alcohol Depend. 2018;191:338-342. doi:10.1016/j.drugalcdep.2018.07.015

12. Vink JM, Treur JL, Pasman JA, Schellekens A. Investigating genetic correlation and causality between nicotine dependence and ADHD in a broader psychiatric context. Am J Med Genet Part B Neuropsychiatr Genet. 2021;186(3):423-429. doi:10.1002/ajmg.b.32822

13. Zuckerman M. Sensation seeking (psychology reivews): beyond the optimal level of arousal. Psychology Press; 2014.

14. Carey CE, Knott AR, Conley ED, Hairi AR, Bogdan R. Reward-related ventral striatum activity links polygenic risk for attention-deficit/hyperactivity disorder to problematic alcohol use in young adulthood. Biol Psychiatry Cogn Neurosci Neuroimaging. 2017;2(2):180-187. doi:10.1016/j.bpsc.2016.10.003

15. Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry. 2014;13(1):28-35. doi:10.1002/wps.20087

16. Yücel M, Oldenhof E, Ahmed SH, et al. A transdiagnostic dimensional approach towards a neuropsychological assessment for addiction: an international Delphi consensus study. Addiction. 2019;114(6):1095-1109. doi:10.1111/add.14424

17. Luijten M, Schellekens AF, Kühn S, Machielse MJW, Seskes G. Disruption of reward processing in addiction. JAMA Psychiatry. 2017;74(4):387-398. doi:10.1001/jamapsychiatry.2016.3084

18. Pilchta MM, Scheres A. Vential-strial responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. Neurosci Biobehav Rev. 2014;38:125-134. doi:10.1016/j.neubiorev.2013.07.012

19. van Hulst BM, de Zeeuw P, Bos DJ, Rijks Y, Neggars SFW, Durston S. Children with ADHD symptoms show decreased activity in ventral striatum during the anticipation of reward, irrespective of ADHD diagnosis. J Child Psychol Psychiatry. 2017;58(2):206-214. doi:10.1111/jcpp.12643

20. Hägge C, Schlagenauf H, Rapp M, et al. Dimensional psychiatry: reward dysfunction and depressive mood across psychiatric disorders. Psychopharmacology. 2015;232(2):331-341. doi:10.1007/s00213-014-3662-7

21. von Rhein D, Cools R, Zwiers MP, et al. Increased neural responses to reward in adolescents and young adults with attention-deficit/hyperactivity disorder and their unaffected siblings. J Am Acad Child Adolesc Psychiatry. 2015;54(5):394-402. doi:10.1016/j.jaac.2015.02.012.Increased

22. Ströhle A, Stoy M, Wrase J, et al. Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. Neuroimage. 2008;39(3):966-972. doi:10.1016/j.neuroimage.2007.09.044

23. Scheres A, Milham MP, Knutson B, Castellanos FX. Ventral striatal hypersensitivity during reward anticipation in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2007;61(5):720-724. doi:10.1016/j.biopsych.2006.04.042

24. Yau W-YW, Zubieta J-K, Weiland BJ, Samudra PG, Zucker RA, Heitzeg MM. Nucleus accumbens response to incentive stimuli lying adolescent vulnerability to substance use. J Neurosci. 2019;201(2):128-135. doi:10.1016/j.neuroimage.2019.11.012

25. Stice E, Yokum S. Brain reward region responsivity of adolescents with and without parental substance use disorders. Psychol Addict Behav. 2014;28(3):805-815. doi:10.1037/a0034460

26. Bjork JM, Knutson B, Hommer DW. Incentive-elicited striatal activation in adolescent children of alcoholic. Addiction. 2008;103(8):1308-1319. doi:10.1111/j.1360-0443.2008.02250.x

27. Ivanov I, Liu X, Shulz K, et al. Parental substance abuse and function of the motivation and behavioral inhibition systems in drug-naïve youth. Psychiatry Res - Neuroimag. 2012;201(2):128-135. doi:10.1016/j.pscychresns.2011.08.004

28. Ivanov I, Schulz K, Li X, Newcorn J. Reward processing in drug-naïve youth with various levels of risk for substance use disorders: a pilot study. J Child Adolesc Psychopharmacol. 2019;29(7):516-525. doi:10.1089/cap.2018.0175

29. Tervo-clemmens B, Quach A, Calabro FJ, Foran W, Luna B. Neuroimage meta-analysis and review of functional neuroimaging differences underlying adolescent vulnerability to substance use. Neuroimage. 2020;209:116476 doi:10.1016/j.neuroimage.2019.116476

30. von Rhein D, Mennes M, van Ewijk H, et al. The NeuroIMAGE study: a prospective phenotypic, cognitive, genetic and MRI study in children with attention-deficit/hyperactivity disorder. Psychol Med. 2011;41(2):359-366. doi:10.1017/S0033291710002277

31. Kaufman J, Ph D, Birmaher B, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36(7):980-988. doi:10.1097/00004583-199707000-00021

32. Conners CK, Erhardt D, Epstein JN, Parker JDA, Sintenrios G, Sparrow E. Self-ratings of ADHD symptoms in adults I: factor
