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Susceptibility to interference between Pavlovian and instrumental control predisposes risky alcohol use developmental trajectory from ages 18 to 24

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Abstract

Pavlovian cues can influence ongoing instrumental behaviour via Pavlovian-to-instrumental transfer (PIT) processes. While appetitive Pavlovian cues tend to promote instrumental approach, they are detrimental when avoidance behaviour is required, and vice versa for aversive cues. We recently reported that susceptibility to interference between Pavlovian and instrumental control assessed via a PIT task was associated with risky alcohol use at age 18. We now investigated whether such susceptibility also predicts drinking trajectories until age 24, based on AUDIT (Alcohol Use Disorders Identification Test) consumption and binge drinking (gramme alcohol/drinking occasion) scores. The interference PIT effect, assessed at ages 18 and 21 during fMRI, was characterized by increased error rates (ER) and enhanced neural responses in the ventral striatum (VS), the lateral and dorsomedial prefrontal cortices (dmPFC) during conflict, that is, when an instrumental approach was required in the presence of an aversive Pavlovian cue or vice versa. We found that a stronger VS response during conflict at age 18 was associated with a higher starting point of both drinking trajectories but predicted a decrease in binge drinking. At age 21, high ER and enhanced neural responses in the dmPFC were associated with increasing AUDIT-C scores over the next 3 years until age 24. Overall, susceptibility to interference between Pavlovian and instrumental control might be viewed as a predisposing mechanism towards hazardous alcohol use during young adulthood, and the identified high-risk group may profit from targeted interventions.

KEYWORDS
interference control, Pavlovian-to-instrumental transfer, risky drinking

1 | INTRODUCTION

The interaction of Pavlovian conditioned cues with instrumental behaviour may explain how certain stimuli can trigger drug-seeking in spite of a conscious decision against consumption.[1] Through Pavlovian learning a previously neutral stimulus can elicit conditioned responses—approach or avoidance tendencies—that are then elicited independently of the unconditioned stimulus. Such conditioned responses can influence (goal-directed) instrumental behaviour, which is learned via associations between actions and outcomes. For example, the enticing scent of food (Pavlovian) from a restaurant may trigger some approach tendencies and encourage people to dine (instrumental) inside eventually. The Pavlovian-to-instrumental transfer (PIT) paradigm is an essential experimental tool that allows to investigate the influence of Pavlovian cues on ongoing instrumental behaviour. Previously, we have demonstrated that susceptibility to interference caused by non-drug related Pavlovian cues that conflict with required instrumental behaviour is associated with risky drinking behaviour at age 18.[2] Notably, decreased functional activation elicited by the PIT effect in the lateral prefrontal cortex and a trend towards increased activation in the ventral striatum was associated with high-risk drinking in young adults. These results suggest a tipping of the balance between cortical and subcortical circuitry during PIT towards the ventral striatum, which may impact on inhibitory control, risk-seeking behaviour and the motivation to consume drugs.[3] It is thus of interest to assess how the interference effect during the PIT task, on both the behavioural and neural level, is associated with the development of risky drinking behaviour during the early intoxication and binge drinking phases in young adults.

Our PIT experiment[4] is comprised of two phases that separately induce instrumental and Pavlovian learning with monetary outcomes. Transfer effects are then assessed in a third phase, during which the participant must provide instrumental responses in the presence of Pavlovian cues from part two. Previous research has demonstrated that the valence of the Pavlovian cues can influence instrumental responding. Specifically, appetitive Pavlovian cues could promote approach or inhibit avoidance, while aversive Pavlovian cues could promote avoidance or inhibit approach behaviour.[5–7] Previous studies from our group detected increased instrumental responding with respect to the Pavlovian-associated monetary outcomes that incrementally increase in value among patients with alcohol dependence, and increased brain activity in the nucleus accumbens among patients with a poor treatment outcome.[8–10]

Employing an additional approach to the analysis, which considers both valences of the Pavlovian cues and the required (approach or avoidance) instrumental actions, we have identified further differences in instrumental behaviour based on the congruity between the two. To elaborate, Pavlovian cues can interfere with a required instrumental response when they are incongruent with the expected outcome. For example, when an approach response is required in the presence of a negatively valenced Pavlovian cue, the participant may erroneously provide an "avoid" response. This interference effect of Pavlovian cues on instrumental behaviours can be assessed by the error rate, which was indeed found to be higher in the incongruent as compared with the congruent condition.[2,11,12] Besides commonalities, interference during PIT has some fundamental differences compared to inhibitory control assessed with 'cold' psychological tasks such as Stroop and Simon tasks (see Diamond[13] for a review). In these tasks, conflict is elicited when automated response tendencies and the required responses are not concordant. In contrast, during the 'hot' interference in the PIT task, the conflict is elicited by the motivational responses elicited by Pavlovian cues that interfere with the required instrumental responses. Importantly, patients with Alcohol Use Disorder (AUD), particularly individuals who went on to relapse, were shown to commit more errors in the incongruent condition than control participants.[11,12] The same effect was also found in high-risk compared to low-risk drinkers at age 18 in the preclinical group investigated in the current study.[2] However, a recent study that assessed a full PIT task using food rewards found that the valence of the Pavlovian cues did not influence the performance of the AUD and the control group differently.[14]

On the neural level, we have previously shown that a higher error rate during the incongruent condition was associated with stronger neural responses in the ventral striatum (VS) and the lateral and dorsomedial prefrontal cortices (lPFC and dmPFC). This finding suggests relationships between the influence of the Pavlovian cues and ongoing instrumental behaviour that encompass both bottom-up and top-down neural pathways. In contrast to the studies that investigate greater reward sensitivity as a risk factor to AUD (e.g., Radoman et al.[15]), where the striatal activation to the reward is the key indicator, top-down cognitive control may also play a critical role during PIT, especially when the Pavlovian cues conflict with the instrumental responses. Support for the hypothesis that top-down control plays a key role during conflict trials comes from another school of literature in which a valenced go/no-go task was used. In this task, instead of assessing the PIT effect during a separate transfer phase following the instrumental and Pavlovian trainings, the Pavlovian conflict was embedded in the ongoing trial-and-error learning processes.[16–19] More specifically, the Pavlovian bias could be elicited when a 'no-go' instrumental response was required in the potential rewarding state or a 'go' instrumental response in the potential losing state. It was found that medial-frontal theta oscillations are stronger when successfully overcoming the Pavlovian bias that conflicts with the instrumental behaviour, indicating successful top-down control over Pavlovian bias during the instrumental learning process.[17,18]

Following our baseline report at age 18,[2] we endeavoured to test whether the behavioural performance along with the neural responses during the PIT task can predict the drinking trajectories of our sample during a six-year follow-up. Given that young adulthood is a stage when drinking behaviour escalates,[20,21] increased alcohol consumption or binge drinking behaviour during this stage may predispose the development of AUD in later stages of life. If the PIT effects were to be associated with increased alcohol use during young adulthood, it could potentially reflect a mechanism predisposing to AUD. To examine whether interference PIT effects can predict the drinking trajectories of our sample over 6 years (ages 18 to 24), we employed latent

growth curve modelling. In addition to the PIT assessment at age 18, we included PIT data from one additional assessment that was assessed 3 years after study inclusion at age 18, that is, at age 21.

We have previously reported an association between goal-directed and habitual control with risky drinking trajectories from age 18 to 21 in this sample.[22] Consistent with the drinking trajectories modelled in this previous report, here, the first drinking trajectory of interest is an AUDIT-C trajectory (sum of the first three items of the Alcohol Use Disorders Identification Test[23]), which assesses the frequency of drinking, the quantity of drinking in a typical drinking occasion, and the frequency of binge drinking since the last assessment. The second trajectory of interest is a binge drinking score trajectory that assesses the grammes of ethanol intake during a typical drinking occasion. According to the World Health Organization,[24] 60 g of ethanol or five standard drinks per drinking occasion can be considered the binge drinking threshold. However, this binary classification reduces dimensionality in the analysis, so the inclusion of a binge drinking score trajectory offers a continuous approach in assessing this behaviour.

The overall aim of the study was to test whether interference during PIT increases the liability for the development of risky drinking behaviours during young adulthood. We hypothesized that a more pronounced interference effect on the behavioural level and a stronger neural response in the VS would be associated with riskier drinking trajectories (i.e., positively associated with the slopes of the drinking trajectories) and that weaker neural responses in the lPFC and dmPFC would predict riskier drinking trajectories during the six-year follow-up period (i.e., showing negative associations with the slopes of the drinking trajectories). In addition, psychosocial and socioeconomic factors are known to contribute to the development of risky drinking during this period of life.[25,26] In order to gain a more comprehensive overview of predisposing factors underlying the development of risky drinking during young adulthood, secondary aims of the study were to explore whether other factors, such as drinking motives and socioeconomic status, may also contribute to the development of different drinking trajectories.

2 | MATERIALS AND METHODS

2.1 | Participants and general procedure

The participants were recruited from the local registration offices in Berlin and Dresden (more details in Chen et al.[2]). At the beginning of the study, we included 201 males who are right-handed and eligible for MRI, with neither history of nor current mental disorders, and with no substance dependence except for nicotine (details on use of Tobacco and other substances are shown in Supporting Information S3). The participants needed to have at least two drinking occasions during the last 3 months. Only males were recruited due to the predominance of male patients with AUD and dysfunctional alcohol consumption compared to female patients.[27]

Participants performed the experimental procedure with two on-site appointments at baseline (age 18; $N = 201$) and the assessment 3 years later (age 21; $N = 132$). During the first appointment, participants completed the Munich-Composite International Diagnostic Interview (M-CIDI)[28,29] based on the German version of the DSM-IV[30] and filled in other questionnaires that measure drinking-related behaviour (descriptive statistics of the questionnaires of interest are displayed in Supporting Information S2); cognitive ability assessments including processing speed, working memory and crystalized intelligence were also performed (details in Chen et al.[2]). During the second appointment, participants performed the PIT task that consisted of four phases. The Pavlovian and PIT phases were done in the scanner, while the instrumental and query trials were conducted outside the scanner. The imaging data were acquired using a Siemens 3-Telsa MRI scanner (Magnetom Trio, Siemens, Erlangen, Germany). The details of the sequences and the preprocessing procedures are described in Supporting Information S1. After quality control (more information in Chen et al.[2]), 191 behavioural and 139 neural datasets were included for the baseline analysis.

Drinking behaviours were assessed over a 6-year period from ages 18 to 24. In addition to the two on-site assessments, the participants were asked to fill in the AUDIT questionnaire online at 6-month intervals. Unfortunately, the AUDIT questionnaire was not available for the baseline assessment but only started 6 months after the baseline (at age 18.5). Besides the two on-site M-CIDI interviews at ages 18 and 21, M-CIDI telephone interviews were done every year when there were no on-site assessments. Regarding the main drinking behaviour assessments that we analysed for the current study, there were 12 AUDIT assessments (from age 18.5 to 24; every 6 months) and 7 M-CIDI interviews (ages 18–24; every year), which comprise of two on-site and five telephone interviews. In addition, participants needed to fill in other online questionnaires every year; more details about these assessments are mentioned in the corresponding analyses, and the descriptive statistics are displayed in Supporting Information S10.

2.2 | Alcohol drinking assessment

Consistent with our previous report on the 3-year drinking trajectories,[22] we primarily focused on the AUDIT consumption score (AUDIT-C) and the gramme/occasion variable from the M-CIDI interview. The AUDIT-C score was used to describe the alcohol consumption trajectory, given that it has been suggested to be sensitive to risky drinking and can be even more effective than the 10-item AUDIT total score.[31,32] The gramme/occasion variable from the M-CIDI interview assesses how many grammes of alcohol the participants consume on a typical drinking occasion during the last year. As previously mentioned, this variable was used to measure the binge drinking behaviour in a continuous way, as participants who continually consume more alcohol on a typical drinking occasion are more likely to be binge drinkers. Using a continuous variable instead of a

binary categorization as binge and non-binge drinkers, we preserve more information in the variable, which also aligns with the DSM-V[33] suggestions to characterize alcohol addiction with a more dimensional approach.

2.3 | PIT paradigm

The PIT paradigm is shown in Figure 1. This task has been described in more detail in the previous studies of our group.[8,9]

2.4 | Group-level PIT data analysis

2.4.1 | Behavioural PIT effect

Eight subjects were excluded from the dataset at age 21 due to data loss caused by technical problems, leaving 124 complete datasets. Among these subjects, we excluded seven participants who did not have valid baseline data; therefore, 117 subjects who had valid PIT behavioural data at both ages 18 and 21 were included in the behavioural analyses. Consistent with the baseline paper,[2] we calculated

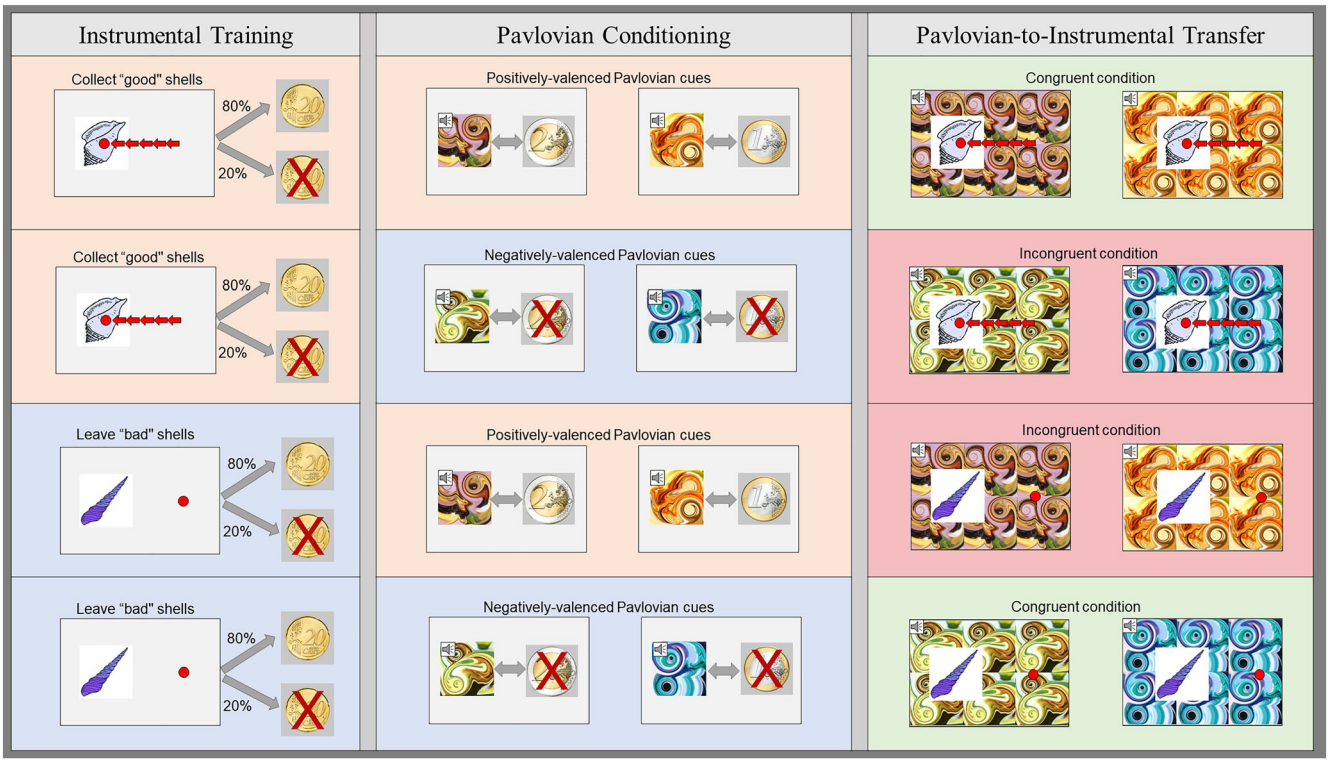

FIGURE 1 PIT paradigm. Instrumental training: Participants learned to collect good shells (press the button five or more times to move the dot towards the shell; coloured in orange) and leave the bad shells (nothing needed to be done; coloured in blue). A correct response yielded a €0.20 cent reward with the probability of 80% or a €0.20 cent monetary loss with a probability of 20%. After 60 trials, the instrumental training ended if the participants achieved the learning criterion (80% correct choices over 16 trials) or when a total number of 120 trials were reached. Pavlovian conditioning: Participants learned the association between five compound audiovisual stimuli (fractal images paired with pure tones) and the positive (€1, €2; coloured in orange), neutral (€0) and negative (€-1, €-2; coloured in blue) outcomes. The neutral condition is not shown in the figure since this condition cannot be categorized as 'congruent' or 'incongruent'. The Pavlovian conditioning phase consisted of 80 trials, with each fractal appearing 16 trials. Pavlovian-to-instrumental transfer phase: Participants performed the instrumental task again with the fractal images tiled in the background; the pure tones were also played simultaneously. This phase was done in the MRI scanner and under nominal extinction to prevent further learning. Based on whether the Pavlovian background values were concordant with the instrumental stimulus or not, the experimental trials could be categorized into congruent (positively valenced Pavlovian cues with 'good' shells or negatively valenced Pavlovian cues with 'bad' shells; coloured in green) and incongruent trials (positively-valenced Pavlovian cues with 'bad' shells or negatively valenced Pavlovian cues with 'good' shells; coloured in red). Each pairing of instrumental shell and Pavlovian cue appeared nine times during the transfer phase, resulting in 90 trials (9 trials × good/bad shells × five Pavlovian stimuli) in total. Among these trials, 36 trials belonged to the congruent, and 36 trials belonged to the incongruent conditions. Additionally, there were 72 trials during the transfer phase with water or alcohol pictures presented in the background. However, given that we have previously reported that the valence of water and alcohol backgrounds was perceived similarly to the neutral Pavlovian cue (Chen et al 2021), the alcohol/water trials along with the neutral trials were all excluded from the analyses. Query trials: Participants were instructed to select one the two Pavlovian cues presented to them within 2 s. Each possible pair of Pavlovian cues appeared three times in randomized orders. The four phases of the experiment were done in the consecutive order within one experimental session.

the difference in error rate between the incongruent condition and the congruent condition (ΔER) during the PIT phase at both ages 18 and 21. During the PIT phase, participants were instructed to perform the instrumental task according to what they had learned during the instrumental phase. Therefore, in the presence of the previously learned Pavlovian cues, the ΔER variable reflected the extent to which individuals were susceptible to the influence of Pavlovian cues. Higher ΔER values reflected more difficulty or inability to deal with the Pavlovian interference.

After characterizing the ΔER as the behavioural PIT effect at both ages 18 and 21, we first calculated the Pearson's correlation between them. This tested how strongly the behavioural PIT effects from the two time points were associated and can also indicate the test–retest reliability. A paired sample *t* test was done to investigate whether there were significant changes in the behavioural PIT effect over the 3 years on the group level. The ΔER from ages 18 and 21 were then used as the two PIT behavioural predictors to predict the individual drinking trajectories.

2.4.2 | Neural PIT effect

Regarding the neural data at age 21, we excluded four participants who had missing imaging data and four more participants who had either more than 3 mm volume-to-volume movement or more than 3 degrees of rotation. After further excluding those participants who did not have valid baseline neural data, 79 subjects with valid neural data from ages 18 and 21 remained for the fMRI analyses. The data analyses were performed with SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). The first- and second-level models were constructed in the same way as our baseline paper.[2] More specifically, mirroring our behavioural analysis, the incongruent versus congruent contrast was defined individually as the first-level model. This contrast was then entered into the second-level analysis as a one-sample t-test. The individual behavioural PIT interference effect (ΔER) was included as the covariate on the second level; the site information (whether the experiment was performed in Berlin or Dresden) was additionally included as a covariate of no interest to control for the potential site differences (described with more details in Supporting Information S4).

At baseline, we have shown that the neural responses in the VS, lPFC and dmPFC in the incongruent versus congruent contrast were positively associated with the behavioural PIT effect.[2] Following this, we now first investigated neural correlates of the behavioural PIT interference effect at the whole-brain level with an uncorrected threshold of $p < 0.001$ and a cluster size $k \geq 50$. We then extracted the parameter estimates during the incongruent condition within the same sets of regions of interest (ROI) to obtain neural PIT predictors from both ages (i.e., 18 and 21) for the latter drinking trajectory analysis. We chose to extract the neural responses in the ROIs during the incongruent trials as the main neural predictors to predict the drinking trajectories, since these neural correlates of the PIT interference effect had been found to be associated with risk status at age 18 in our baseline report.[2] The three ROIs, including the VS, lPFC and dmPFC, were defined based on previous meta-analyses (details in Supporting Information S5). We did not extract the parameter estimates from the amygdala since no association with the interference PIT effect was found in the baseline analyses. After extracting the parameter estimates from the three ROIs, we again calculated the Pearson's correlation coefficients between neural responses at ages 18 and 21 to check whether the neural responses within the three ROIs were reliable. Additionally, we performed paired sample *t* tests to check whether there were significant changes in the neural responses during the incongruent condition across the 3 years on the group level.

2.5 | Group-level drinking behaviour analysis

To gain an impression of the drinking behaviour on the group level, we first plotted the histograms of both variables (Figure 2). Regarding the AUDIT-C development on the group level (Figure 2B), there seemed to be a minor decrease over time; we thus regressed this variable against time (as a categorical variable) to test whether this decrease was significant. According to Figure 2D, on average, the gramme/occasion variable first decreased and then increased. Therefore, we regressed this variable against both a linear term and a quadratic term (squared time; time^2) to check whether the increase and decrease were significant on the group level.

2.6 | Individual drinking trajectory analysis

2.6.1 | Latent growth curve modelling approach

The latent growth curve modelling (LGCM) approach offers a multilevel framework that investigates both intra- and inter-individual changes in longitudinal studies. On the first level (intra-individual level), individual intercepts and slopes can be used to characterize the intra-individual developmental trajectories when linearity is assumed. A quadratic slope could also be added to the first-level model if a quadratic developmental pattern is assumed. On the second level, one can include different predictors in the model to investigate the association between these predictors and individual intercepts, linear and quadratic slopes. We implemented the LGCM analyses with the 'lavaan' package in R Studio.[34] With the lavaan package, the missing data could be handled via the full-information-maximum likelihood (FIML) method, where likelihood functions are estimated for the individuals according to the available information. Importantly, when assuming the missing data to be random, this method is suggested to be unbiased.[35] In order to assure that our data meet this assumption, we performed the Little's missing completely at random test[36] to make sure that the missing values are not associated with the variables of interest, that is, the PIT predictors. To achieve this, we ran two tests separately on the behavioural and the neural data sets. The two data sets include the behavioural or neural PIT predictors, along

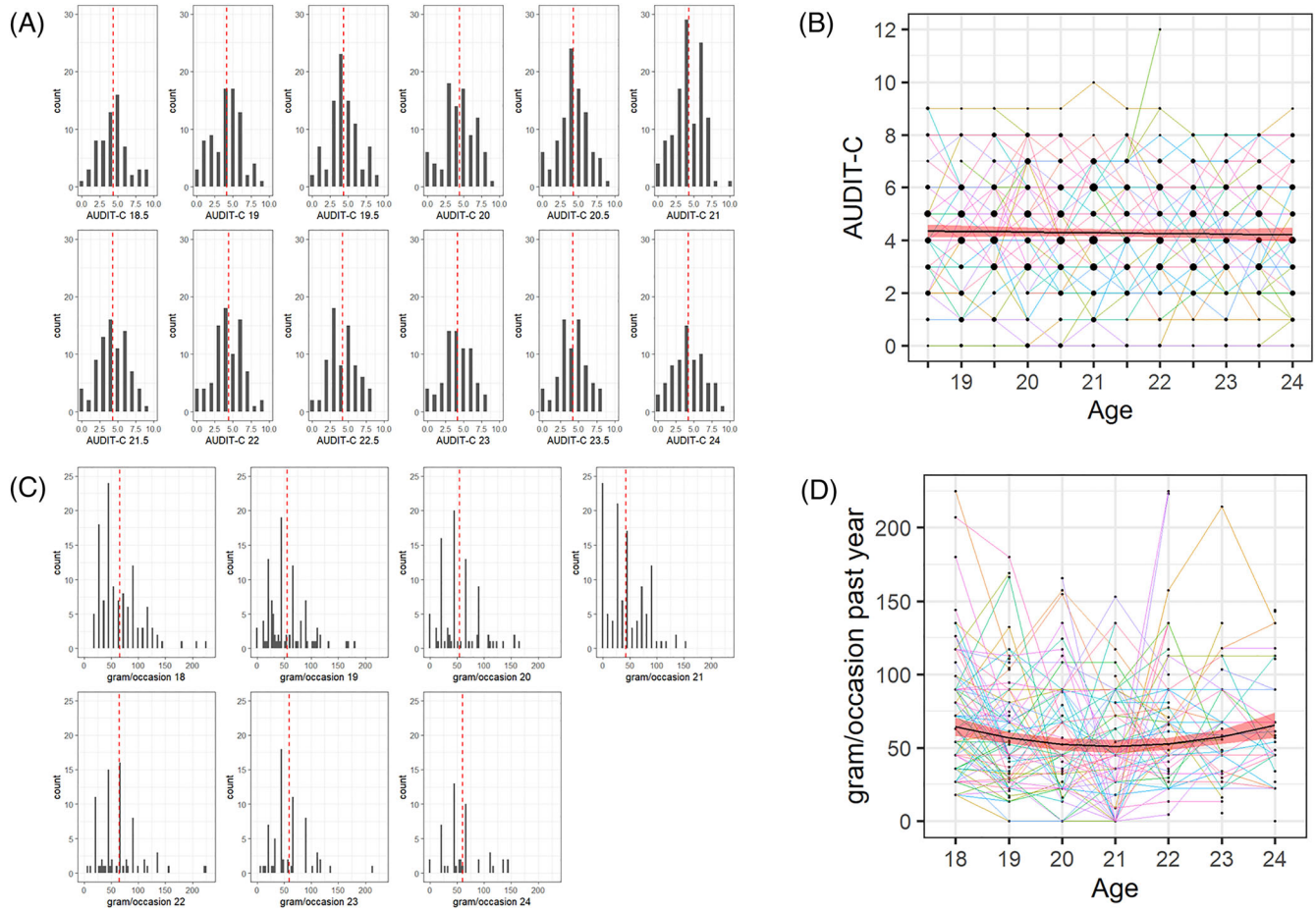

FIGURE 2 (A and C) Histograms from all available measurements for the AUDIT-C and gramme/occasion variables. The group means are indicated by the solid black lines. (B and D) Individual trajectories, shown in different colours, are plotted against age. Group means are shown with the bold, solid lines, and the red areas around the group mean lines indicate standard error.

with all the AUDIT-C and gramme/occasion variables. Both tests failed to reject the null hypothesis that the missing data were completely at random (behavioural data: $\chi^2 = 1483.24$, df $= 1445$, $p = 0.237$; neural data: $\chi^2 = 1271.08$, df $= 1278$, $p = 0.549$). Therefore, the FIML method should provide unbiased estimates.

2.6.2 | Comparison of individual drinking trajectory models

To investigate how the interference PIT effects were associated with the development of risky drinking behaviour, we created two drinking trajectories with the variables of interest: AUDIT-C and gramme/occasion. Before including any predictors, we first compared models with a linear slope, a quadratic slope and linear + quadratic slopes to decide which best described the intra-individual drinking trajectories.

Essentially, formalizing trajectories with a linear and a quadratic term, allows to capture more types of developmental courses compared to a linear function only, which best fits constant decreases, no changes or constant increases over time. For example, when the linear term is negative, and the quadratic term is positive, the drinking behaviour decreases initially; later on, the positive quadratic term can contribute to an increase of the drinking behaviour after a turning point. To demonstrate how the different combinations of intercept, linear and quadratic slopes can lead to different trajectories, we plotted six examples of drinking trajectories (Supporting Information S12).

We compared the linear and quadratic slope model with the linear + quadratic slope model with chi-squared tests, given that they are nested models. When the linear and quadratic slope models showed a better fit than the linear + quadratic slope model, we based our final decision on each model's Bayesian Information Criterion (BIC). The model with the lowest BIC was determined to be the superior model. Additionally, we computed the correlation between the intercepts and slopes from the two unconditional drinking trajectory models to check whether the two drinking trajectories developed differently over time. The detailed results of model

comparison and the correlation between intercepts and slopes are shown in Supporting Information S7.

2.6.3 | Individual behavioural models

In the next step, we included the PIT predictors into the best-fitting trajectory model. We built separate models with either behavioural or neural PIT effects as the predictors for the two drinking trajectories (four models in total). In order to preserve more behavioural data sets, we did not include all predictors (behavioural and neural) into one model, as done in Chen et al.[22] Otherwise, it would have meant that only 79 subjects who had complete behavioural and neural data could be included in the behavioural analysis. The behavioural model for the AUDIT-C trajectory is displayed in Figure S2A. The figure shows that all the behavioural PIT paths at age 18 to the intercept and slopes were freely estimated. We only included the paths from the behavioural PIT effect at 21 to the slopes but not to the intercepts because this PIT assessment occurred later than the baseline drinking behaviour. The covariance structures between ages 18 and 21 were also freely estimated. The same model structure was specified for the binge drinking score model.

2.6.4 | Individual neural model

The neural PIT models were constructed following the same line of reasoning as the behavioural PIT model (see Figure S2B for the AUDIT-C model). Specifically, we included the VS, lPFC and dmPFC neural responses during the incongruent trials at ages 18 and 21 as six neural predictors. Compared to our baseline report, where we used the data-driven activated clusters, we used the neural responses from the ROIs to maintain consistency between the two assessments at ages 18 and 21. The paths from the three baseline neural predictors to the intercept and slopes of the drinking trajectories were freely estimated. For the three neural predictors at age 21, the paths were again only directed from the neural predictors to the slopes. Additionally, covariance structures were estimated between all pairs of neural responses at the same time point and between the neural responses within the same ROI across the two assessments.

2.7 | Exploratory analyses

To better understand the association between the behavioural PIT effect and the AUDIT-C trajectories, we performed cluster analyses to identify distinctive developmental patterns. The behavioural PIT effect at the two assessments, as well as the change in the behavioural PIT effect from age 18 to 21 were also compared between the clusters. We additionally explored whether other questionnaires of interest (descriptive statistics in Supporting Information S10) could characterize the cluster profiles through logistic regression. We described these exploratory analyses together with the motivation behind it in details in Supporting Information S8.

Further, to gain more insights into the difference between AUDIT-C and gramme/occasion variables, we calculated the correlation coefficients between AUDIT-C, gramme/occasion, and the obsessive compulsive drinking scale (OCDS) total score,[37,38] as well as the alcohol dependence scale (ADS)[39] sum score whenever they were assessed at the same time point. The motivation of this analysis is explained in more details in Supporting Information S9.

3 | RESULTS

3.1 | Behavioural PIT effect on the group level

Recently, we reported the behavioural PIT effect in 191 participants.[2] The current study only reports the behavioural PIT effects of the 117 participants who performed the PIT task at both ages 18 and 21. At age 18, the 117 participants showed an increase in ER by 15.1% in the incongruent condition compared to the congruent condition on average ($t = 5.58$; df $= 116$; $p = 1.63 \times 10^{-7}$; Cohen's $d = 0.52$). At age 21, a similar pattern was found. The ER in the incongruent condition was increased by 17.0% compared to the congruent condition ($t = 5.72$; df $= 116$; $p = 8.41 \times 10^{-8}$; Cohen's $d = 0.53$). The correlation between the behavioural PIT effects at ages 18 and 21 was significant ($r[115] = 0.29$, $p = 0.002$). There was no significant change in the behavioural PIT effect across the two assessments as indicated by a paired-sample t test ($t = -0.56$, df $= 116$, $p = 0.578$; Cohen's $d = 0.07$).

3.2 | Neural PIT effect on the group level

In the initial analysis of 139 participants, we found a neural interference PIT effect in the VS, lPFC and dmPFC.[2] Now, we analysed a subsample of 79 participants who had valid neural PIT data at both time points. At age 18, we found that the neural PIT effect of this subsample was comparable to the neural activation pattern previously reported with the 139 subjects (Table 1). As shown in Figure 3A, the neural PIT effect was found in the caudate (extended to the ventral striatum; $k = 74$, $t = 4.04$, peak MNI coordinate: 12/16/2), lPFC, and dmPFC (within the same cluster; $k = 8109$, $t = 5.53$, peak MNI coordinate: 8/18/48) with an uncorrected whole-brain threshold of $p < 0.001$ and a cluster size of $k \geq 50$.

Using the same threshold, the neural PIT effect at age 21 was again found in the caudate (also extended to the ventral striatum; $k = 465$, $t = 4.64$, peak MNI coordinate: 14/14/8) and lPFC ($k = 73$, $t = 3.73$, peak MNI coordinate: 38/52/10). The analysis also revealed a cluster in the anterior cingulate cortex ($k = 61$, $t = 3.62$, peak MNI coordinate: 6/44/18) (Figure 3B), close to our dmPFC ROI. Within the dmPFC ROI itself, the brain response was below the predefined level of significance but could be seen at a lower threshold of $p < 0.005$. At

TABLE 1 fMRI results table

Incongruent vs. congruent contrast in association with the behavioural PIT effect (ΔER)						
Whole-brain results ($p_{uncorrected.}$ < 0.001, cluster size≥50)						
		Peak MNI				
Region	**Side**	**x**	**y**	**z**	**Peak-level T-score**	**Cluster size**
Age 18 (*N* = 79)						
Supplementary motor area (including the lPFC and dmPFC clusters)	R	8	18	48	5.53	8,109
Supramarginal gyrus	R	54	−44	38	5.46	1,579
Inferior parietal gyrus	L	−50	−46	40	4.87	1,035
Middle frontal gyrus, orbital part	R	36	44	−10	4.50	106
Inferior frontal gyrus, triangular part	L	−44	36	26	4.40	203
Superior frontal gyrus, medial	R	14	60	6	4.28	142
Median cingulate and paracingulate gyri	R	6	−38	34	4.08	325
Caudate (extended to ventral striatum)	R	12	16	2	4.04	74
Superior frontal gyrus, dorsolateral	L	−18	58	22	3.79	60
Thalamus	L	−6	−26	−2	3.76	53
Calcarine	R	18	−66	8	3.67	74
Calcarine	L	−6	−82	16	3.58	50
Precuneus	L	−14	−66	38	3.50	79
Age 21 (*N* = 79)						
Caudate (extended to ventral striatum)	R	14	14	8	4.64	465
Pallidum	L	−16	0	2	4.50	92
Superior frontal gyrus, medial	L	−8	24	40	4.08	69
Putamen	L	−24	16	−6	3.78	78
Middle frontal gyrus (including the lPFC cluster)	R	38	52	10	3.73	73
Anterior cingulate and paracingulate gyri	R	6	44	18	3.62	61

this level of significance, the anterior cingulate cortex cluster also extended to the dmPFC mask we applied in the initial report. Please note that we only lowered the predefined threshold for a sanity check of the data, this does not influence our planned ROI analysis, where activation from all voxels within the ROI were averaged irrespective of the threshold.

The correlation between the neural responses in the ROIs during the incongruent trials at ages 18 and 21 was moderate for the VS ($r[77] = 0.43$, $p = 8.03 \times 10^{-5}$) and weak for lPFC ($r[77] = 0.29$, $p = 0.009$) and dmPFC ($r[77] = 0.33$, $p = 0.003$). According to the paired-sample t tests ($p > 0.53$), there were no significant changes between the neural responses in the incongruent condition between ages 18 and 21.

3.3 | Drinking behaviour on the group level

On the group level, there was no significant change in the AUDIT-C over the 6 year period (Beta = −0.01, $p = 0.54$), with the mean AUDIT-C score ranging between 4.03 and 4.44 across the 6 years. Concerning the gramme/occasion variable, the statistical analysis confirmed that this variable first decreased and increased as time passed (Beta = −12.27; $p < 0.001$ for the linear term; Beta = 1.56; $p < 0.001$ for the quadratic term). On average, the mean alcohol intake per drinking occasion decreased from 66 to 43 g from ages 18 to 21 and then increased to 60 g at age 24. The descriptive statistics of the two variables of interest, along with other drinking-related variables are shown in Supporting Information S2. Importantly, individuals showed different patterns in their drinking trajectories regardless of whether or not there was a change on the group level (refer to the trajectory plots in Figure 2 displayed above).

3.4 | Individual behavioural models

Before including the PIT predictors, we conducted model comparison to select the best-fitting model for both AUDIT-C and gramme/occasion trajectories (detailed results in Supporting Information S7). The best-fitting AUDIT-C trajectory model included both linear and quadratic slopes. In contrast, for the gramme/occasion trajectory, the model comparison favours the model with only linear but not the quadratic slope.

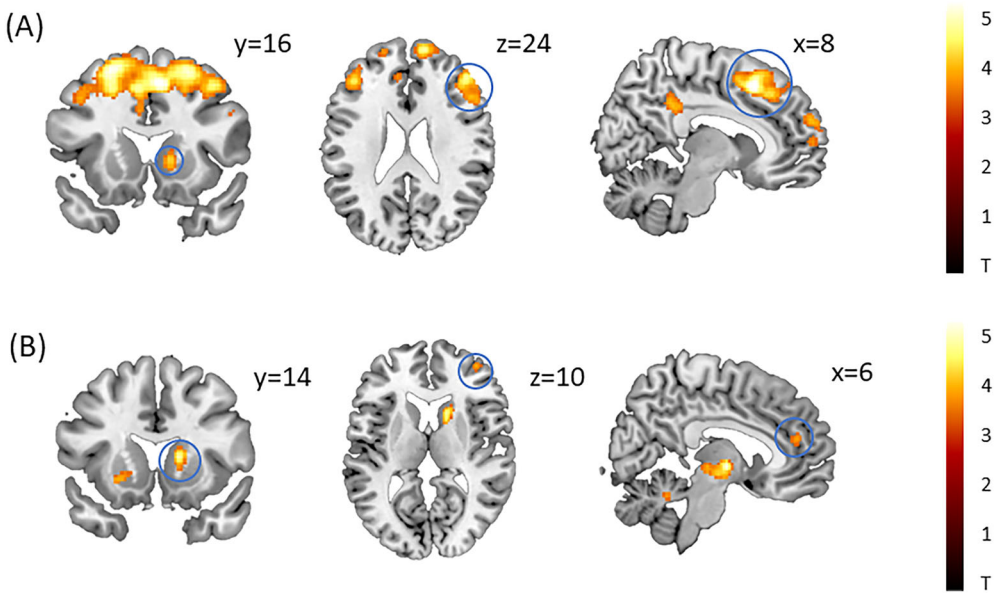

FIGURE 3 (A) Neural interference PIT effect (neural responses during interference correlated with the behavioural PIT effect) at baseline was found in the caudate (extended to the ventral striatum; $k = 74$, $t = 4.04$, peak MNI coordinate: 12/16/2), lPFC, and dmPFC (within the same cluster; $k = 8{,}109$, $t = 5.53$, peak MNI coordinate: 8/18/48); displayed with the threshold of $p < 0.001$, cluster size $k \geq 50$ (N = 79). (B) Neural interference PIT effect at age 21 was found in the caudate (also extended to the ventral striatum; $k = 465$, $t = 4.64$, peak MNI coordinate: 14/14/8), lPFC ($k = 73$, $t = 3.73$, peak MNI coordinate: 38/52/10), as well as anterior cingulate cortex ($k = 61$, $t = 3.62$, peak MNI coordinate: 6/44/18); displayed with the same threshold

TABLE 2 LGCM results

		Path	Estimate (unstandardized)	SE	Estimate (standardized)	*Z*	*p* value	Explained variances
AUDIT consumption score								
Behavioural	delta ER - 18	delta ER → intercept	0.588	0.638	0.096	0.922	0.357	2.13%
		delta ER → linear slope	0.044	0.142	0.047	0.308	0.758	0.94%
		delta ER → quadratic slope	−0.004	0.013	−0.042	−0.282	0.778	0.18%
	delta ER - 21	delta ER → linear slope	−0.351	0.126	−0.412	−2.780	**0.005**	**16.97%**
		delta ER → quadratic slope	0.031	0.012	0.392	2.602	**0.009**	**19.54%**
Neural	VS - 18	VS → intercept	0.186	0.073	0.420	2.560	**0.010**	**22.09%**
		VS → linear slope	−0.018	0.019	−0.240	−0.958	0.338	5.76%
		VS → quadratic slope	0.001	0.002	0.092	0.361	0.718	2.02%
	lPFC - 18	lPFC → intercept	−0.035	0.076	−0.101	−0.460	0.646	1.02%
		lPFC → linear slope	−0.017	0.019	−0.285	−0.874	0.382	8.12%
		lPFC → quadratic slope	0.001	0.002	0.284	0.838	0.402	11.16%
	dmPFC - 18	dmPFC → intercept	−0.069	0.071	−0.214	−0.975	0.329	4.58%
		dmPFC → linear slope	0.022	0.019	0.394	1.167	0.243	19.71%
		dmPFC → quadratic slope	−0.001	0.002	−0.233	−0.671	0.502	5.43%
	VS - 21	VS → linear slope	0.019	0.019	0.219	1.036	0.300	7.24%
		VS → quadratic slope	−0.002	0.002	−0.209	−0.910	0.363	4.37%
	lPFC - 21	lPFC → linear slope	0.008	0.018	0.115	0.482	0.630	2.72%
		lPFC → quadratic slope	−0.001	0.002	−0.193	−0.744	0.457	3.72%
	dmPFC - 21	dmPFC → linear slope	−0.031	0.017	−0.430	−1.857	0.063	18.49%
		dmPFC → quadratic slope	0.003	0.002	0.506	2.027	**0.043**	**30.91%**

(Continues)

TABLE 2 (Continued)

		Path	Estimate (unstandardized)	SE	Estimate (standardized)	Z	p value	Explained variances
Binge drinking score (gramme alcohol/drinking occasion) past year								
Behavioural	delta ER - 18	delta ER → intercept	14.209	10.429	0.155	1.362	0.173	4.20%
		delta ER → linear slope	−1.592	2.670	−0.089	−0.596	0.551	0.79%
	delta ER - 21	delta ER → linear slope	0.512	1.902	0.031	0.269	0.788	0.66%
Neural	VS - 18	VS → intercept	3.120	1.079	0.508	2.890	**0.004**	**31.14%**
		VS → linear slope	−0.535	0.254	−0.554	−2.109	**0.035**	**30.69%**
	lPFC - 18	lPFC → intercept	0.088	1.138	0.018	0.077	0.938	0.46%
		lPFC → linear slope	0.036	0.282	0.009	0.129	0.898	0.35%
	dmPFC - 18	dmPFC → intercept	−1.590	1.038	−0.355	−1.532	0.126	12.60%
		dmPFC → linear slope	0.269	0.253	0.381	1.061	0.289	18.58%
	VS - 21	VS → linear slope	0.417	0.237	0.371	1.759	0.079	17.72%
	lPFC - 21	lPFC → linear slope	0.052	0.210	0.056	0.249	0.803	1.12%
	dmPFC - 21	dmPFC → linear slope	−0.037	0.191	−0.041	−0.196	0.845	0.17%

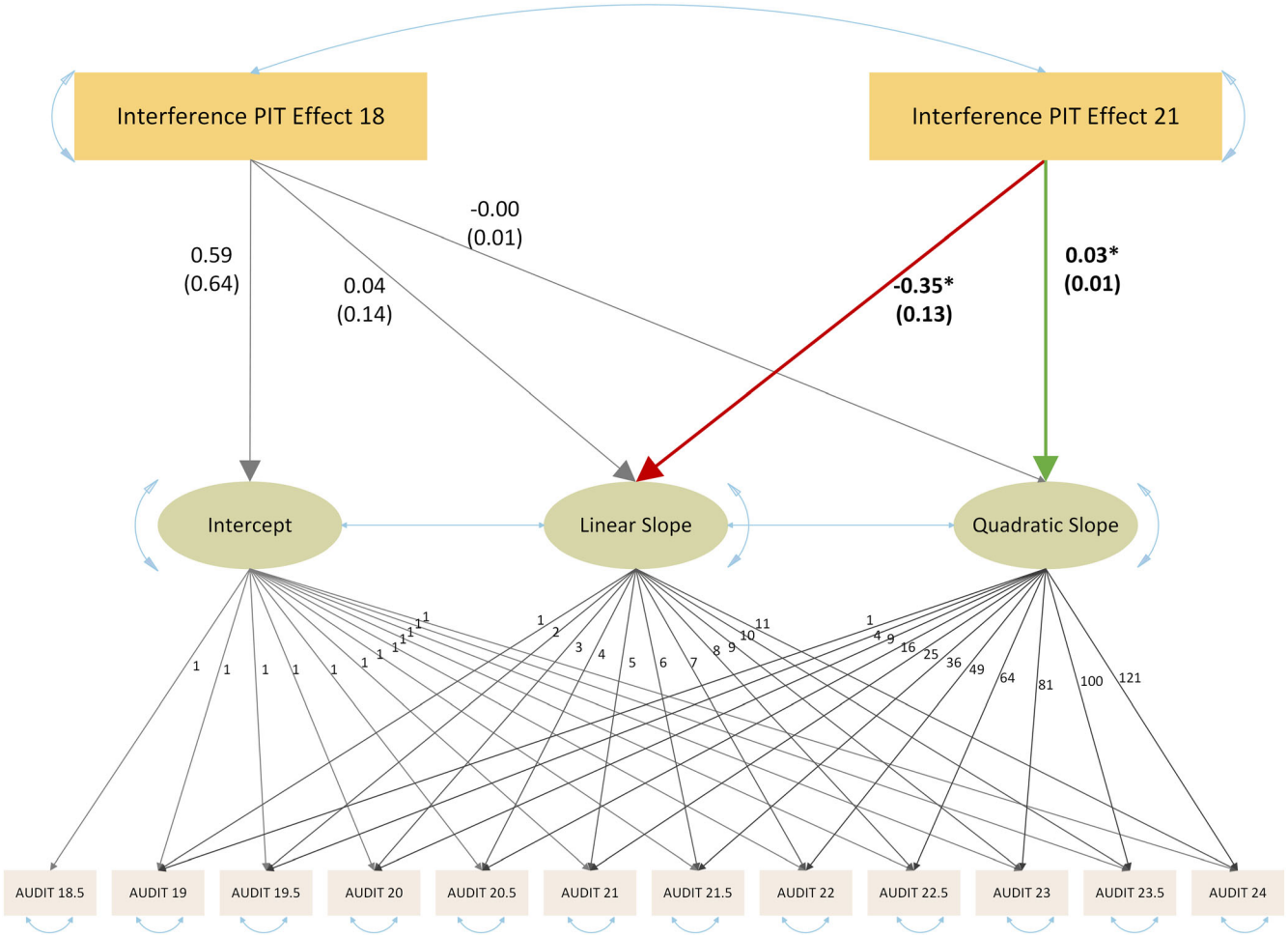

FIGURE 4 Behavioural LGCM model for the AUDIT-C trajectory. The observed variables are displayed within rectangles; the blue double-headed arrows specify the estimated variances. Three latent variables (intercept, linear and quadratic slopes) were created for the AUDIT-C model, with the fixed loadings shown along the paths. The path estimates are also displayed in the figure. It was found that the behavioural PIT effect at age 21 was negatively associated with the linear slope (red path) but positively associated with the quadratic slope (green path).

We then tested whether the PIT behavioural interference effect at ages 18 and 21 was associated with the linear and quadratic slopes of the AUDIT-C trajectory. The AUDIT-C model showed a good model fit ($\chi2 = 114.39$, $df = 79$, $p = 0.006$, CFI = 0.972, RMSEA = 0.062, SRMR = 0.050). The path estimates of all associations are displayed in Table 2.

We found no associations between the behavioural PIT effect at age 18 and the intercept or slopes. In contrast, behavioural PIT effect at age 21 was negatively associated with the linear slope (Beta = −0.351; $p = 0.005$), but positively associated with the quadratic slope (Beta = 0.031, $p = 0.009$) (Figure 4). The difficult to grasp associations between the behavioural PIT effect and both the linear and quadratic trajectories are visualized in Figure 6A. We plotted the standardized estimates to show how a behavioural PIT effect one standard deviation below or above the group mean would affect to the AUDIT-C trajectory. As can be seen in Figure 6A, the negative association with the linear slope, but positive association with the quadratic slope indicates that in individuals with a high behavioural PIT effect at age 21 drinking decreased in the 3 years before (from age 18 on), but due to the quadratic term these individuals are then (at age 21) at a turning point after which their consumption finally escalates over the next 3 years till age 24.

The gramme/occasion model fit was acceptable ($\chi2 = 45.39$, $df = 29$, $p = 0.027$, CFI = 0.886, RMSEA = 0.070, SRMR = 0.100), and we did not find any significant associations between the PIT behavioural effects with the gramme/occasion trajectory (results displayed in Table 2).

3.5 | Individual neural models

The AUDIT-C neural model showed a good model fit ($\chi2 = 223.39$, $df = 124$, $p < 0.001$, CFI = 0.912, RMSEA = 0.101, SRMR = 0.102). As shown in Figure 5, the only significant association we found at age 18 was a positive association between the neural response in the VS and the intercept of the AUDIT-C trajectory (Beta = 0.186, $p = 0.010$). At age 21 dmPFC responses were positively associated with the quadratic slope (Beta = 0.003, $p = 0.043$). This effect is visualized in Figure 6B.

The gramme/occasion model showed an acceptable model fit ($\chi2 = 72.03$, $df = 57$, $p = 0.087$, CFI = 0.953, RMSEA = 0.058,

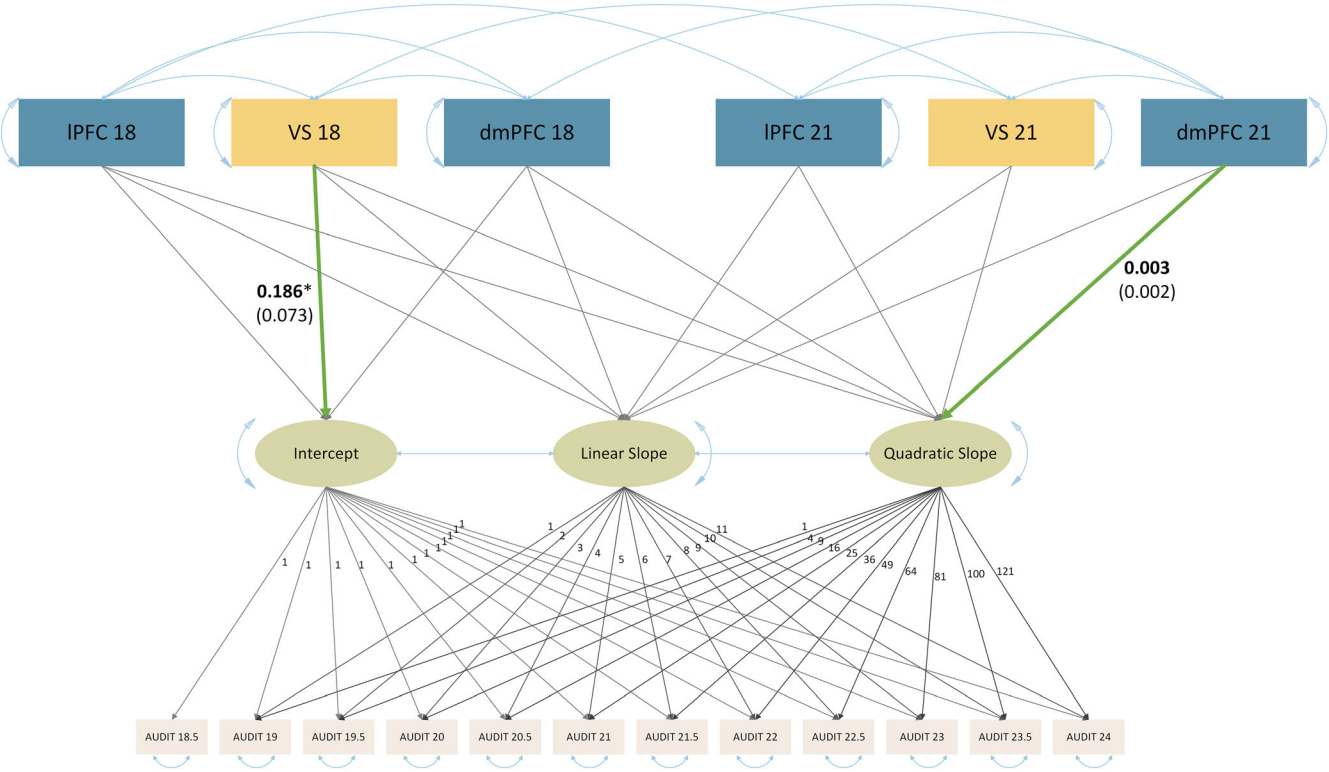

FIGURE 5 Neural LGCM model for AUDIT-C. The observed variables are shown in rectangles. The VS, lPFC, and dmPFC responses during the incongruent trials at ages 18 and 21 were used as predictors. The loadings from the intercept, linear, and quadratic slopes to the AUDIT-C were fixed. Other regressions and covariance as indicated by the blue arrows were freely estimated. The bold green path (left) showed that there was a positive association between the VS response in the incongruent trials at age 18 and the intercept of the AUDIT-C trajectory. Additionally, the dmPFC responses during incongruent condition were positively associated with the quadratic slope (right green path). For the readability of the graph, we only showed the significant paths; the estimates of the paths that did not show significant effects are displayed in Table 1.

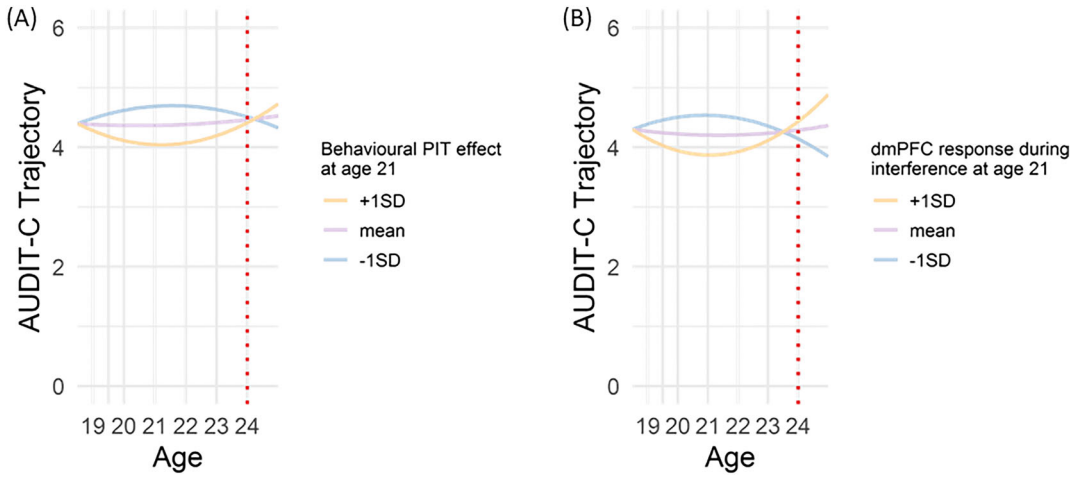

FIGURE 6 Illustration of the association between the behavioural PIT effect and dmPFC neural responses during incongruent trials at age 21 and the AUDIT-C quadratic trajectory. The three lines specify how the AUDIT-C trajectories develop when the PIT behavioural effect or dmPFC neural responses at age 21 are at the group mean as well as one standard deviation (SD) below or above the group mean. In order to plot this effect, we centred all the variables and re-estimated the behavioural and neural AUDIT-C models. In this way, the mean estimates of intercept, linear and quadratic slopes indicate the trajectories where the behavioural PIT effect and dmPFC neural responses were set at the group mean (AUDIT-C behavioural trajectory = intercept + linear slope × t + quadratic slope × t^2 = 4.397–0.016 × t + 0.002 × t^2; AUDIT-C neural trajectory = 4.300–0.034 × t + 0.003 × t^2). For the trajectories at one SD below or above the group mean, the linear and quadratic slopes were adjusted according to the change that is associated with one SD change in the behavioural PIT effect or dmPFC responses (SD_{PIT} × [path estimate PIT → linear/quadratic slope]). Since neither the behavioural PIT effect nor the dmPFC neural responses at age 21 were assumed to be associated with the intercept, we used a fixed starting point according to the intercept estimate. Specifically, it is plotted with the following equation: AUDIT-C behavioural trajectory = intercept + (linear slope ± SD_{PIT} × [path estimate behavioural PIT → linear slope]) × t + (quadratic slope ± SD_{PIT} × [path estimate behavioural PIT → quadratic slope]) × t^2 = 4.397 + (−0.016 ± 0.322 × [−0.355]) × t + (0.002 ± 0.322 × 0.031) × t^2; AUDIT-C neural trajectory = 4.300 + (−0.034 ± 4.451 × [−0.030]) × t + (0.003 ± 4.451 × 0.003) × t^2

SRMR = 0.124). The VS response during incongruent condition at age 18 was positively associated with the intercept of this trajectory (Beta = 3.120, p = 0.004) but negatively associated with the linear slope (Beta = −0.535, p = 0.035).

3.6 | Results of the AUDIT-C clustering analysis

As described in Supporting Information S8, we conducted an explorative cluster analysis based on the linear and quadratic slopes, using a fixed cluster number of two. The first cluster had a positive linear but negative quadratic slope, and vice versa for the second cluster. The mean trajectories of the two clusters (cf. Figure 7A) reveal that the first cluster peaked around age 21 and decreased afterwards. In contrast, the second cluster first decreased and then developed prominently until or further beyond age 24. We thus labelled the two clusters as 'early peaker' (N = 59) and 'late riser' (N = 58) group, respectively.

When comparing the behavioural PIT effect between the two subgroups (Figure 7B,C), we found that the two groups did not show any differences in the behavioural PIT effect at age 18 (t[114] = −0.30, p = 0.765), but at age 21: The 'late riser' group showed a three times higher interference PIT effect as compared to the 'early peaker' group (t[105] = −3.27, p = 0.001). These results are in line with the LGCM analysis. Further, they suggest that the association between the behavioural effect and the linear, as well as quadratic slopes, were mainly driven by the 'late riser' group. Moreover, as displayed in Figure 7D, the change of the PIT effect from age 18 to 21 was different between the two groups (t[114] = −2.58, p = 0.011): The late risers showed a significant increase in the PIT effect (t[57] = 2.14, p = 0.037), while the 'early peakers' seemed to show a nominal decline, though this change was not significantly different from zero (t[58] = −1.48, p = 0.146).

Mirroring this pattern on the behavioural level, the 'late riser' group, as compared with the 'early peaker' group, showed stronger dmPFC responses during conflict at age 21 (t[77] = −2.43; p = 0.017), but neither a significant difference to dmPFC responses at age 18 (t[75] = −0.88; p = 0.380) nor different changes in dmPFC responses from age 18 to 21 (t[69] = −0.85; p = 0.398). These effects are depicted in Figure 7E–G. Conversely, the two groups did not differ regarding their VS and lPFC responses during conflict at age 18 or 21; changes in neural responses from age 18 to 21 within these two regions were not significant (p > 0.099).

Through logistic regression, we finally explored whether other questionnaires of interest, in addition to the behavioural PIT effect at age 21, could explain why people belong to different subgroups. All the questionnaires included for the analysis are described in Supporting Information S8; the descriptive statistics of these variables at all available time points is displayed in S10. The logistic regression showed that, in addition to the behavioural PIT effect at age 21, a

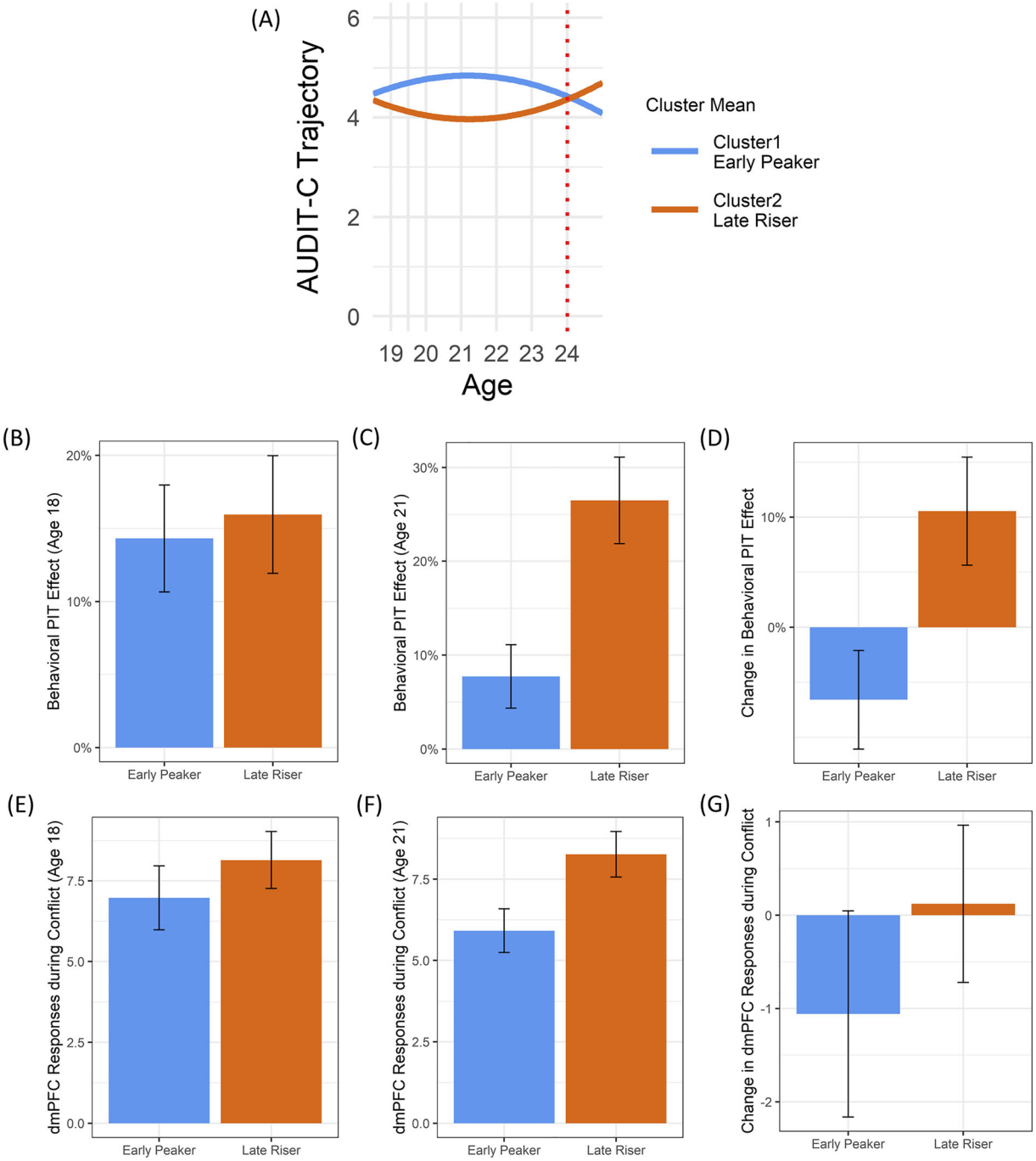

FIGURE 7 Results of AUDIT-C clustering analysis. (A) Trajectory of the two groups. Cluster 1 ($N = 59$; mean starting point = 4.47; mean linear slope = 0.139; mean quadratic slope = −0.013) reached the peak around age 21 and was thus labelled as 'early peaker' group. In contrast, cluster 2 ($N = 58$; mean starting point = 4.35; mean linear slope = −0.142; mean quadratic slope = 0.013) first decreased and then developed prominently and labelled as the 'late riser' group. (B) The two groups did not differ at age 18 with respect to the behavioural PIT effect. (C) The 'late riser' group showed higher interference PIT effect at age 21 as compared to the "early peaker" group. (D) The change in the interference PIT effect from age 18 to 21 was significantly different between the two groups. The 'late riser' group also showed a change that was significantly different from zero, whereas the change was not different from zero for the 'early peaker' group. (E) The two groups did not show different dmPFC responses during the conflict at age 18. (F) The dmPFC responses during conflict were stronger in the 'later riser' group. (G) The changes in the dmPFC responses were not significantly different between the two groups. All the error bars in the figure represent standard error.

stronger social motive to consume alcohol at age 21 ($B = 0.38$, $p = 0.037$) and higher socioeconomic status at age 18 were associated with a higher likelihood of being in the 'late riser' group. Conversely, more physical neglect during childhood (B = -0.79; p = 0.027) and higher alexithymia score ($B = -0.13$, $p = 0.045$) were associated with the membership of 'early peaker' group. The

TABLE 3 Correlation between OCDS and ADS with different drinking measures

Obsessive compulsive drinking scale (OCDS)					Alcohol dependence scale (ADS)			
	OCDS and AUDIT-C		OCDS and gramme/occasion		ADS and AUDIT-C		ADS and gramme/occasion	
Age	spearman's rho	*p*	spearman's rho	*p*	spearman's rho	*p*	spearman's rho	*p*
18	–	–	0.257	0.005*	–	–	0.442	<0.001***
19	0.535	<0.001***	0.266	0.016*	0.550	<0.001***	0.409	<0.001***
20	0.629	<0.001***	0.330	0.004*	0.678	<0.001***	0.413	<0.001***
21	0.602	<0.001***	−0.001	0.992	0.593	<0.001***	0.214	0.021*
22	0.666	<0.001***	0.136	0.301	0.613	<0.001***	0.250	0.054
23	0.600	<0.001***	0.035	0.809	0.606	<0.001***	0.240	0.089
24	0.750	<0.001***	0.022	0.886	0.628	<0.001***	0.218	0.150

*P value < 0.05.
***P value < 0.001.

complete results of the logistic regression are displayed in Supporting Information S11.

3.7 | Association between different drinking behaviours and craving and dependence

As shown in Table 3, the correlations between the OCDS and ADS and the AUDIT-C ranged from moderate to high at all available assessments and nominally increased over time. In contrast, the association between gramme/occasion and OCDS was weak from age 18 to 21, but this association was absent from age 21 to 24. A similar pattern was found with the ADS sum score: the correlations with gramme/occasion were moderate from age 18 to 21 but attenuated after age 21.

4 | DISCUSSION

In this study, we investigated the association between the interference PIT effect at ages 18 and 21 and drinking trajectories over 6 years until age 24 in a male community dwelling sample. The interference effect during PIT is behaviourally characterized by an increased ER during the conflict, that is, when instrumental approach is required in the presence of a negatively valenced Pavlovian cue or vice versa (instrumental avoidance required in the presence of a positively valenced Pavlovian cue). At age 18, behavioural PIT effects (ER) were not significantly associated with drinking variables, however, a higher VS response during incongruent trials was associated with a higher baseline of the AUDIT-C and binge drinking score trajectories, but, contrary to what we hypothesized, a lower slope of the binge drinking score trajectory. Analyses of behavioural PIT data at age 21 indicated that a high interference effect predicted the increase of the AUDIT-C until age 24. This pattern was mirrored at the neural level: a stronger dmPFC response at age 21 was also associated with an increase in the AUDIT-C over the next 3 years. Exploratory cluster analysis with respect to the AUDIT-C trajectory revealed an 'early peaker' group whose drinking behaviour peaked already around age 21 and declined afterwards, and a 'late riser' group whose drinking behaviour started to develop prominently after age 21. Compared with the 'early peakers', the 'late risers' showed not only a stronger behavioural interference PIT effect at age 21 but also a more pronounced increase of this effect from age 18 to 21.

The results from the cluster analysis indicated that the interference PIT effect might point to an underlying mechanism driving the distinctive drinking patterns during young adulthood. But are there other variables associated with the different drinking patterns of the two groups? The profiles of the two groups may offer some insights. Specifically, the 'early peakers' were found to experience more physical neglect during childhood and difficulties in describing their feelings. Previous studies supported the role of alexithymia in mediating the association between childhood trauma and alcohol addiction.[40,41] Conversely, the 'late risers' who developed prominently starting from age 21 had higher socioeconomic status and strong social motives when consuming alcohol. Although assessed on different levels, these findings indicate that a link may exist between environmental or psychosocial variables and cognitive measures like PIT, in line with the recommendation to integrate socioeconomic and psychosocial aspects into the models of addiction.[42–44]

Consistent with what we reported earlier in 139 participants with the baseline data,[2] we found that the VS responses during conflict were positively associated with the baseline of both the AUDIT-C and the binge drinking score in this subsample ($N = 79$). This supports the notion that the VS may play a central role during the initial bingeing and intoxication phase.[45] This notion might also explain why no association between the VS responses and drinking behaviours was detected at age 21. Contrarily, stronger functional VS activations during interference at age 18 were associated with more decrease or less increase in the binge drinking score over time. It is important to note that the statistical evidence for this association was weaker compared with the baseline associations; therefore, one needs to be

cautious not to over-interpret this result. However, increased VS activation associated with less rather than more alcohol intake was also found with respect to alcohol cue exposure and alcohol PIT paradigms.[46,47] If VS activation reflects attribution of salience to relevant cues,[48,49] it may under certain conditions contribute to behaviour control.

Also, contrary to our hypothesis, we did not find any longitudinal association between the behavioural PIT effect and the binge drinking score trajectory. Why did we not detect such an association, given that the behavioural PIT effect at age 21 was associated with the AUDIT-C development? When examining the correlations between the linear slopes of the two drinking trajectories, we found that the individual AUDIT-C slopes were not significantly associated with the linear slopes of the binge drinking score trajectory. The low correlations indicate that the AUDIT-C develops differently and captures different information; indeed, alcohol intake may be high if frequently repeated, even if it is rather low per occasion. Through an exploratory analysis, we found that the AUDIT-C was highly correlated with alcohol craving and dependence throughout the 6 years, while the association between the per occasion drinking behaviour and alcohol craving or dependence was only significant from ages 18 to 21 but became insignificant later. Therefore, in contrast to the AUDIT-C that evaluates both frequency and quantity of drinking, the sole amount of alcohol consumed during a typical occasion may not reflect craving or dependence during later stage of young adulthood.

Interestingly, stronger dmPFC responses during conflict at age 21 were associated with a more hazardous AUDIT-C trajectory (Figure 6B). Further cluster analysis confirmed this result – 'late risers' showed stronger dmPFC responses at age 21, which resembled the associations found with the behavioural PIT effect (Figure 7E–G). Previously, we found that stronger VS and weaker lPFC responses during conflict were associated with high-risk drinking and suspected that dmPFC might play similar roles as the lPFC.[2] However, the result here may suggest alternative functions of the dmPFC. On the one hand, it may encode a salience signal,[50] and lower dmPFC responses might indicate that participants could focus attention towards stimuli relevant for the instrumental response and ignore distracting Pavlovian cues that interfere with the required instrumental behaviour. In fact, stronger neural responses both in the medial prefrontal cortex and the VS have previously been found to be associated with enhanced motivation towards alcohol cues.[47,51,52] Alternatively, dmPFC responses may reflect error monitoring during conflict.[53] In support of this idea, when checking the association between the dmPFC responses and the behavioural PIT effect (i.e., ER), we found that they were positively correlated at both time points: The correlation was only significant at age 21 ($r[77] = 0.26$, $p = 0.023$), but not at age 18 ($r[77] = 0.15$, $p = 0.183$). Since this also suggests that there might be changes in the role of dmPFC from ages 18 to 21, investigating the role of dmPFC during the conflict between Pavlovian and instrumental control in more detail could help to address the role of this brain area in error monitoring during addiction development. Interestingly, low-risk drinkers showed stronger effective connectivity from the VS to the lPFC when dealing with the interference during PIT via a dynamic causal modelling approach (DCM).[2] Network connectivity could be a critical factor for the development of drinking behaviour during young adulthood.[54]

The PIT predictors we included in our study had reliability ranging from 0.29 to 0.43, which could be considered as weak to moderate,[55] which may reflect the specific state-dependent components rather than stable traits. Our data indicate that such a state-dependent component may indeed exist, given that the change of the behavioural PIT effect predicted drinking trajectories, when we explored the differences between the two clusters ('early peakers' vs. 'late risers' in consumption). In fact, given that only the behavioural PIT effect at age 21, but not at age 18, was associated with the AUDIT-C trajectory, one might conclude that it is the state component of behavioural PIT effect that drives the development of drinking behaviours. This is in line with changes in associated neurobiological systems including mesolimbic dopamine and cortical functions this development period.[56–58] In accordance with the substantial changes in fronto-striatal circuits during this developmental period in late adolescence and early adulthood, the state component in the neural responses during the conflict was not consistently associated with the development of drinking behaviours.

As noted earlier in the introduction, besides the commonalities, the interference control assessed via the PIT task is also different from other classical tasks such as Stroop[59] and Simon[60] tasks. In these tasks, conflict is elicited when the 'cold' automatic tendency, that is, responding to the meaning of the word or tendency to respond to a stimulus from the same side, interferes with the required actions. Similarly, in tasks that assess response inhibition,[61] like the go/no-go or stop-signal tasks, participants need to withhold or stop their initiated responses when a certain stimulus is presented. Here, the inhibitory control is also recruited through "cold" instruction. In contrast, after conditioning, the Pavlovian cues promote conditioned approach or avoidance tendencies through motivational processes during PIT. These motivational responses to the incongruent Pavlovian cues then conflict with the required ongoing instrumental behaviours. The whole process requires not only the prefrontal cortex but also the ventral striatum,[2] which makes the PIT task a valuable empirical tool since both motivational circuits and executive functions, as well as the balance between the two, are critical for understanding the development of alcohol use disorders.[3] Nevertheless, since poorer inhibitory control has been also demonstrated in AUD participants[62] and young binge drinkers,[63] it could be an interesting avenue for future studies to investigate empirically how the interference PIT effect is associated with the effect in these classical tasks to better understand their relationship.

Several limitations have to be addressed: first, we found different trajectory patterns (linear and quadratic slopes for AUDIT-C but linear trajectory for gramme/occasion) to be optimal for the two trajectories. Since the binge drinking score and the AUDIT-C were assessed with different frequencies, we cannot rule out the possibility that this discrepancy may have happened since there were more AUDIT-C assessments available than the binge drinking score assessments, which allowed for more degrees of freedom in fitting a more

complicated model to the individual-level drinking data. To test whether the AUDIT-C trajectory is different from binge drinking score trajectory, future studies should conduct more assessments within the same time interval.

Second, we used a fixed cluster number of two for the clustering analysis due to the limited sample size; future studies with a larger sample size could explore whether more subgroups with distinctive profiles could be identified. Additionally, since the cluster analyses and the logistic regression were conducted as exploratory post-hoc tests, no statistical corrections were done for these sets of analyses. Thus, future research might therefore specifically test these hypotheses.

Third, on the behavioural level, only around two-thirds of the participants (62% at age 18 and 66% at age 21) showed a non-zero ER, which may have limited the power to predict the individual differences in the drinking trajectories. Future studies could improve the sensitivity of the measures to capture more subtle effects. Lastly, we only included male participants, so these results cannot be generalized to non-male populations.

In summary, our 6-year longitudinal study revealed that high error rates due to conflict between Pavlovian and instrumental control and their neural correlates can predict alcohol use trajectories. Through cluster analyses of the drinking trajectories, we identified two subgroups: the drinking behaviour in the 'late riser' group escalated after age 21, whereas the drinking of 'early peakers' culminated at this age and then declined. The 'late risers' showed enhanced dmPFC responses during conflict and three-times higher error rates during conflict between Pavlovian cues and instrumental responses in the PIT paradigm at age 21. Interestingly, this group also exhibited an increased behavioural PIT effect from age 18 to 21. Future studies could thus explore the dynamics of this interference PIT effect to predict risky drinking behaviours, potentially with more frequent PIT assessments. Such high-risk groups may then profit from targeted prevention and interventions.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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