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METHODS: We identified 304 (out of 424 at baseline) drug and alcohol naïve adolescents (age 14; 147 female) from the IMAGEN Consortium, with complete data at baseline (age 14) and a 2-year follow-up. This cohort was stratified into groups based on the number of occasions of lifetime alcohol use at follow-up: 0 occasions (n=83), 1-9 occasions (n=133), 10-19 occasions (n=42), 20-39 occasions (n=34), and >40 occasions (n=12). Longitudinal changes in trait impulsivity and delay discounting (measured via the Temperament and Character Inventory and the Monetary-Choice Questionnaire, respectively) were assessed. Since fMRI data on the Monetary Incentive Delay task was acquired only at baseline, multiple

linear regression models with activation in ventral striatum (VS) for reward anticipation and medial orbitofrontal cortex (mOFC) for reward outcome at the drug naïve baseline were used to predict alcohol use severity at follow-up.
RESULTS: Change in trait impulsivity showed a dose-response with change in alcohol use from baseline to follow-up, such that it decreased in the 0 occasions and 1-9 occasions groups, did not change in the 10-19 occasions and 20-29 occasions groups, and uncharacteristically increased in >40 occasions group. Delay discounting decreased across all groups from baseline to follow-up independent of alcohol use. Further, blunted mOFC activation during reward outcome at baseline significantly predicted higher alcohol use severity at follow-up, above and beyond behavioral and clinical variables.
CONCLUSION: High trait impulsivity, a known risk factor for the development of substance use disorders, may also be associated with high alcohol use in adolescents. Moreover, blunted activity of the mOFC during reward outcome may underscore a predisposition to the development of more severe alcohol use in adolescents. This distinction is clinically important as it informs early intervention efforts for adolescents developing problematic substance use behavior and may thereby help in preventing the onset of substance use disorder.

Substance use initiation in drug naïve adolescents – possible predictors and consequences from a large cohort naturalistic study

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Abstract

BACKGROUND: Neurobiological evidence points to a cortical and behavioral co-development, such that behavioral disinhibition decreases as neural substrates subserving motivational drive mature with age during adolescence. Deviations from such neurotypical development are posited to be associated with elevated substance use behavior in adolescents. However, it is not clear whether these deviations are neurobiological predispositions for developing substance use, or if they are associated with severity of such behavior. To fill this knowledge gap, the current large-cohort longitudinal study assesses impulsivity and neural reward processing in drug-naïve adolescents who go on to develop alcohol use with varying severity two years later.

METHODS: We identified 304 (out of 424 at baseline) drug and alcohol naïve adolescents (age 14; 147 female) from the IMAGEN Consortium, with complete data at baseline (age 14) and a 2–year follow-up. This cohort was stratified into groups based on the number of occasions of lifetime alcohol use at follow-up: 0 occasions (n=83), 1-9 occasions (n=133), 10-19 occasions (n=42), 20-39 occasions (n=34), and >40 occasions (n=12). Longitudinal changes in trait impulsivity and delay discounting (measured via the Temperament and Character Inventory and the Monetary-Choice Questionnaire, respectively) were assessed. Since fMRI data on the Monetary Incentive Delay task was acquired only at baseline, multiple linear regression models with activation in ventral striatum (VS) for reward anticipation and medial orbitofrontal cortex (mOFC) for reward outcome at the drug naïve baseline were used to predict alcohol use severity at follow-up.

RESULTS: Change in trait impulsivity showed a dose-response with change in alcohol use from baseline to follow-up, such that it decreased in the 0 occasions and 1-9 occasions groups, did not change in the 10-19 occasions and 20-29 occasions groups, and uncharacteristically increased in >40 occasions group. Delay discounting decreased across all groups from baseline to follow-up independent of alcohol use. Further, blunted mOFC activation during reward outcome at baseline significantly predicted higher alcohol use severity at follow-up, above and beyond behavioral and clinical variables.

CONCLUSION: High trait impulsivity, a known risk factor for the development of substance use disorders, may also be associated with high alcohol use in adolescents. Moreover, blunted activity of the mOFC during reward outcome may underscore a predisposition to the development of more severe alcohol use in adolescents. This distinction is clinically important as it informs early intervention efforts for adolescents developing problematic substance use behavior and may thereby help in preventing the onset of substance use disorder.

Introduction

Adolescence is a critical period for drug experimentation. Moreover, adolescent substance abuse is a significant public health issue with far reaching consequences, both for adolescents' own lives as well as for the society at large [1-3]. Some have suggested that adolescence is a period of naturally occurring developmental dissociation between motivational drive (i.e. propensity to seek activities experienced as "rewarding") and the ability to control those types of drives (i.e. behavioral inhibition [4]. This combination between a strong drive for rewards on one hand and behavioral disinhibition on the other seem to be complimentary predisposing factors for drug experimentation and use during adolescence. This combination between a strong drive for rewards on one hand and behavioral disinhibition on the other seem to be complementary predisposing factors for drug experimentation and use during adolescence. This behavioral mismatch has been linked to the functioning of neuronal networks associated with behavioral motivation and control [5] and therefore it is reasonable to stipulate that altered activation in those networks during adolescence may underpin the propensity for increased drug use [6-10].

The relationship between impulsivity constructs and reward sensitivity has been extensively studied despite some serious conceptual limitations. For instance, impulsivity is not a unitary construct but rather a complex set of behaviors that include sub components such as motoric impulsivity (impulsive action), cognitive impulsivity (impulsive choice), novelty seeking (preference for highly exciting and novel stimuli) and temporal discounting (preference for immediate but small vs. delayed but large rewards, or impulsivity with positive and negative urgency)[11]. These impulsivity components may be related to later life outcomes, including the development of substance use disorders (SUD) [5,12-16]. However, these constructs are not

interchangeable and it is still unclear whether their developmental trajectory is perturbed with substance use.

Similarly, there is little consensus on reward sensitivity as a risk factor for substance abuse. First, the development of reward sensitivity scales (e.g. the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) [17] entail the inclusion of multiple constructs that are conceptually and grammatically complex and probably are not appropriate for adaptation to child and adolescent versions of such instruments. Second, identifying appropriate behavioral measures as indicators for "reward sensitivity" has been challenging and it has been proposed that behavioral indices of reward sensitivity are important only as secondary indicators of underlying neuroadaptive processes [18], which in turn can be examined by the use of neuroimaging. Indeed, recent evidence suggests that functional neuroimaging can index underlying physiological abnormalities even before the full development of the clinical phenotype (i.e. before SUD onset) [9] and that neuroimaging biomarkers and clinical risk factors may have different roles as predictors of treatment outcomes [19-21]. All together this suggests that neuroimaging can play a crucial role in the study of reward sensitivity in relation to risk for SUD.

It also stands to reason that behavioral traits (e.g. impulsivity, altered reward sensitivity) may have a bidirectional relationship with drug experimentation in adolescence, such that while these traits may predispose adolescents to problematic drug use, initial drug exposure may also alter (even exacerbate) such a trait. However, one common limitation for investigations of risk factors for SUD is that they are carried out in populations that have had different levels of exposure to drugs of abuse. Therefore, it seems imperative to investigate the "baseline" states of behavioral and biological markers that underlie the impulsivity – reward sensitivity constitutional

relationships in a sample with no prior exposure to abusable substances, examine it longitudinally as problematic substance use behavior unfolds and compare it with those who either stay drug-naïve or don't present the problematic use pattern.

Furthermore, by selecting and following up a young adolescent sample that has never been exposed to drug/alcohol use one can identify baseline factors that may predict these clinically consequential drug use patterns. Such investigations might have important relevance to the clinic. For example, important insights may follow from investigating the effects of initial exposure to drugs on naturally occurring maturational changes during adolescence and from identifying patterns of impulsivity changes in drug naïve individuals that may be linked to elevated risk for more frequent/severe drug experimentation during adolescence. The available data from the IMAGEN consortium offers an excellent opportunity to address these issues. It allows us to examine patterns of reward processing and obtain various impulsivity measures within a large cohort of adolescent participants who have been assessed at the same age on the same assessment battery including self-report, behavioral and imaging measures.

The aim of the current study was to examine whether changes in impulsivity [measured using the Temperament and Character Inventory (TCI-I) [22]] as well as delay discounting [assessed via the Monetary-Choice Questionnaire (MCQ-DD) [13]] in drug naïve adolescents age 14 were related to the development of alcohol use at age 16. Moreover, we examined whether functional activations of the ventral striatum (VS) during reward anticipation or medial orbitofrontal cortex (mOFC) during reward outcome of the monetary incentive delay (MID) task at baseline may predict the development of more severe alcohol use.

Methods and Materials

Participants

Participants were from the IMAGEN project, a large longitudinal European multi-center genetic-neuroimaging study [23] that collected data on impulsivity, reinforcement sensitivity and emotional reactivity in adolescence. At baseline, healthy adolescents were aged 13-14 years and were recruited at 8 sites located in England, France, Ireland, and Germany. The IMAGEN protocol was approved by local ethics committees and written informed assent and consent were obtained from all participants and their legal guardians. Details on the standard operating procedures for IMAGEN as well as a comprehensive list of inclusion/exclusion criteria are available at http://www.imagen-europe.com/en/Publications_and_SOP.php [23].

Baseline Characteristics

All adolescents were screened for psychiatric disorders with the help of the Development and Well-Being Assessment questionnaire [24]. Participants' intellectual functioning was assessed using the Perceptual Reasoning, Matrix Reasoning and Similarities, and Vocabulary scales from the Wechsler Intelligence Scale for Children-IV [25]. Participants who met criteria for the diagnoses of schizophrenia or bipolar disorder, neurodevelopmental disorders [such as autism, and Attention-Deficit Hyperactive Disorder (ADHD)], or had an IQ of less than 70 were excluded from the study. Pubertal status was assessed by the Puberty Development Scale [26]. Participants' socioeconomic status was assessed using a composite score that indexed the weighted sum of mother's education score, father's education score, family stress unemployment score, financial difficulties score, home inadequacy score, neighborhood score, financial crisis score, mother employed score, and father employed score [27]. The follow up, 2 years after the

baseline assessment at ages 15-16, was conducted where data were collected online and via phone interview, and no fMRI scans were conducted at follow up.

Exposure: Identification of the sample of drug naïve youth

The main goal of this investigation was to identify a subsample of adolescents who had no prior exposure to substances of abuse at baseline, and of whom some went on to use alcohol at two-year follow-up. The assessment for the participants' personal history of substance use was based on the European School Survey Project on Alcohol and Drugs [ESPAD; [28]], including assessments of frequency of use and symptoms of abuse for a range of illicit drugs (e.g. marijuana, inhalants, tranquillizers, amphetamines, lysergic acid diethylamide, magic mushrooms, crack, cocaine, heroin, narcotics, ecstasy, ketamine, anabolic steroids). In addition, nicotine use was measured with the Fagerström Test for Nicotine Dependence (FTND [29]) and alcohol use was also measured with the alcohol use disorder identification test (AUDIT [30]) questionnaire. Among the IMAGEN baseline sample, 422 adolescents reported no drug use at baseline. Of these 422 adolescents, follow-up drug use data was available for 304 adolescents. These adolescents were then stratified into groups based on the number of occasions of alcohol consumption, as done in ESPAD, since the prior visit (i.e., baseline), yielding 5 subgroups: 0 occasions (n=83), 1-9 occasions (n=133; here we merged original groups of 1-2, 3-5, and 6-9 occasions into one group), 10-19 occasions (n=42), 20-39 occasions (n=27), and 40 or more occasions (n=19). Importantly, increased number of occasions of alcohol use was significantly positively correlated with number of binge drinking occasions (r_s=0·683, p<0·0001), therefore, this ESPAD stratification can be considered as a proxy for problematic drinking behavior. Other drugs were less prevalent; for example, at follow-up 231 of the 304 adolescents reported no cigarette use. Demographic data at baseline for each group is presented in **Table 1**.

Outcome: Psychometric and Behavioral Impulsivity

We selected measures that indexed different aspects of impulsivity with a specific focus on those that are considered risk factors for later substance use. Such factors included "impulsivity" from the TCI-R [22], and "delay discounting" from the MCQ [13]. The TCI-R is a computerized, self-rating personality questionnaire with the scale impulsiveness versus reflection as one of the novelty seeking facets. Participants provided answers by means of a five-point Likert scale. By adding up the scores of the nine items of interest, a total was computed with higher values signifying higher impulsiveness. The MCQ uses a series of 27 choices between a hypothetical smaller, sooner and a larger, later reward. A subjective discount parameter (k) is calculated as an indicator of individual differences in one's propensity to choose sooner but smaller over later but larger rewards, which has been shown to correlate well with more precise but also more time-consuming delay discounting measures [31].

Family History (FH) of SUD

Family history of SUD was assessed by, 1) a family history interview and 2) a questionnaire battery. During the interview, the participating parent(s) was asked for any mental health problem in first- or second-degree biological relatives of the adolescent and prompts (e.g., depression, alcoholism) were provided to indicate what was considered a mental health problem. If parents indicated the presence of such problem(s), they were asked for the specific disorder of that relative and whether this relative was either diagnosed by a medical doctor or psychologist, and/or was in treatment because of it. The questionnaire battery included the following questionnaires related to parents' own substance use behavior: the Michigan Alcoholism Screening Test (MAST) [32] , the AUDIT [30] and the FTND [29]. With a modified version of the Drug Abuse Screening Test (DAST) [33] we assessed frequency of use and symptoms of abuse for a

range of illicit drugs (including marijuana, inhalants, tranquillizers, amphetamines, lysergic acid diethylamide, magic mushrooms, crack, cocaine, heroin, narcotics, ecstasy, ketamine, anabolic steroids).

Based on the reports from the family history interview and the scores from the questionnaire battery FH status was determined for both alcohol and other drugs. Family history (FH) status for SUD was defined as: (A) FH negative (FH–; n=153) when there was no report of alcohol/drug abuse in first or second degree relatives (as per FH questionnaire) and the Parent-AUDIT <= 3, Parent-MAST <= 2; Parent DAST < 6 for all substances; and, (B) FH positive (FH+; n=151) when there was a positive report of alcohol/drug abuse in the family in at least one first (mother, father, brother, sister) or second (grandparents, half siblings, as per FH questionnaire) degree relatives (Parent-AUDIT >3, Parent- MAST > 2, Parent-DAST >= 6 for any substance, Parent FTND > 2). Individuals were further classified as FH+ if they endorsed one of the following "diagnostic" items from the MAST questionnaire: 'Have you ever attended a meeting of Alcoholics Anonymous?', 'Have you ever gone to anyone for help about your drinking?', 'Have you ever been in a hospital because of drinking?' The distribution of FH- and FH+ within the study groups is outlined in **Table 1**.

Monetary Incentive Delay (MID) MRI Task

During fMRI scanning participants performed a modified version of the MID task [34]. Similar to the original task this modified version included four distinct components: cue presentation, an anticipatory delay, a response phase with target presentation and outcome. Cues indicated three possible amounts of reward for a given trial (none, small or large). Half of the cues for each particular amount were presented on the left and half on the right side of the screen, followed by a variable anticipation interval (4000–4500 ms). Participants were instructed to respond as fast as

they could by pressing the left or right button corresponding to the target location. The target presentations varied adaptively between 250 and 400 ms, which allowed participants achieve correct responses (i.e., participants responded while the target was on the screen) on 66 percent of all trials. The outcome feedback (1450 ms) included both the number of points participants won in the current trial and their total cumulative gain. Trials were separated by variable inter-trial intervals (3500–4150 ms). After task completion the total winnings were converted to chocolate candies. The MID task consisted of 66 trials, 22 for each reward level, and had a total duration of 11 minutes. Data were acquired in one run. Participants underwent a short training session before scanning to ensure that they learned the association between cues and their corresponding win values.

Although this version of the MID task contained the same phases as the original task [35], it had two notable modifications. The first modification was the omission of loss trials, due to time constraints related to other assessments in this large-scale study. This modification was deemed appropriate since prior studies have shown the same pattern of ventral striatum response during reward anticipation and anticipation of loss avoidance [36-39]. Another modification was the conversion of winnings to chocolate candy in contrast to other studies that have used monetary rewards. This substitution was implemented due to requests by local ethics committees and the need to have unified methods of reward reinforcement for all participants.

MRI Data Acquisition and Preprocessing

Images were processed as previously described by the IMAGEN consortium [23]. To accomplish the goal of the study, we selected the regions of interest (ROIs) that have previously been implicated in reward processing and have shown to robustly activate with the MID task. The ROIs included the ventral striatum (VS) during the reward anticipation phase of the task [40,41], and

medial orbitofrontal cortex (mOFC) during the outcome phase of the task [42]. The VS masks used coordinates from a meta-analysis of fMRI reward tasks [43] and were composed of 12-mm diameter spheres centered at the x, y, and z values of −14, 8, and −8 and 14, 8, and −8, respectively (Montreal Neurological Institute coordinates), for the left and right VS as previously described [44]. The mOFC mask was constructed based on anatomical boundaries of the region according to the AAL atlas. We extracted estimates for anticipation and feedback conditions for Large Win – No Win and Large Win – Small Win contrasts for each individual in these ROIs and processed data with SPSS19 (PASW Statistics 19, SPSS, Inc., Chicago, IL, USA).

Scanning was performed with 3 Tesla MR scanners from different manufacturers [Siemens (Munich, Germany), Philips (Amsterdam, Netherlands), General Electric (Fairfield CT, USA), Bruker (Billerica, MA, USA)]. Functional images were acquired with a gradient echo echo-planar imaging (EPI) sequence (repetition time = 2·2 s, echo time = 30 ms, flip angle = 75°). For each subject 300 volumes were obtained. They consisted of 40 slices aligned to the anterior commissure–posterior commissure line (2.4-mm thickness, 1-mm gap with a 64 × 64-matrix size over a 218 × 218-mm field of view, leading to a final voxel size of $3{\cdot}4 \times 3{\cdot}4 \times 3{\cdot}4\ mm^3$). To exclude structural abnormalities and for anatomical references, T1-weighted images were acquired from each participant using a modified protocol based on the ADNI project (http://adni.loni.ucla.edu/methods/documents/mri-protocols/). The images comprised 160 slices with $1{\cdot}1 \times 1{\cdot}1 \times 1{\cdot}1\ mm^3$ voxel size.

fMRI preprocessing and data analysis

All imaging preprocessing steps and statistical analyses were performed with SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing was performed using an automated pipeline. Individuals' fMRI images were slice time corrected using the first slice as reference.

They were then spatially realigned and resliced, and non-linearly warped onto Montreal Neurological Institute (MNI) space using a custom EPI template. This custom-made template was created on the average of a set of 240 randomly selected subjects' (30 for each imaging site) EPI images from the IMAGEN study. Data were smoothed with a 5-mm Gaussian isotropic kernel. A first-level model was constructed for each subject containing three regressors for the anticipation of large, small and no rewards, and six regressors for success (win) and no success (no win) feedback for large, small and no rewards. Trials with no responses were modeled separately as error trials with two additional regressors for anticipation and feedback. The baseline comprised the inter-trial intervals. The events were convolved with SPM's canonical hemodynamic response function. Movement parameters (three translation and three rotation parameters) were included as covariates for each subject. Contrast images were created for each subject.

To verify that our version of the MID task provoked the expected responses in the VS and in mOFC as it did previously [35-38] we analyzed (i) anticipation of large win reward versus no reward for the VS ROI and (ii) feedback of large win versus no win for the mOFC ROI.

Analyses

Longitudinal changes in impulsivity measures and their interaction with groups were assessed using 2 (Time: Baseline, and Follow-up) × 3 (Groups: 0, 1-9, 10-19, 20-39, >40 occasions) mixed analyses of variance (ANOVA), separately for each impulsivity measure (TCI-R-I, and MCQ-DD). Main effects and interaction, if statistically significant, were further explored using post hoc tests.

Subsequently, hierarchical linear regression models were conducted to investigate whether key demographic, psychometric, and/or neural (task-related ROI activations) variables at baseline

(age 14) can predict the severity of alcohol use (i.e., number of alcohol use occasions) at follow-up (age 16). Seven dummy variables for the eight data acquisition sites were introduced in the first level, demographic baseline variables [handedness, verbal and nonverbal IQ, socio-economic status, and scores on the puberty development scale (PDS)] in the second, TCI-R-I, and MCQ-DD in the third, family history status for SUD in the fourth, and brain activation (in the averaged bilateral VS and mOFC during "Large Win - No Win" contrast during the anticipation and outcome phases, respectively) from the MID task in the fifth level. Separate regression models were used for VS activation during the reward anticipation and mOFC activation during reward outcome. Average contrast estimates across bilateral ROIs were used, which allowed us to restrict the number of analyses and reduce the potential of type I errors. Each regression model was bootstrapped with 1000 iterations. All tests of statistical hypotheses were done on the two-sided 5% level of significance. SPSS was used for all statistical analyses.

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Results

Longitudinal changes in impulsivity

Mixed 2 (Time: Baseline, Follow-up) × 5 (Groups: 0, 1-9, 10-19, 20-39, >40 occasions) ANOVA on TCI-R-I revealed a statistically significant Time × Group interaction [$F(4,296)=5{\cdot}40$, $p=0{\cdot}0003$, $\eta^2=0{\cdot}068$], but the main effects of Time [$F(1,296)=0{\cdot}269$, $p=0{\cdot}604$, $\eta^2=0{\cdot}001$] and Group [$F(4,296)=1{\cdot}659$, $p=0{\cdot}159$, $\eta^2=0{\cdot}022$] did not reach statistical significance.

The significant Time × Group interaction was further probed using within- and between-group comparisons. Paired t-tests showed a dose effect of alcohol use severity on the longitudinal change in impulsivity, such that while impulsivity decreased from Baseline to Follow-up in 0- [$t(79)=2{\cdot}995$, $p=0{\cdot}004$] and 1-9 Occasions [$t(132)=4{\cdot}502$, $p=0{\cdot}000015$] groups, it did not statistically significantly change in 10-19 [$t(41)=1{\cdot}062$, $p=0{\cdot}294$] and 20-39 Occasions [$t(26)=0{\cdot}299$, $p=0{\cdot}767$]. However, impulsivity uncharacteristically increased in those with 40 or more alcohol use occasions [$t(18)=-2{\cdot}144$, $p=0{\cdot}046$]. Multivariate between-group analysis showed that unlike at baseline where impulsivity did not differ between groups [$F(4,296)=0{\cdot}668$, $p=0{\cdot}614$, $\eta^2=0.009$], it differed significantly at follow-up [$F(4,296)=5{\cdot}099$, $p=0{\cdot}001$, $\eta^2=0{\cdot}064$]. Pairwise *post hoc* comparisons using Tukey HSD showed that this group difference in impulsivity at follow-up was driven by increased impulsivity in those with 40 or more alcohol use occasions compared to all other groups [0 ($p=0{\cdot}00035$); 1-9 ($p=0{\cdot}00015$), 10-19 ($p=0{\cdot}006$), and 20-39 ($p=0{\cdot}004$) Occasions] (**Table 2; Figure 1**).

Mixed 2 (Time: Baseline, Follow-up) × 5 (Groups: 0, 1-9, 10-19, 20-39, >40 occasions) ANOVA on MCQ-DD revealed a significant Time main effect [$F(1,245)=52{\cdot}025$, $p<0{\cdot}00001$, $\eta^2=0{\cdot}175$], however the Group main effect [$F(4,245)=0{\cdot}105$, $p=0{\cdot}981$, $\eta^2=0{\cdot}002$] and the Time × Group interaction [$F(4,245)=0{\cdot}117$, $p={\cdot}976$, $\eta^2=0{\cdot}002$] did not reach significance. These results showed that delay discounting decreased from baseline to follow-up across all groups (**Table 2; Figure 1**).

Prediction of Alcohol Use Severity by fMRI Task Activations at Baseline

Hierarchical linear multiple regression models were used to predict alcohol use severity at follow-up, using environmental (scanning sites), demographic (sex, verbal and non-verbal IQ, and SES), developmental (PDS), behavioral (impulsivity and delay discounting), familial (family

history of SUD) and neurobiological (VS activation to reward anticipation OR mOFC activation to reward outcome) variables at baseline.

The hierarchical linear multiple regression model with averaged VS activation during reward anticipation did not significantly predict alcohol use severity [$F(16,213)=1{\cdot}610$, $p=0{\cdot}068$], with the cumulative R^2 of 10.8%. However, the model that included mOFC activation during reward outcome yielded a statistically significant regression equation [$F(16,210)=1{\cdot}903$, $p=0{\cdot}022$], with a cumulative R^2 of 12·7%. In that model, data acquisition sites explained 4·9% of the variance [$F_{change}(7,219)=1{\cdot}597$, $p=0{\cdot}137$], demographic variables explained an additional 4·1% [$F_{change}(5,214)=1{\cdot}935$, $p=0{\cdot}090$], behavioral variables explained 0·7% [$F_{change}(2,212)=0{\cdot}779$, $p=0{\cdot}460$], family history explained 0·1% [$F_{change}(1,211)=0{\cdot}145$, $p=0{\cdot}704$], and the mean bilateral mOFC activation to the outcomes phase explained 3·0% [$F_{change}(1,210)=7{\cdot}122$, p=0·008] of the variance. Within this model nonverbal IQ ($\beta=0{\cdot}205$, $p=0{\cdot}009$) and bilateral mOFC ($\beta=-0{\cdot}181$, $p=0{\cdot}008$) significantly predicted alcohol use severity, however, only bilateral mOFC survived bootstrapping ($p_{bootstrapped}=0{\cdot}005$; **Figure 2**). Standardized and unstandardized regression coefficients and the test statistic for each independent variable in the model are listed in **Table 3**. The prediction strength of mOFC remained significant when independent variables were included in the regression in a different order.

Discussion

The main goal of this investigation was to assess the relationship between impulsivity measures and indices of reward processing and onset of drinking in drug naïve adolescents that were followed-up for from ages 13-14 to age 16. Our main finding is that more frequent alcohol use

between the ages of 14 to 16 is associated with increased scores in trait impulsivity in contrast to less frequent or no alcohol use that was associated with decreased scores in trait impulsivity. We also identified a purported neural marker in the brain reward system at baseline, namely decreased activation in the medial orbitofrontal cortex (mOFC) during receipt of large wins (compared to no wins) that predicted alcohol use severity 2 years later.

As existing evidence shows that impulsivity tends to decline from early to mid and late adolescence in a linear fashion [5] our results suggest that such developmental changes in impulsivity measures may be different for youth who were drug-naïve at age 14 and developed more frequent alcohol use by age 16, compared to those who had low levels of use or remained drug free by age 16. Moreover, as adolescence is an active period of brain development it is possible that effects of drug use might be more pronounced during adolescence compared to other periods of life. This proposition is supported by some existing data. For instance, one report demonstrated that binge ethanol consumption causes differential brain damage in young adolescent rats compared with adult rats and that cortical degeneration from alcohol abuse may increase impulsivity contributing to the development, persistence and severity of alcohol use disorders [45] causing reversal learning deficits indicative of loss of executive function [46]. Similarly, human research has provided results indicating that adolescent binge drinkers show significantly lower net scores on a behavioral reward task (e.g. the Iowa Gambling task) compared to never-drinkers, and that these results were consistent with a decision-making impairment attributed to hypersensitivity to reward [47] . Specific effects of drug use on the mOFC have been documented for drugs other than alcohol (e.g. cocaine), showing that cocaine-induced changes in the mOFC disrupt the basis of flexible and adaptive 'model-based' behavioral control, possibly leading to an overemphasis on less flexible, maladaptive behaviors associated with drug

addiction [48]. Taken together, heavy alcohol use seems to be associated with a myriad of neuropsychological deficits including possibly deviant trajectory of impulsivity changes during adolescence.

Our results showing that mOFC hypoactivation is associated with later drug use is in line with other existing reports that also documented hypoactivation in regions of the brain reward system in youth at SUD risk [49,50]. However, our results extend these previous findings in several ways. First, in contrast to prior reports we document that the attenuated activation of mOFC was indexed during notification of large win – no win contrast of the MID task. Existing studies using the MID task have largely focused on VS activation during anticipation. Thus, this is perhaps one of the first reports to suggest that brain activation during outcomes in MID task may represent an imaging marker of vulnerability for the development of alcohol use behavior in mid adolescence. Furthermore, while reward anticipation has been consistently shown to engage predominantly the VS, reward outcomes have been shown to engage a wide distributed network of brain regions [51]. Of those mOFC has been well recognized as a key region involved in the assessment of reward outcomes [52,53]. As mOFC has been implicated in the processes of decision making, reward processing, attention and drug reinstatement [54] one can speculate that reduced mOFC activation during reward notification/outcome may reflect compromised ability to assess the value of the rewarding stimuli; in other words, both large and small wins might seem equally rewarding (or non-rewarding). Such compromised ability to distinguish between large and small rewards may be extended to drug use as one's compromised ability to discriminate between the rewarding property of small vs. large amounts of drug (i.e. a few vs. many drinks). This hypothesis finds support in exiting reports from adults with chronic cocaine use disorders [55 56]. In consequence, one may need to obtain a larger amount of drug in order to experience its

rewarding effects. Therefore, it stands to reason to suggest that individuals with such purported deficits may be at elevated risk for the development of problematic alcohol or other drug use behavior in adolescence.

Second, these results are based on data from one of the largest samples of drug naïve [i.e., no exposure to *any* substance (including prescription medications with abuse potential) both during pregnancy and in one's lifetime] adolescents followed longitudinally. The sample was not enriched for risks for developing SUD, including high levels of impulsivity, high rates of familial SUD or childhood diagnosis of disruptive behavior disorders (e.g. ADHD, ODD, CD). While many groups have examined drug naïve samples [57], the majority of prior reports come from relatively small sample studies who recruited at-risk youths based on the presence of family history of SUD or childhood ADHD/CD or a combination of those [58]. Additionally, the majority of studies have been confounded by individual drug use. As a result, existing reports of either hyper- or hypoactivation in key regions of the brain reward system (e.g. VS), specifically during anticipation of reward, seems to present a mixture of findings in youths across a rather wide age range (ages 8 to 21) who have identifiable risk factors for SUD and have had various levels of drug exposure. Therefore, our findings can be viewed as novel in relation to identifying a possible biological marker for the development of problematic drug use (e.g. binging) during a concise time period of development in a larger sample of well characterized normotypical adolescents.

The value of imaging biomarkers as indicators of later substance use remains a subject of debate. For instance, a recent review that focused on the clinical added value of neuroimaging in neuropsychiatric disorders suggests that in SUD, behavioral and psychometric variables may be better predictors and that brain imaging variables may contribute little in augmenting clinical

prognoses [59]. While this position might be most relevant to individuals with known clinical risk factors for SUD, some reports suggest otherwise. For example, existing reports from the IMAGEN sample have emphasized the value of brain measures as indicators for future use. One study found that imaging markers (activation during response inhibition, reward processing and face recognition tasks) ranked third after life history and personality measures when identifying abstainers and drinkers in a 2-year period (from ages 14 to 16) [27]. Specifically, ventromedial PFC was identified as a region relevant to binging at age 14 but not as predictor for future use. Another study examined 144 novelty-seeking adolescents to determine whether neural activity in response to anticipated rewards may longitudinally predict problematic drug use. This study found that a combined (neural and psychological) model and a neural variables only model had similar prediction accuracy but lower accuracy than a model containing only psychological variables [49]. Altogether those reports as well as the current study show that the IMAGEN cohort has provided new evidence for the possible role of brain markers for the development of drug use in adolescents from ages 14 to 16 in various sub-populations (i.e. adolescents with binging [27] vs novelty seeking adolescents with some drug use [49] vs drug naïve adolescents).

Although specificity of these findings to alcohol use disorder *per se* can be argued given that the data are acquired from a naturalistic study with a sample comprised of normotypically developing adolescents, these findings are certainly of crucial clinical relevance. Based on these results one can hypothesize about inter related effects of constitutionally altered brain functions that predispose to initial drug exposure which in turn may produce further alterations in brain functions, leading to the maintenance of behaviors that can perpetuate more drug use. As this is be one of the first reports to clearly show the association between the developmental changes in impulsivity and the frequency of alcohol exposure in early to mid-adolescence, these results need

to be validated in other samples as well as back-translated to pre-clinical studies to investigate whether a causal link between alcohol use and changes in impulsivity exist. Lastly, these finding provide grounds for hypotheses development for future studies and can be used as basis for hypotheses testing from other existing large dataset such as the ABCD study [60].

Although the MID task was originally developed to tease apart the anticipation from the outcome phases of reward processing [35] over the years, studies using this task suggest that it may be better suited to study anticipation than to study outcome [61]. However, some have reported that individuals with behavioral addiction (gambling) have demonstrated decreased activation in the brain reward system during reward outcome [62]. Such discrepant reports suggest that the MID task *can* index differences in reward outcomes between cohorts with different characteristics (e.g. levels of impulsivity). The need to expand studies in reward outcome in relation to substance use has been outlined by others [61]. Additionally, data on substance use both from adolescents and their parent were collected via self-report. Indeed, self-reports are recognized for crucial pitfalls that affect their reliability and validity, including the influence of demand characteristics [63] social desirability bias [64] and compromised self-awareness [65]. To counter some of these effects, the substance use questionnaires also asked about consumption of a fictitious drug "Relevin", which respondents did not report, underscoring the integrity of self-report data in this sample.

In summary, early to mid-adolescence is a highly susceptible developmental period during which drug experimentation may alter the maturational course of particular behaviors, especially of impulsivity, thus creating vulnerabilities for the transition from occasional drug use to drug dependence. The findings from this report provide new evidence to support this notion. Further, we report that hypoactivation in the brain reward system, particularly mOFC, during reward

receipts can be a potential biomarker for the development of alcohol use in normotypical adolescents. Such findings may further lead to the development of indicators to identify at risk youth. Together these findings can be used as an illustrative tool for clinicians providing psycho-education to adolescents and their families as well as further hypothesis development and hypothesis testing.

Research in Context

Evidence before this study

We searched PubMed, Scopus, and Google Scholar databases from Jan 1, 1990, to Dec 31, 2018, using the search terms "drug naive*", "binge *", "alcohol*", "fMRI*", "ventral striatum*", and "orbito-frontal cortex*", with no language restrictions. Papers relevant to the subject of our report were identified including reviews discussing the utility of behavioral and imaging indexes as predictors for the development of adolescent SUD [21,53,54,61] and papers summarizing findings from studies in drug naive youth [50,57]. It should be noted that different groups have produced numerous publications from longitudinal cohorts such as the Michigan and San Diego longitudinal studies among others. With that in mind it is important to point out that the IMAGEN sample is so far the largest cohort that is focused in studying longitudinally factors that contribute to the development of drug use during adolescence. More importantly these other samples are enriched for youth with positive family history of alcoholism recruited from the same geographic areas. In contrast the IMAGEN sample consists of community recruited pre-adolescents recruited from 8 sites across Western Europe. In that sense the IMAGEN sample is well suited for examining processes that purportedly take place in normative development and in theory may provide information relevant to alterations across the trajectory of typically developing youth vs youth at elevated risk (i.e. who represent a subgroup in the large adolescent population). Moreover, we were able to identify the largest cohort of drug naive pre-adolescent youth (e.g. ages 13-14) and examine changes in behavioral variables across a span of 2 years. Considering these unique characteristics of the IMAGEN sample and the cohort identified for this particular project the results in this report are novel as we do not replicate any prior investigations. We should acknowledge that there are 2 existing reports from IMAGEN that have examined factors that may predict changes in drug use from ages 14 to 16 [27,49]. However, these included participants with various levels of drug use at baseline (e.g. age 14) so in that respect this study is not a replication of these previously reported results and, instead, is a novel analysis.

Added value of this study

Significance of this study is in its examination of the association between initial exposure to alcohol and longitudinal changes in impulsivity (a behavior that is relevant to the development of substance use disorder) from drug-naïve age 14 to age 16, in a relatively large community sample (n=424) of young adolescents. This study further assesses the purported predictive value of a set of sociological, psychological and biological factors in relation to the transition from no use to most frequent use in this same period. The findings indicate that (i) initial exposure to alcohol during early adolescence appears to have a dose dependent effect on the changes in impulsivity measures from ages 14 to 16, such that youth with more frequent use (leading to binge drinking) show lower decreases in impulsivity scores at follow up (e.g. age 16) compared to their scores at baseline (e.g. age 14), and (ii) hypo activation in the medial OFC during reward receipt may be a biological marker for vulnerability to develop binging during early adolescence. While medial OFC has been implicated in the development of SUDs [52,53], this report presents two novel aspects – first, the hypoactivation is detected during reward notification as opposed to reports of hypoactivation during reward anticipation and second, these patterns of hypoactivation are indexed in the largest drug naïve cohort that has been longitudinally followed.

Implications of all the available evidence

Current findings are highly relevant for understanding the relationship between alcohol use initiation and developmental changes in impulsivity. Further, current results highlight the predictive strength of childhood neurobiology for evaluating risk for later antisocial personality disorder (ASPD) in adulthood, and potentially also for direct treatment development and outcome evaluation. Together, these results provide preliminary evidence for a novel mechanism associated with problematic alcohol use in adolescence and can be leveraged for developing subsequent hypotheses to either test on an even larger dataset (e.g., ABCD Study) or on more specifically designed cohort studies. This information can certainly be also used for both psycho-education and for the development of behavioral interventions to support normative healthy development and motivate individuals, especially the ones at elevated SUD risk, to minimize or avoid drug use during vulnerable periods of development.

Declaration of interests

Dr. Ivanov has received honoraria a member of the data safety monitoring committee for Lundbeck. Dr. Banaschewski has served as an advisor or consultant to Bristol-Myers Squibb, Desitin Arzneimittel, Eli Lilly, Medice, Novartis, Pfizer, Shire, UCB, and Vifor Pharma; he has received conference attendance support, conference support, or speaking fees from Eli Lilly, Janssen McNeil, Medice, Novartis, Shire, and UCB; and he is involved in clinical trials conducted by Eli Lilly, Novartis, and Shire; the present work is unrelated to these relationships. Dr. Barker has received honoraria from General Electric Healthcare for teaching on scanner programming courses and acts as a consultant for IXICO. The other authors report no biomedical financial interests or potential conflicts of interest.

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Table 1: Demographics of the study sample at baseline and between-group statistics. Asterisk (*****) represents statistically significant difference, $p<0.05$.

	0 Occasion	**1 – 9 Occasions**	**10 – 19 Occasions**	**20 – 39 Occasions**	**40 or more Occasions**	**Between Group Test Statistic**
Number of Participants	83	133	42	27	19	
Age	14·50 ± 0·40	14·41 ± 0·39	14·42 ± 0·37	14·51 ± 0·48	14·43 ± 0·40	F=0·890
Pubertal Development	3·45 ± 0·80	3·46 ± 0·79	3·57 ± 0·77	3·59 ± 0·64	3·37 ± ·90	F=0·444
Sex (Male/Female)	42/41	65/68	23/19	15/12	12/7	χ^2=1·783
Handedness (Left/Right)	13/63	15/112	4/35	1/25	2/15	χ^2=3·538
Verbal IQ	107·97 ± 15·35	110·59 ± 13·96	109·30 ± 15·14	110·23 ± 13·19	112·17 ± 18·93	F=0·551
Non Verbal IQ	103·50 ± 14·93	108·28 ± 14·58	106·30 ± 16·82	110·23 ± 11·26	116·67 ± 17·04	F=3·669*
Family History of SUD (FH-/FH+)	41/42	68/65	19/23	13/14	12/7	χ^2=1·800
Socio-Economic Status	17·94 ± 3·90	18·42 ± 3·54	17·48 ± 3·76	17·22 ± 3·24	17·11 ± 3·20	F=1·267

Table 2: Mean TCI-assessed Impulsivity and MCQ-assessed Delay Discounting separately for each alcohol severity-based group at baseline and follow-up. Statistically significant ($p<0.05$) longitudinal changes are highlighted with the shaded cells.

		0 Occasion	**1 – 9 Occasions**	**10 – 19 Occasions**	**20 – 39 Occasions**	**>40 Occasions**
Impulsivity	Number of Participants	80	133	42	27	19
	Baseline (Mean ± SD)	11·53 ± 2·27	11·56 ± 2·21	11·40 ± 1·89	10·85 ± 2·14	11·26 ± 1·66
	Follow up (Mean ± SD)	10·75 ± 2·13	10·73 ± 2·00	11·00 ± 2·13	10·74 ± 1·65	12·94 ± 2·39
Delay Discounting	Number of Participants	61	111	38	23	17
	Baseline (Mean ± SD)	-5·72 ± 1·70	-5·78 ± 1·36	-5·60 ± 1·70	-5·85 ± 1·89	-5·50 ± 0·97
	Follow up (Mean ± SD)	-4·88 ± 1·56	-4·90 ± 1·54	-4·77 ± 1·32	-5·04 ± 1·59	-4·53 ± 1·67

SD: Standard deviation; TCI-R: Temperament and Character Inventory-Revised; MCQ: Monetary-Choice Questionnaire.

Table 3: Summary of Hierarchical Linear Regression Analysis for Variables (including bilateral OFC activation) predicting alcohol use severity at follow-up. P-values < 0·05 and < 0·01 are presented in bold and italic fonts, respectively.

Variables	***B***	***β***	***t***	***p-value***	***Bootstrap p-value****	***R***	***R^2***	***F***	***p-value***	***∆F***	***∆F p-value***
Model 1						.220	.049	1.597	.137	1.597	.137
Sites†	<.770	<.256	<2.69	**>.008**	**>.004**						
Model 2						.300	.090	1.758	.057	1.935	.090
Sex	-.329	-.141	-1.79	.075	.087						
Non-Verbal IQ	.016	.205	2.621	**.009**	**.015**						
Verbal IQ	-.006	-.073	-.941	.348	.378						
SES	-.013	-.042	-.576	.565	.612						
PDS	.146	.096	1.205	.230	.235						
Model 3						.310	.096	1.615	.077	.779	.460
Impulsivity	-.031	-.055	-.820	.413	.370						
Delay Discounting	.047	.065	.966	.335	.373						
Model 4						.311	.097	1.511	.103	.145	.704
Family History	.174	.074	1.056	.292	.313						
Model 5						.356	.127	1.903	**.022**	7.122	**.008**
Bilateral OFC	-.513	-.181	-2.67	**.008**	**.005**						

***** *Based on 1000 iterations*
†Seven dummy variables were created to code for 8 sites.

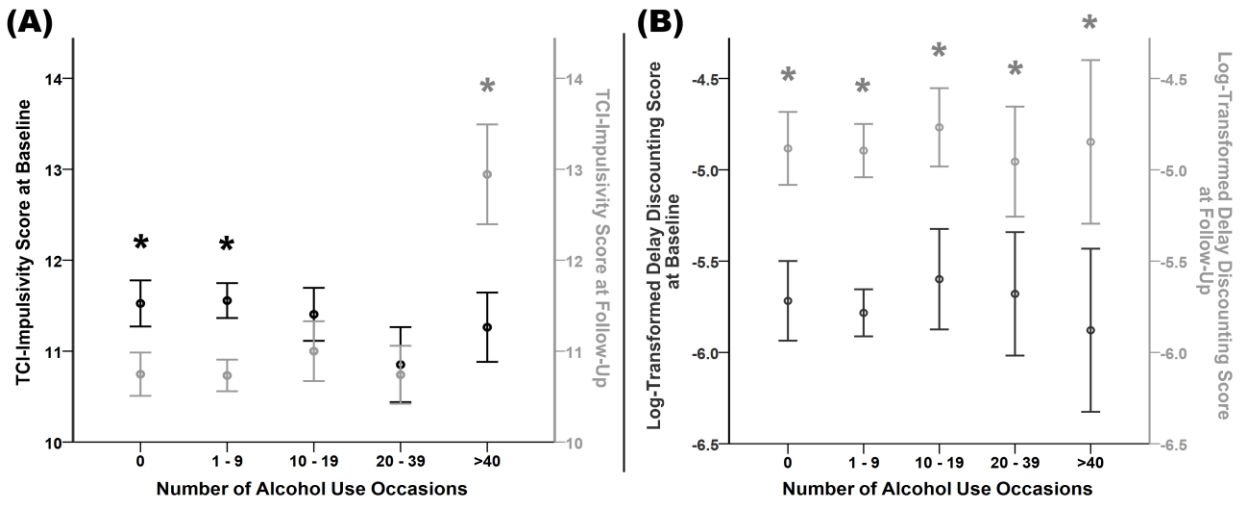

Figure 1: (A) Impulsivity (TCI-R-I), and **(B)** Delay Discounting (MCQ-DD) scores at baseline (black) and follow-up (gray), separately for adolescents with different severity of alcohol use since baseline (assessed via ESPAD). Graphs show that unlike MCQ-DD that increased from baseline to follow-up as expected across all groups, the expected decrease in TCI-R-I was only evident in in groups with no or low (0 and 1 – 9 occasions) alcohol use but not in moderate drinkers (10 – 19 and 20 – 39 occasions), whereas an uncharacteristic increase in impulsivity was observed in heavy drinkers (>40 occasions). Error bars represent standard error; black and gray asterisks (*****) represent statistically significant differences ($p<0{\cdot}05$) for Baseline>Follow-up and Follow-up>Baseline comparisons, respectively.

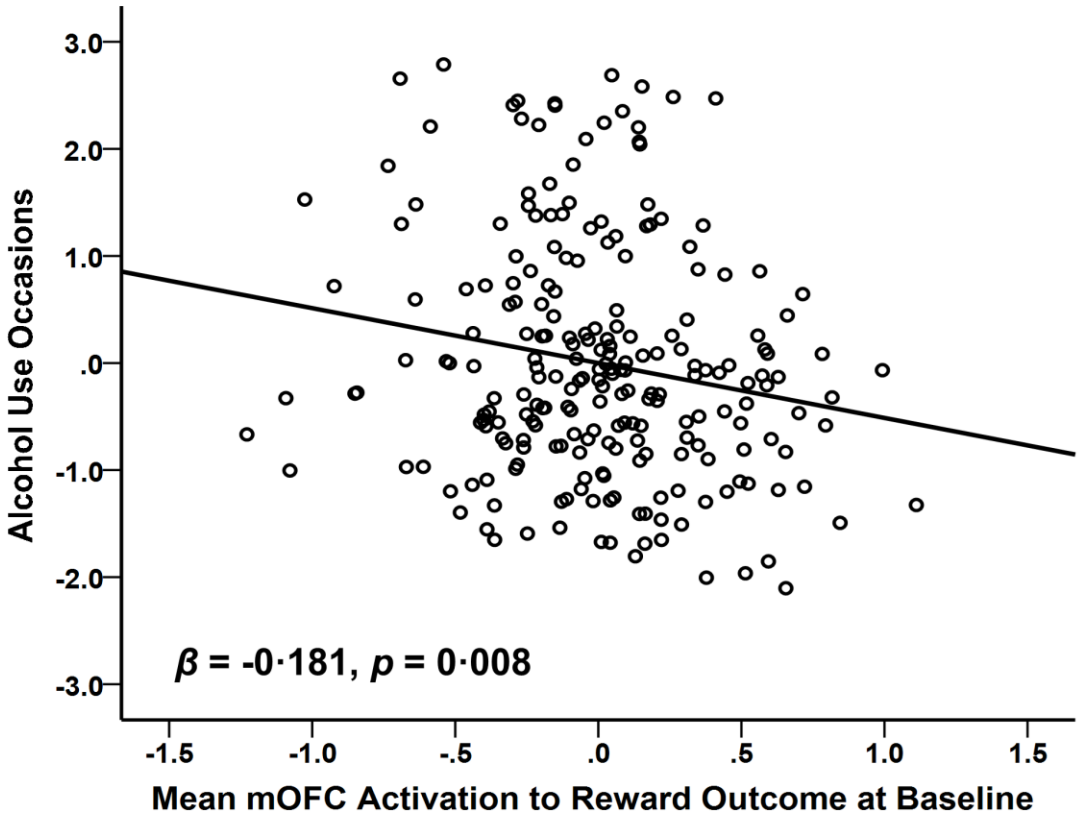

Figure 2: Partial regression plot showing averaged bilateral medial mOFC activation to reward outcomes at baseline significantly predicts alcohol use severity in adolescents at follow-up.

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