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A robust brain network for sustained attention from adolescence to adulthood that predicts later substance use

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Abstract

Substance use, including cigarettes and cannabis, is associated with poorer sustained attention in late adolescence and early adulthood. Previous studies were predominantly cross-sectional or under-powered and could not indicate if impairment in sustained attention was a consequence of substance-use or a marker of the inclination to engage in such behaviour. This study explored the relationship between sustained attention and substance use across a longitudinal span from ages 14 to 23 in over 1,000 participants. Behaviours and brain connectivity associated with diminished sustained attention at age 14 predicted subsequent increases in cannabis and cigarette smoking, establishing sustained attention as a robust biomarker for vulnerability to substance use. Individual differences in network strength relevant to sustained attention were preserved across developmental stages and sustained attention networks generalized to participants in an external dataset. In summary, brain networks of sustained attention are robust, consistent, and able to predict aspects of later substance use.

Teaser

A robust brain network for sustained attention at age 14 predicts cigarette and cannabis use from ages 14 to 23.

eLife assessment

This study presents a **valuable** finding on the relationship between brain activity related to sustained attention and substance use in adolescence/early adulthood with a large longitudinal dataset. The evidence supporting the claims of the authors is **solid**, although the inclusion of more details of methods, results, and data analyses would have strengthened the study. The work will be of interest to cognitive neuroscientists, psychologists, and clinicians working on substance use or addiction.

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Main text

Sustained attention is a critical cognitive process in daily life, playing a significant role in academic achievement, social communication, and mental health (Esterman and Rothlein, 2019) and can be defined as “the focus on performance on a single task over time, with the goal of explaining both the fluctuations within an individual as well as the individual differences in overall ability to maintain stable task performance” (p. 174)(Esterman and Rothlein, 2019). Sustained attention notably improves between the ages of 9 and 16 years-old (Thomson et al., 2022), concomitant with cognitive maturation and brain development during adolescence

(Paus, 2005). The functional neuroanatomy of sustained attention involves cingulate, prefrontal, and parietal cortices; supplementary motor area (SMA); frontal eye field; and cerebellum (Bauer et al., 2020; Pinar et al., 2018). Key neurotransmitters associated with sustained attention include dopamine (Marshall et al., 2019), noradrenaline (Greene et al., 2009), and acetylcholine (Gill et al., 2000).

Cross-sectional studies suggest that substance use during adolescence, including cigarette smoking (Treur et al., 2015), alcohol consumption (Ueno et al., 2022), and cannabis use (Wallace et al., 2019), is associated with poorer sustained attention. For instance, adolescents (14-17 years-old) using cannabis a minimum of 4 days per week for at least the last 6 months showed impaired sustained attention in the Rapid Visual Information Processing Task (RVP), and in the Immediate Memory Task versus non-users (Broyd et al., 2016; Figueiredo et al., 2020). Adolescents (12-17 years-old) in a high tetrahydrocannabinol (THC; the primary psychoactive component in cannabis) group exhibited lower accuracy on the RVP task than a low THC group (Shannon et al., 2010). Cigarette users aged 18-29 years-old showed significant cognitive impairments in sustained attention than non-smokers in the RVP task (Chamberlain et al., 2012). A systematic review of the next-day cognitive effects of heavy alcohol consumption demonstrated impairments in sustained attention during alcohol hangovers using meta-analysis (Yakir et al., 2007). These findings highlight the negative associations between substance use and sustained attention.

Given the cross-sectional nature of the behavioural and neuroimaging studies above, it remains unclear if impaired sustained attention predates the initiation of substance use and/or if it is a consequence of substance use. Only one longitudinal study (Harakeh et al., 2012) has examined the association between sustained attention and cigarette smoking, employing measurements across three-waves and involving a large sample of 1,797 adolescents. Poor sustained attention; unlike other neurocognitive functions such as working memory, attention flexibility, or perceptual sensitivity; was associated with the increased probability of adolescents subsequently initiating cigarette smoking between ages 11 and 13 and with a higher chance of being a daily smoker by age 16.

Harakeh and colleagues' findings suggest that poor sustained attention may precede the onset of cigarette smoking. However, as their study was based on a behavioural level, the neural correlates underlying these associations remain untested. It is biologically plausible that poorer sustained attention predates substance use. Nicotine and THC increase availability of the neurotransmitters such as dopamine, noradrenaline, and acetylcholine in the prefrontal cortex and striatum (Bloomfield et al., 2016; Fitzgerald, 2013; McGehee and Role, 1995; Narayanaswami et al., 2013; Wise and Robble, 2020). Furthermore, reducing these neurotransmitters via pharmacological challenges has been associated with impaired sustained attention (Thiele and Bellgrove, 2018). Similar to a "self-medication hypothesis" in schizophrenia, where substance use has been related to low striatal dopamine (Awad and Voruganti, 2015), it is plausible that there is a link between lower sustained attention and later substance use.

Although lower sustained attention has been associated with subsequent cigarette smoking, individuals commonly engage in the concurrent use of multiple substances (Crummy et al., 2020), perhaps due to shared pathological substrates for substance use. A meta-analysis identified common neural alterations in primary dorsal striatal, and frontal circuits, engaged in reward/salience processing, habit formation, and executive control across various substances (nicotine, cannabis, alcohol, and cocaine) (Thiele and Bellgrove, 2018). Those involved in substance use often co-use both cannabis and cigarettes (Agrawal et al., 2012; Hindocha et al., 2016; Weinberger et al., 2018). Agrawal et al. (2012) reported that 90% of cannabis users smoke cigarettes during their lifetime, and the widespread co-use of the two may be attributed to genetic sharing (Agrawal et al., 2010; Stringer et al., 2016) and similar neural mechanism (Klugah-Brown et al., 2020).

Functional brain networks can predict various behavioural traits, such as substance use (Yip et al., 2019) and sustained attention (Rosenberg et al., 2016). Previous studies (e.g., (Rosenberg et al., 2018)) have used brain connectivity to develop predictive models of sustained attention that can be generalized to healthy and clinical populations. However, while behavioural changes in sustained attention have been documented and functional brain networks that predict substance use have been identified (Yip et al., 2019), the underlying change in sustained attention brain networks from adolescence to adulthood and their relation to substance use are relatively less well described. Lower sustained attention has been accompanied by both stronger reductions in neural activity in the visual cortex, as well as stronger recruitment of the right supramarginal gyrus with increasing time on a sustained attention task with central cues in cigarette smokers as opposed to non-smokers (Vossel et al., 2011). In a resting-state functional magnetic resonance imaging (fMRI) paradigm, cannabis users aged 16-26 had stronger connectivity between the left posterior cingulate cortex and the cerebellum, correlated with poorer performance on sustained attention/working memory and verbal learning measures (Ritchay et al., 2021). While most brain connectomic research has utilized resting-state fMRI data, it has been shown that functional connectivity (FC) during task performance, especially task-related FC (Zhao et al., 2023), outperforms typical task-based and resting-state FC at predicting individual differences over time, in addition to having the potential to capture more behaviourally relevant information (Dhamala et al., 2022; Greene et al., 2018; Yoo et al., 2018).

Previous studies found that FC patterns predicted individual differences in sustained attention (e.g., (Chen et al., 2022; O'Halloran et al., 2018; Sripada et al., 2020), yet relatively little is known about the relationship between brain activity related to sustained attention and substance use over time. In this study, we used task-fMRI from the IMAGEN dataset, a longitudinal study with >1,000 participants at each timepoint (ages 14, 19, and 23 years-old). We first obtained task-related whole-brain connectivity and then used connectome-based predictive modeling (CPM) to predict sustained attention from ages 14 to 23. Additionally, a latent change score model was applied to quantify bidirectional longitudinal relations between sustained attention and substance use over time, shedding light on how substance use impacts sustained attention and its associated brain activity, and vice versa. Our objective was to estimate the relationship between sustained attention and substance use over time. Given the substantial sample size and longitudinal design of Harakeh et al.'s study, we hypothesized that behavioural and predictive networks associated with lower sustained attention would predict increased substance use (particularly cigarette smoking) over time.

Results

1. Behavioural changes over time

Participants' demographic information for all analyses is shown in **Table 1** (see also Tables S1-S2). We used the intra-individual coefficient of variation (ICV) from Go trials to index sustained attention. Lower ICV indicates better sustained attention. A linear mixed model analysis showed significant fixed effects of age (i.e., timepoint) on ICV ($F_{1895.3} = 51.14$, $P < 0.001$) (**Fig. 1A**). Post-hoc analysis showed that ICV decreased with age: ICV at age 14 was significantly higher than ICV at ages 19 ($t = 6.535$, $P < 0.001$) and 23 ($t = 10.109$, $P < 0.001$). ICV at age 19 was also significantly higher than that at age 23 ($t = 4.768$, $P < 0.001$). The full results of the linear mixed model analysis are shown in Tables S3-S4. In addition, we found that individual differences in each ICV were significantly correlated between the three timepoints (**Fig. 1B** and Table S5, all $P < 2.8e^{-7}$).

	Age 14	Age 19	Age 23
N (Three timepoints)	2,148		
Sex (M/F)	1055/1093		
Age (Years)	14.4 ± 0.4	19 ± 0.7	22.6 ± 0.7
Mean FD (mm)	0.28 ± 0.32	0.18 ± 0.17	0.18 ± 0.12
GO RT (ms)	466.6 ± 80	400.7 ± 71.8	403.9 ± 73.8
ICV	0.234 ± 0.038	0.224 ± 0.051	0.217 ± 0.052
Stop RT (ms)	461.5 ± 114.8	360 ± 82.4	363.6 ± 78.2
SSD (ms)	319.3 ± 148.1	188.1 ± 132.4	190 ± 158.4
SSRT (ms)	217.8 ± 37.2	213.3 ± 43.3	216.2 ± 42.6
pOmission (%)	4.4 ± 10.5	2.6 ± 8.6	3.7 ± 11.1
pChoiceError (%)	4.7 ± 6.6	4.8 ± 4.7	5.2 ± 7.6
pCommission (%)	47.9 ± 6.3	47.5 ± 6	47.2 ± 6.9

Note: These data pertain to the participants included in the behavioural analyses. N, number of subjects; FD, framewise displacement of MR images; ICV, intra-individual coefficient of variation (assay for sustained attention); SSRT, stop signal reaction time; GO RT, reaction time in Go trials; Stop RT, reaction time in stop fail trials; SSD, stop signal delay; pOmisssion, probability of go omissions (no response); pChoiceError, probability of choice errors on Go trials; pCommission, probability of commission on Stop trials.

Table 1.

Demographic information of adolescents in the linear mixed model across three timepoints.

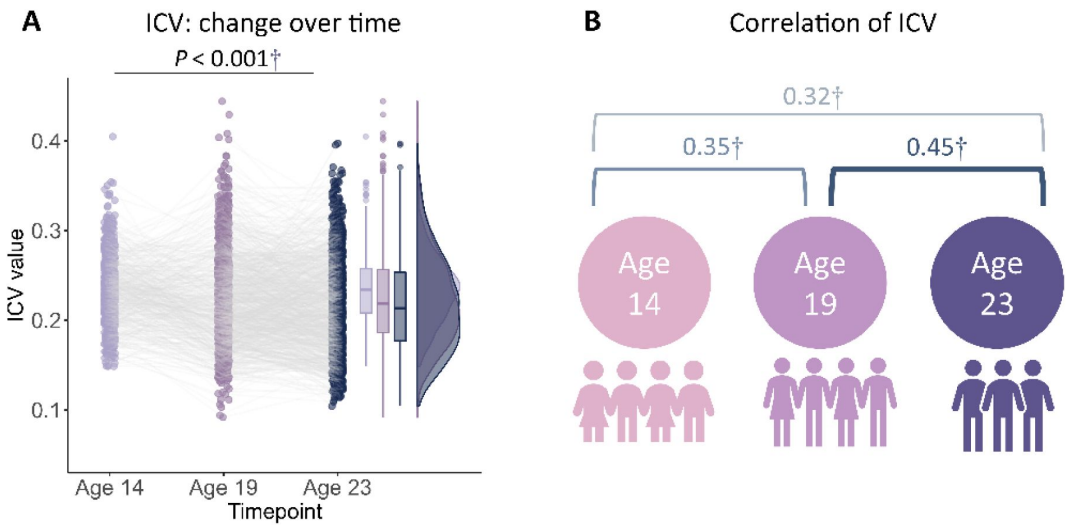

Fig. 1

Intra-individual coefficient of variation (ICV) changes over time.

(A) ICV changes over time. **(B)** Correlation of ICV between timepoints within subjects. †, P < 0.001.

2. Cross-sectional brain connectivity

We used three networks to predict behavioural variables: positive, negative, and combined networks. The calculation of these networks was based on connectivity analyses of the whole brain, determining whether a connection between brain areas (i.e., edges) was correlated positively or negatively beyond a significance threshold of $P < 0.01$ with ICV. The network strength of positive networks (or negative networks) was determined in each individual by summing the connection strength of each positively (or negatively) correlated edge. The combined network was determined by subtracting the strength of the negative network from the positive network.

Positive, negative, and combined networks derived from Go trials significantly predicted ICV: at age 14 (r = 0.25, r = 0.25, and r = 0.28, respectively, all $P < 0.001$) (**Fig. 2A**), at age 19 (r = 0.27, r = 0.25, r = 0.28, respectively, all $P < 0.001$) (**Fig. 2B**) and at age 23 (r = 0.38, r = 0.33, and r = 0.37, respectively, all $P < 0.001$) (**Fig. 2C**). The connectome patterns of predictive networks are shown in **Figs. 2D-I**. Fig. S2 summarizes the connectivity within and between functional networks and depicts their respective contribution to the predictive network. The above results were validated using 10-fold cross validation (CV); similar results were obtained when using 5-fold CV and leave-site-out CV (Table S6). The predictive networks had similar connectome patterns when different exclusion criteria for head motion were used (mean framewise displacement, mean FD < 0.2 - 0.4 mm) (Figs. S4-S6A).

Positive, negative, and combined networks derived from Successful stop trials significantly predicted ICV: at age 14 (r = 0.22, $P < 0.001$; r = 0.12, $P = 0.017$; and r = 0.20, $P < 0.001$, respectively) (**Fig. 3A**), at age 19 (r = 0.19, $P < 0.001$; r = 0.15, $P = 0.001$; and r = 0.18, $P < 0.001$, respectively) (**Fig. 3B**), and at age 23 (r = 0.24, r = 0.21, and r = 0.23, respectively, all $P < 0.001$) (**Fig. 3C**). The connectome patterns of predictive networks are shown in **Figs. 3D-I**. Fig. S3 summarizes the connectivity within and between functional networks and the proportion of brain networks involved in the predictive network. We obtained similar results using a 5-fold CV and leave-site-out CV (Table S6). The predictive networks had similar connectome patterns when different exclusion criteria for head motion were used (mean FD < 0.2 - 0.4 mm) (Figs. S4-S6B).

To examine the specificity of sustained attention networks identified from CPM analysis, the correlations between the network strength of positive and negative networks and performances from a neuropsychology battery (CANTAB) (Fray et al., 1996) were calculated at each timepoint separately. All positive and negative networks derived from Go and Successful stop trials significantly correlated with a behavioural assay of sustained attention – the RVP task – at ages 14 and 19 (all P values < 0.028). Age 23 had no RVP task data in the IMAGEN study. There were sporadic significant correlations between constructs such as delay aversion/impulsivity and negative network strength, for example, but the most robust correlations were with the RVP. Detailed information is shown in Supplementary materials and Table S11.

3. ICV prediction across time

Positive, negative, and combined networks derived from Go trials defined at age 14 predicted ICV at ages 19 (r = 0.16, r = 0.14, and r = 0.16, all $P < 0.001$) (**Fig. 4A**, top row) and 23 (r = 0.20, r = 0.12, and r = 0.17, all $P < 0.001$) (**Fig. 4A**, middle row) respectively. Likewise, positive, negative, and combined networks derived from Go trials defined at age 19 predicted ICV at age 23 (r = 0.30, r = 0.26, and r = 0.31, respectively, all $P < 0.001$) (**Fig. 4A**, bottom row).

Positive, negative, and combined networks derived from Successful stop trials defined at age 14 predicted ICV at age 19 (r = 0.11, r = 0.12, and r = 0.13, all $P < 0.001$) (**Fig. 4B**, top row) and 23 (r = 0.14, r = 0.15, and r = 0.15, all $P < 0.001$) (**Fig. 4B**, middle row) respectively. Positive, negative,

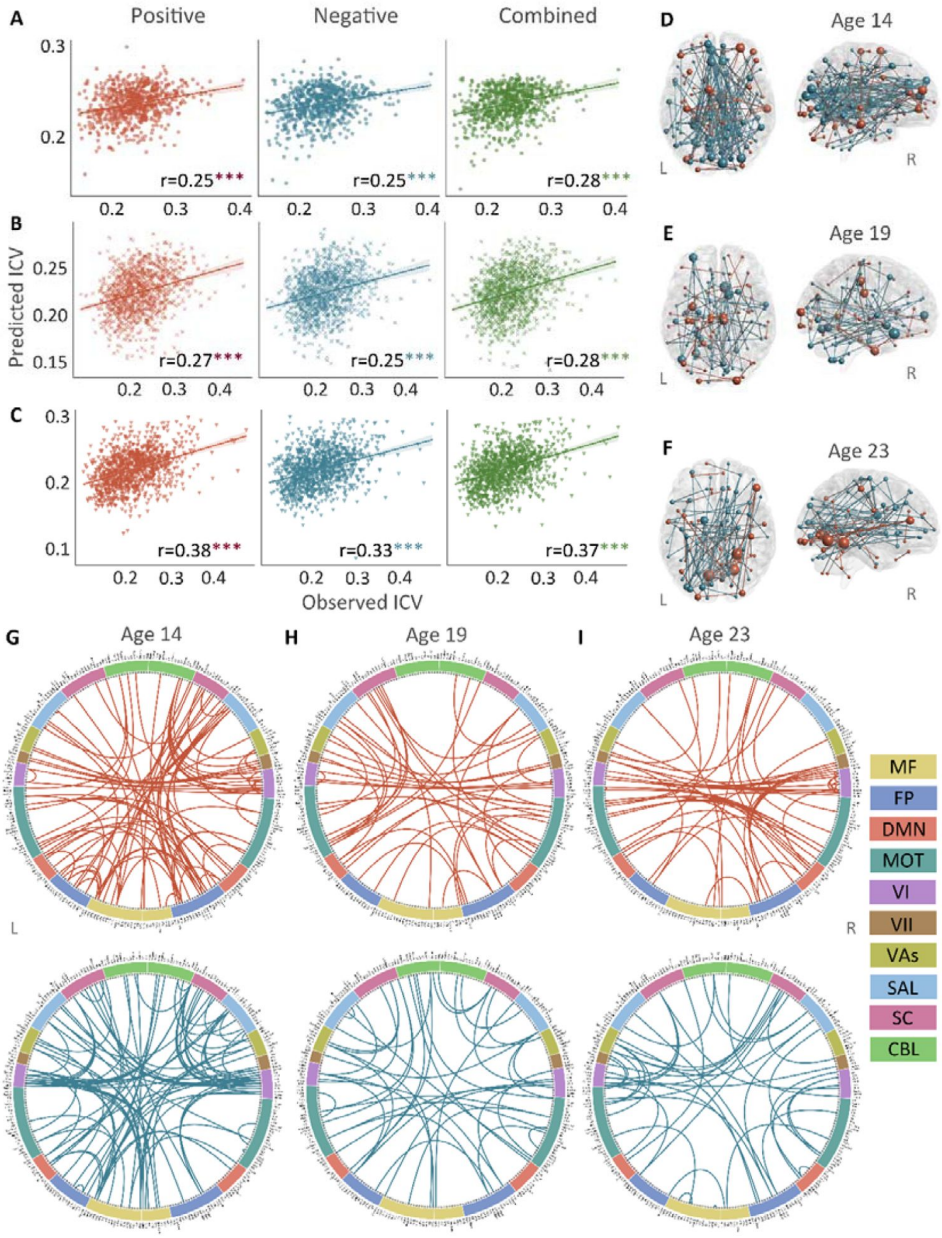

Fig. 2

The predictive performances and networks of intra-individual coefficient of variation (ICV) per timepoint derived from Go trials.

Correlation between observed and predicted ICV in positive, negative, and combined networks at **(A)** age 14, **(B)** age 19, and **(C)** age 23. Predictive networks for ICV are at **(D)** age 14, **(E)** age 19, and **(F)** age 23. Connectome of positive and negative networks of ICV at **(G)** age 14, **(H)** age 19, and **(I)** age 23. The edges depicted above are those selected in at least 95% of cross-validation folds. Red, blue, and green spheres/lines/scatters represent positive, negative, and combined networks separately. MF, Medial frontal; FP, Frontoparietal; DMN, Default mode; MOT, Motor; VI, Visual I; VII, Visual II; VAs, Visual association; SAL, Salience; SC, Subcortical; CBL, Cerebellar. R/L, right/left hemisphere. ***, P < 0.001.

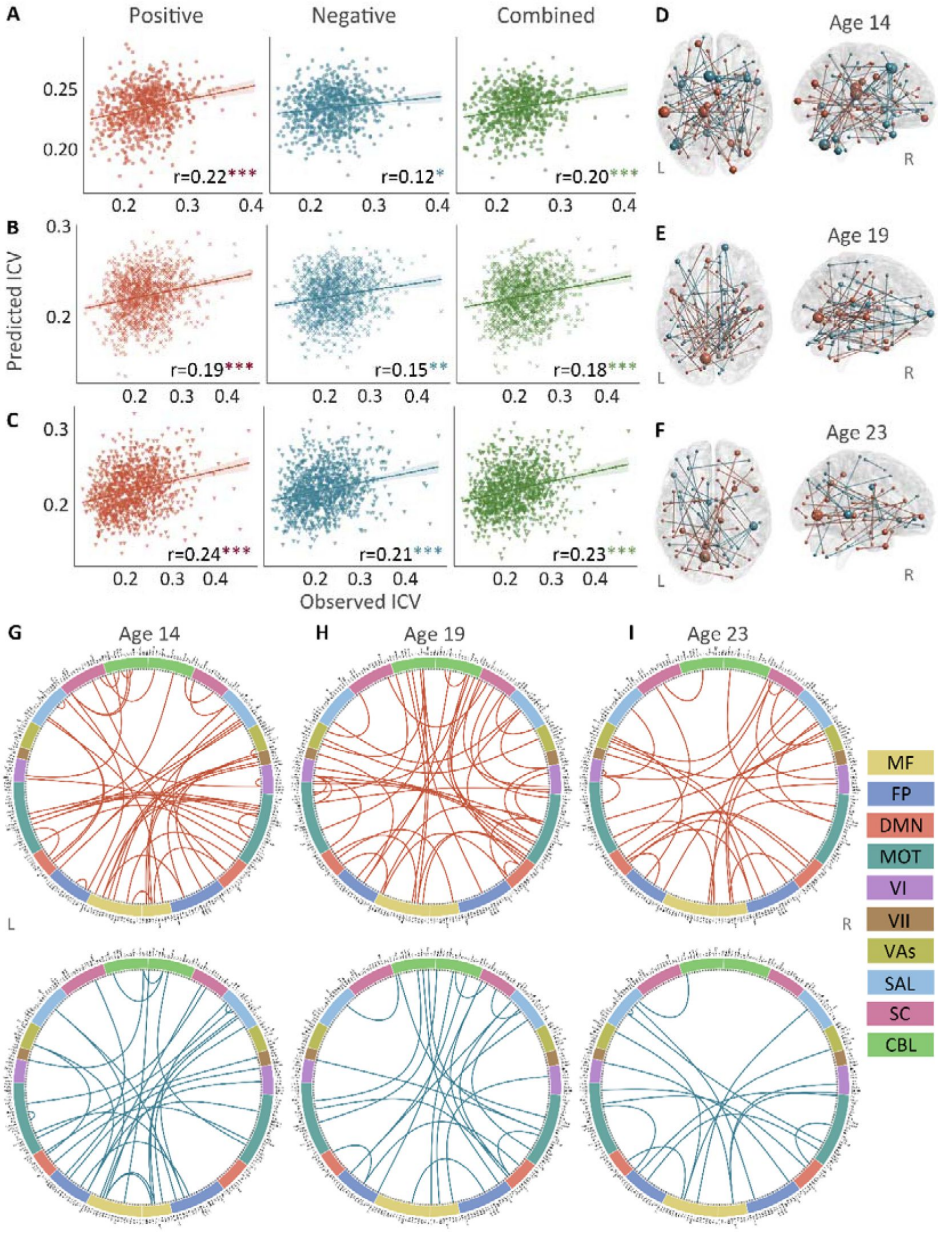

Fig. 3

The predictive performances and networks of intra-individual coefficient of variation (ICV) per timepoint derived from Successful stop trials.

Correlation between observed and predicted ICV in positive, negative, and combined networks at **(A)** age 14, **(B)** age 19, and **(C)** age 23. Predictive networks for ICV are at **(D)** age 14, **(E)** age 19, and **(F)** age 23. Connectome of positive and negative networks of ICV at **(G)** age 14, **(H)** age 19, and **(I)** age 23. The edges depicted above are those selected in at least 95% of cross-validation folds. Red, blue, and green spheres/lines/scatters represent positive, negative, and combined networks separately. MF, Medial frontal; FP, Frontoparietal; DMN, Default mode; MOT, Motor; VI, Visual I; VII, Visual II; VAs, Visual association; SAL, Salience; SC, Subcortical; CBL, Cerebellar. R/L, right/left hemisphere. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

and combined networks derived from Successful stop trials defined at age 19 predicted ICV at age 23 (r = 0.17, r = 0.16, and r = 0.17, respectively, all $P < 0.001$) (**Fig. 4B**, bottom row).

4. Generalization of ICV brain networks

We tested if the predictive networks defined at age 23 in IMAGEN would generalize to an external dataset, namely STRATIFY (N = ~300), comprising individuals also aged 23. When applied to the whole STRATIFY sample, positive, negative, and combined networks derived from Go trials at age 23 in IMAGEN predicted ICV in STRATIFY (r = 0.34, r = 0.34, and r = 0.35, respectively, all $P < 0.001$) (**Fig. 4C**), as did networks derived from Successful stop trials (r = 0.26, r = 0.22, and r = 0.26, respectively, all $P < 0.001$) (**Fig. 4D**).

5. Factor analysis of substance use

Exploratory factor analysis on data from the Timeline Followback (TLFB) (Sobell et al., 1996), an instrument for measuring the consumption of alcohol, drugs, and smoking for participants, yielded two common factors at age 14 and three common factors at ages 19 and 23. According to the rotated factor loading analysis, at age 14, two common factors were identified, which we labeled as (i) *alcohol* and (ii) *cigarette and cannabis* use (*Cig+CB)*. At ages 19 and 23, three common factors were identified, which we labeled as (i) *alcohol*, (ii) *Cig+CB*, and (iii) *drug* (including cocaine, ecstasy, and ketamine) use. Additional details about this data reduction step are shown in Fig. S7 and Table S10.

6. Correlation between behaviour and brain to cannabis and cigarette use

We calculated the Spearman correlation between ICV/sustained brain activity and TLFB factor score per timepoint and across timepoints. Brain activity was measured by the strength of positive and negative networks predicting sustained attention. The *P* values were corrected by false-discovery rate (FDR) correction ($q < 0.05$). **Figs. 5A-C** summarizes the results showing the correlation between ICV and brain and Cig+CB. The correlations between ICV and Cig+CB per timepoint and across timepoints are shown in **Fig. 5A** (Tables S13-14). The correlations between sustained attention network strength derived from Go trials and Cig+CB per timepoint and across timepoints are shown in **Fig. 5B**. In addition, the correlations between sustained attention network strength during Successful stop and Cig+CB use per timepoint and across timepoints are shown in **Fig. 5C** (Tables S17-18). No correlation between alcohol use and ICV and brain activity was found after FDR correction. Detailed results on the correlation between ICV/brain activity and substance use can be found in the supplementary materials (Tables S13-20).

7. Bivariate latent change score model

We used a bivariate latent change score model to explore the relationship between substance use (specifically Cig+CB and alcohol use) and ICV/brain activity. This approach tests for bi-directional associations, examining how substance use at age 14 predicts changes in ICV/brain activity from ages 14 to 23 and vice versa (**Fig. 6**). Below, we present the findings regarding the lagged effects of substance use on ICV/brain activity and the lagged effects of ICV/brain activity on substance use (**Table 2**). The *P* values were corrected by FDR correction ($q < 0.05$).

7.1 Lagged effects of Cig+CB on changes in ICV and brain activity

We examined if Cig+CB use at age 14 predicted the changes in ICV or brain activity (i.e., predictive network strength) associated with sustained attention across ages 14-23. No significance was observed in the lagged effects of Cig+CB on changes in ICV and brain activity (all $P > 0.172$).

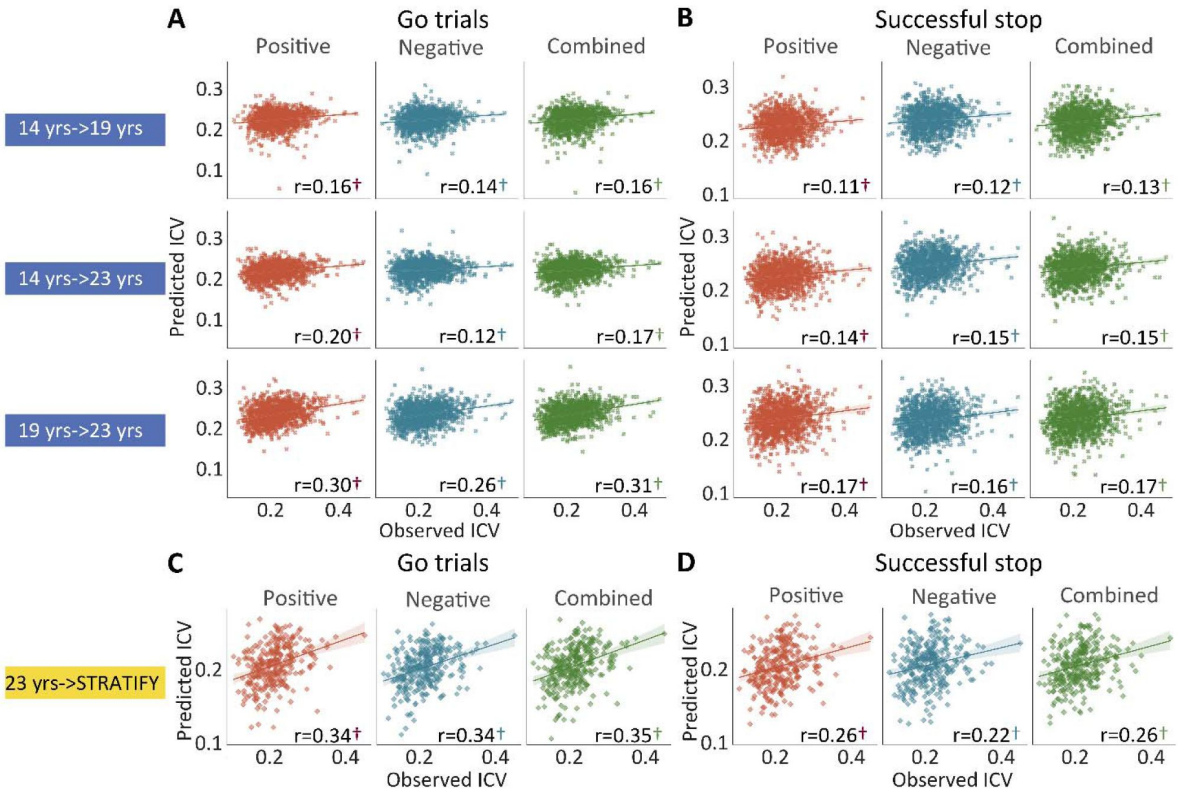

Fig. 4

The predictive performances of intra-individual coefficient of variation (ICV) across timepoints and generalization in STRATIFY.

Predictive performances of ICV **(A)** derived from Go trials and **(B)** derived from Successful stop trials. The top, middle, and bottom rows of (A) and (B) panels show the predictive performance: using models defined at age 14 to predict age 19 (i.e., 14 yrs -> 19 yrs), using models defined at age 14 to predict age 23 (i.e., 14 yrs -> 23 yrs), and using models defined at age 19 to predict age 23 (i.e., 19 yrs ->23 yrs) respectively. Generalization of predictive networks predicting ICV defined at age 23 in STRATIFY (i.e., 23 yrs -> STRATIFY) derived from **(C)** Go trials and **(D)** Successful stop trials. The red, blue, and green scatter represent positive, negative, and combined networks. †, P < 0.001.

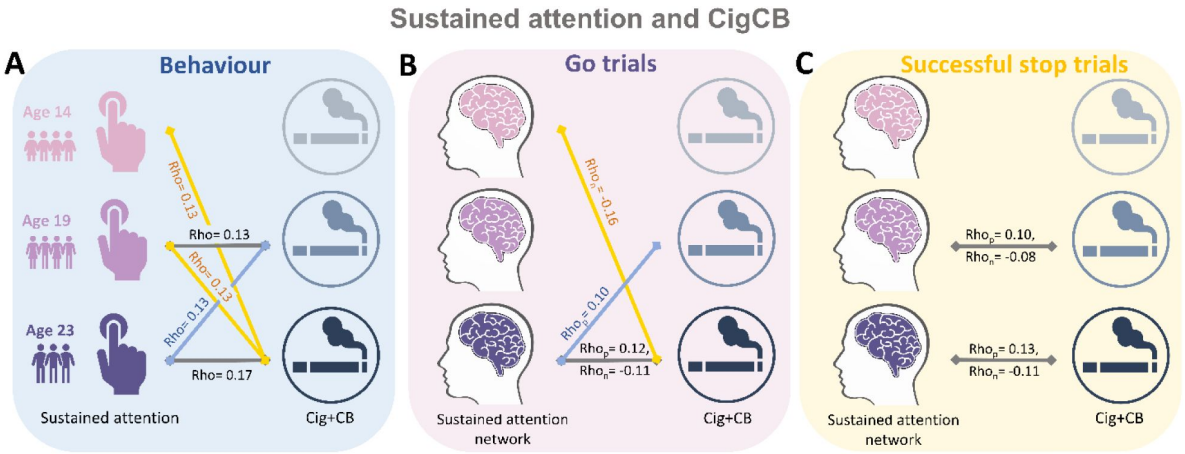

Fig. 5

Significant correlations between sustained attention and substance use across timepoints (FDR correction, q<0.05).

(A) Correlations between the intra-individual coefficient of variation (ICV) and Cigarette and cannabis use (Cig+CB) across timepoints. Correlations between sustained attention network strength and Cig+CB across timepoints **(B)** derived from Go trials and **(C)** derived from Successful stop trials. Rhop: r value between network strength of the positive network. Rhon: r value between network strength of the negative network.

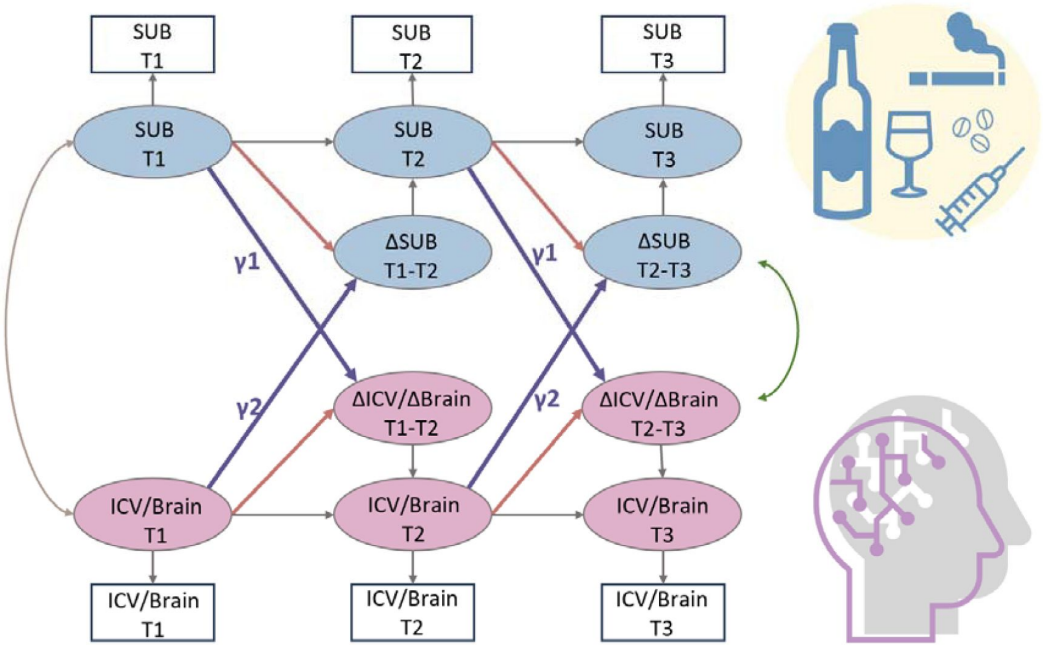

Fig. 6

A simplified bivariate latent change score model for substance use and ICV/brain activity.

SUB, substance use (alcohol, cigarette and cannabis use); Brain, brain network strength of positive/negative network of sustained attention derived from Go trials/Successful stop trials. ICV, intra-individual coefficient of variation. T1, Timepoint 1 (age 14); T2, Timepoint 2 (age 19); T3, Timepoint 3 (age 23). γ1, lagged effects of substance use on ICV or brain activity. γ2, lagged effects of ICV or brain activity on substance use. The square/circle represents the observation/true score in the model.

7.2 Lagged effects of ICV and brain activity on changes in Cig+CB

We examined if ICV or brain activity associated with sustained attention at age 14 predicted changes in Cig+CB use across ages 14-23. Behaviour and brain activity associated with poor sustained attention predicted a greater increase in subsequent cigarette and cannabis use. Specifically, higher ICV at age 14 predicted a greater increase in Cig+CB from ages 14 to 23 (*Std.* β = 0.12, $P < 0.001$). Higher sustained attention network strength for positive network derived from Go trials at age 14 predicted a greater increase in Cig+CB from ages 14 to 23 (*Std.* β = 0.09, $P = 0.006$). Lower sustained attention network strength for the negative network, also derived from Go trials at age 14, predicted a greater increase in Cig+CB from ages 14 to 23 (*Std.* β = -0.09, $P = 0.006$). No other lagged effects of brain activity on changes in Cig+CB remained significant after FDR correction (all $P > 0.047$). **Fig. 7** illustrates the changes in raw scores of cigarette and cannabis use from the TLFB for individuals at age 14 with higher sustained attention (i.e., lower ICV, lower strength of positive network, or higher strength of negative network) and lower sustained attention (i.e., higher ICV, higher strength of positive network, or lower strength of negative network).

7.3 Association between alcohol use and ICV/brain activity

We examined if alcohol use at age 14 predicted changes in ICV or brain activity associated with sustained attention across ages 14-23, or vice versa. No significant results were found for the lagged effects of alcohol use on changes in ICV and brain activity, nor the lagged effects of ICV and brain activity on changes in alcohol use. The *P* values were insignificant after FDR correction (all $P > 0.011$).

Discussion

It is well known that increased substance use, including cigarettes and cannabis, is associated with poorer sustained attention in late adolescence and early adulthood (Chamberlain et al., 2012; Dougherty et al., 2013). However, previous studies, which were predominantly cross-sectional or under-powered, left a critical question unanswered. That is, was the impairment in sustained attention a consequence of substance-use or a marker of the inclination to engage in such behaviour? Using a substantial sample size, our results indicate that behaviour and brain connectivity associated with poorer sustained attention at age 14 predicted a larger increase in cannabis and cigarette smoking from ages 14-23. Furthermore, our findings highlight the robustness of the brain network associated with sustained attention over time, making the latter a potentially useful biomarker for vulnerability to substance use.

Substance use and the sustained attention network

Our study applied a latent change score model on a large longitudinal dataset, testing the precedence between substance use and sustained attention. In contrast to prior research suggesting that substance use impaired sustained attention (Broyd et al., 2016; Figueiredo et al., 2020), our results indicate that lower sustained attention also predates substance use. A link between substance use and sustained attention is plausible, given the underlying neurobiology of this sustained attention. Substantial evidence from neuropharmacological studies in rats and humans has shown the modulatory role of neurotransmitters in sustained attention (Bloomfield et al., 2016; Granon et al., 2000; Marshall et al., 2019). Elevated dopamine and noradrenaline levels in the prefrontal cortex lead to improved sustained attention in a dose-dependent manner (Marshall et al., 2019). In humans, methylphenidate, a psychostimulant commonly used to treat ADHD, increases both noradrenaline and dopamine signaling and improves sustained attention (Dockree et al., 2017). Thus, poorer sustained attention may reflect a lower basal level of

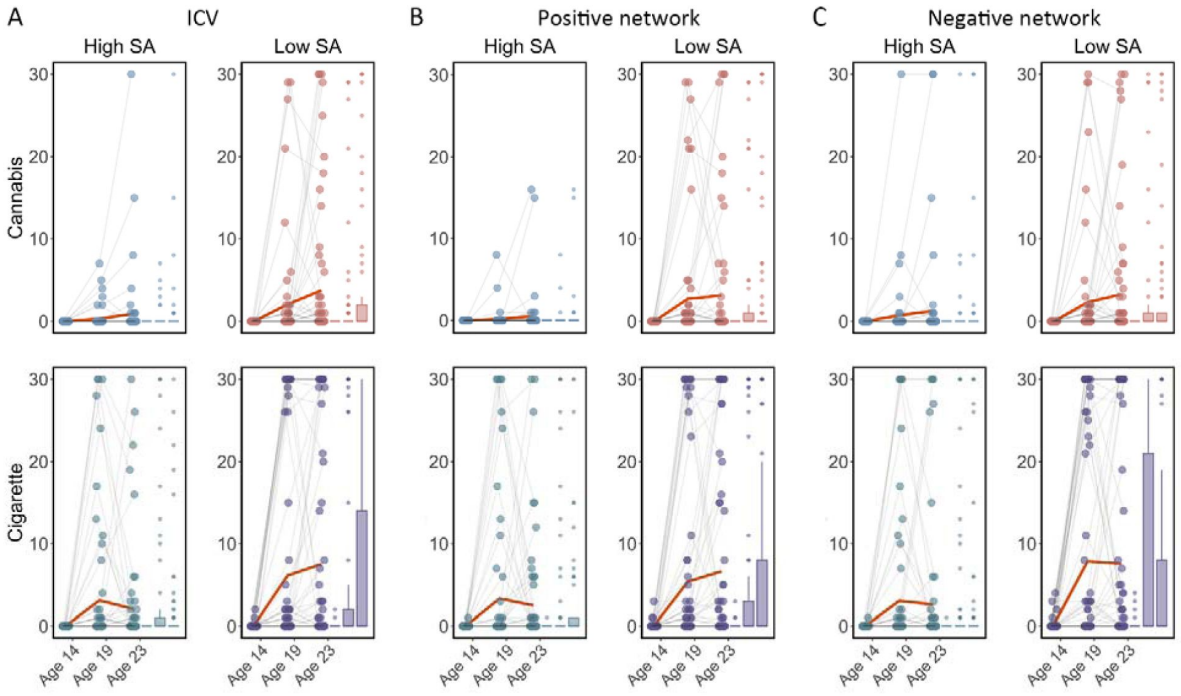

Fig. 7

Cigarette and cannabis score in Timeline Followback changes in individuals with high sustained attention (High SA) and low sustained attention (Low SA) from ages 14 to 23.

Participants were categorized into five equal groups based on the intra-individual coefficient of variation (ICV), strength of positive network, and strength of negative network at age 14. (A) Top ICV (Low SA) and bottom ICV (High SA) groups. (B) The top strength of the positive network (Low SA) and bottom strength of the positive network (High SA) groups derived from Go trials. (C) The top strength of the negative network (High SA) and bottom strength of the negative network (Low SA) groups derived from Go trials. Note that the higher strength of the negative network reflects lower ICV and higher sustained attention.

	Cig+CB		Alcohol use	
	Lagged effects of Cig+CB (γ1)	Lagged effects of ICV/brain networks (γ2)	Lagged effects of alcohol use (γ1)	Lagged effects of ICV/brain networks (γ2)
	Std. *β* (SE)	Std. *β* (SE)	Std. *β* (SE)	Std. *β* (SE)
ICV	0.017 (0.039)	**0.117 (0.031)*** **	0.005 (0.029)	0.057 (0.030)
SA GT PosNet	-0.026 (0.030)	**0.087 (0.032)** **	0.025 (0.030)	0.022 (0.036)
SA GT NegNet	0.012 (0.026)	**-0.094 (0.035)** **	-0.012 (0.030)	-0.059 (0.034)
SA SS PosNet	0.005 (0.025)	0.070 (0.036)	0.101 (0.040)	0.046 (0.039)
SA SS NegNet	0.038 (0.028)	-0.061 (0.031)	-0.003 (0.035)	-0.069 (0.031)

Note: SA GT, sustained attention network derived from Go trials; SA SS, sustained attention network derived from Successful stop trials; PosNet/NegNet, positive/negative network strength; ICV, intra-individual coefficient of variation; Cig+CB, Cigarette and cannabis use. Bold fonts represent the *P* value that survived after the false discovery rate (FDR, q < 0.05) correction for multiple comparisons. **, $P < 0.01$; ***, $P < 0.001$.

Table 2.

Bivariate latent change score model showing the bi-directional association between substance use and ICV/brain networks (False Discovery Rate corrected).

dopamine and noradrenaline. More importantly, studies in primates (Morgan et al., 2002; Nader et al., 2006), rodents (Dalley et al., 2007; Trifilieff et al., 2017), and humans (Casey et al., 2014; Trifilieff and Martinez, 2014; Volkow et al., 2006) have indicated that low basal dopamine levels are markers of vulnerability for increased drug administration. For example, Casey et al. (2014) demonstrated that blunted dopamine release may precede the development of addiction in humans. Nader et al. (2006) found a negative correlation between baseline D2 receptor availability and rates of cocaine self-administration in monkeys. Thus, these findings collectively suggest that sustained attention and its brain network could serve as a biomarker of vulnerability to substance use.

These results emphasize the specificity of sustained attention and its associated brain networks, rather than other cognitive abilities, for predicting substance use over time. Unlike sustained attention, no significant differences in cigarette and cannabis use were observed between individuals with lower and higher working memory at baseline during the Strategy working memory task (Table S22 and Fig. S8). Our results support the behavioural-only findings of a previous study (Harakeh et al., 2012), which found that individuals with poorer sustained attention, rather than other cognitive functions, were more likely to initiate smoking cigarettes. Our study goes further by showing that sustained attention brain networks can predict substance use in the future.

Neural associations between cigarette and cannabis use

We constructed composite scores of substance use. An exploratory factor analysis identified cigarettes and cannabis items as a common factor, aligning with previous studies (Ferland and Hurd, 2020; Hindocha et al., 2016; Weinberger et al., 2018) that indicate concurrent cannabis and cigarette use among users. A national survey in America indicated that 18–23% of cigarette smokers aged 12–17 met the criteria for cannabis use disorder, in contrast to only 2% of non-smoking youth (Weinberger et al., 2018). Another national online survey in the UK reported that 80.8% of cigarette smokers engage in cannabis consumption, indicating a prevalent practice of co-administering cannabis and tobacco through smoking (Hindocha et al., 2021). Shared genetic factors (Agrawal et al., 2010; Stringer et al., 2016) and similar neural associations (Wetherill et al., 2015) contribute to the co-use of cannabis and cigarettes. Stringer et al. (2016) demonstrated a strong and significant genetic correlation between lifetime cannabis use and lifetime cigarette smoking within a large cohort of 32,330 subjects, suggesting a high degree of genetic sharing between the two. Using neuroimaging techniques, Wetherill et al. (2015) indicated that individuals who used cannabis, smoked tobacco, or engaged in co-use exhibited larger gray matter volumes in the left putamen compared to healthy controls. Both nicotine and cannabis have similar effects on mesolimbic dopaminergic pathways engaged, modulating dopamine release in the striatum (Bossong et al., 2009; Dongelmans et al., 2021). Collectively, these findings suggest a similar neural association between cigarette and cannabis use.

Specificity and robustness of sustained attention networks

The brain networks we describe were specific to sustained attention. The strength of the sustained attention brain network was robustly correlated with RVP task performance, a typical sustained attention task, rather than other cognitive measures (Table S11). Importantly, as highlighted in a previous study (Cwiek et al., 2022), emphasizing the importance of generalization in an external dataset, our study found that the sustained attention network derived from Go trials and Successful stop trials generalized to an external dataset (See further discussion on the generalization in subgroups in STRATIFY in Supplemental materials).

We also replicated and extended the developmental pattern of sustained attention and its networks from mid-adolescence to young adulthood. A notable enhancement in sustained attention (i.e., decreased ICV) was observed from ages 14 to 23, as expected (Fortenbaugh et al., 2015; Williams et al., 2005). Sustained attention networks derived from Go and Successful stop

trials predicted behaviour at different timepoints, implying that individual differences in sustained attention and associated networks were preserved throughout development. Previously, in neurodiverse youth, attention networks in individuals remained stable across months to years (Horien et al., 2022). Rosenberg et al. (2020) also illustrated that the same functional connections predicting overall sustained attention ability also forecasted attentional changes observed over minutes, days, weeks, and months. Here, we contribute to these insights by extending the understanding that attention-network stability is not only applicable to neurodiverse populations but also holds in a sizeable cohort of healthy participants. Furthermore, our findings indicate that sustained attention networks remain stable over several years, providing valuable insights into the potential for sustained attention to function as a robust and efficient biomarker for substance use.

In conclusion, robust sustained attention networks were identifiable from ages 14 to 23. Individual differences in sustained attention network strength were predictable across time. Poorer sustained attention and strength of the associated brain networks at age 14 predicted greater increases in cannabis and cigarette smoking from ages 14 to 23.

Materials and Methods

2.1 Subjects

All neuroimaging data and behavioural data were obtained from the IMAGEN study. IMAGEN is a large longitudinal study that recruited over 2000 participants aged 14 to 23 in Europe (Kaiser et al., 2022). This study used the stop signal task fMRI data at ages 14, 19, and 23. In addition, we used an independent dataset STRATIFY as external validation for age 23. STRATIFY (N = ~300) is a sub-dataset within IMAGEN that recruits fMRI data from patients aged 23. The IMAGEN study conformed to the ethical standard outlined by the Declaration of Helsinki and was approved by ethics committees at each site. Written informed consent was obtained from participants and their parents. We followed the exclusion criteria outlined in previous studies (O'Halloran et al., 2018; Whelan et al., 2014). Finally, 717 subjects at age 14, 1081 subjects at age 19, and 1120 subjects at age 23 were used to predict ICV. In STRATIFY, 304 subjects were used to predict ICV.

2.2 Stop signal task

The stop signal task required subjects to respond to a Go signal (arrows pointing left/right) by pressing the left/right button while withholding their response if the Go signal was unpredictably followed by a stop signal (arrows pointing upwards). The Go signal was displayed on the screen for 1000 ms in the Go trials, while the stop signal appeared for 100-300 ms following the go signal on average 300 ms later in unpredictable stop trials. To adjust task difficulty dynamically, we used a tracking algorithm on the delay between the Go signal and stop signal (stop signal delay, SSD, 250-900 ms in 50 ms increments) (Verbruggen et al., 2019), to produce 50% successful and 50% unsuccessful inhibition trials. The task at age 14 included 400 Go trials and 80 variable delay stop trials, with 3 and 7 Go trials between successive stop trials. The task at ages 19 and 23 consisted of 300 Go trials and 60 variable delay stop trials. Before the MRI scan, subjects also performed a practice session with a block of 60 trials to become familiar with the task. ICV is used to assess sustained attention in this task for each subject. ICV reflects short-term within-person variations in task performance (Verbruggen et al., 2019). Specifically, ICV is computed by dividing the standard deviation of mean go RT by the mean go RT. Lower ICV indicates better sustained attention.

2.3 Self-Report Questionnaires

2.3.1 Puberty development scale (PDS)

The PDS, an 8-item self-report assessment, measures the pubertal development of adolescents (Petersen et al., 1988). The PDS evaluates physical development using a 5-point scale where 1 corresponds to prepubertal, 2 to beginning pubertal, 3 to mid-pubertal, 4 to advanced pubertal, and 51to1postpubertal. In addition, the items are adapted for sex, such as voice changes for males or menarche for females.

2.3.2 Timeline Followback (TLFB)

We used the TLFB, a retrospective self-report instrument that uses a calendar method to evaluate prior substance use consumption over the past 30 days (Sobell et al., 1996). The TLFB has strong reliability and validity for assessing alcohol consumption, and we used it to measure the use of alcohol, drugs, and smoking for subjects.

2.4 MRI acquisition and pre-processing

Functional MRI data of the stop-signal task in the IMAGEN study were collected at eight scan sites (London, Nottingham, Dublin, Mannheim, Dresden, Berlin, Hamburg, and Paris), and data in STRATIFY were collected at three scan sites (Berlin, two scanners in London) with 3T MRI scanners. The MR scanning protocols, cross-site standardization, and quality checks are further described in (Whelan et al., 2012). All images were obtained using echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2.2s, echo time (TE) = 30ms, flip angle = 75°, field of view (FOV) = 224 mm × 224 mm, data matrix = 64 × 64, slice thickness = 2.4 mm with 1 mm slice gap, voxel size = 3.5 × 3.5 × 4.38 mm, 40 transversal interleaved slices. The MRI data has 444 volumes at age 14 and 320-350 volumes at ages 19 and 23. Standardized hardware was used for visual stimulus presentation (Nordic Neurolab, Bergen, Norway) at all scan sites.

All fMRI data from the IMAGEN study were pre-processed centrally using SPM12 (Statistical Parametric Mapping, *http://www.fil.ion.ucl.ac.uk/spm/*) with an automated pipeline. The images were corrected for slice timing and then realigned to the first volumes to correct head motions. Subjects were excluded from the study if they had a mean framewise displacement (mean FD) > 0.5mm. Subsequently, the data were non-linearly transformed to the Montreal Neurological Institute Coordinate System (MNI) space using a custom EPI template with the voxels resampled at 31×131×131mm resolution. Finally, the images were smoothed with a Gaussian kernel at a full-width-at-half-maximum (FWHM) of 5 mm.

2.5 General psychophysiological interaction (PPI) analysis

PPI is an approach for describing task-dependent FC between brain regions. Generalized PPI analysis (gPPI) generates task-related FC matrices across the whole brain instead of just a single region. In this study, we adopted gPPI analysis to produce a task-related FC matrix and connectome predictive modeling (CPM) to investigate the predictive brain network from adolescents to young adults. First, we conducted a general linear model (GLM) analysis on the pre-processed fMRI data to examine brain activity during the stop signal task. Two separate GLMs were created for Go trials and Successful stop trials. The Go trials model included three regressors (Go trials, Failed stop trials, and Successful stop trials) and 36 nuisance regressors, which accounted for factors such as head motion and the signal from white matter and cerebrospinal fluid. The 36 nuisance regressors are 3 translations, 3 rotations, mean white matter signal, mean cerebrospinal fluid signal, mean matter signal, their derivatives, and the squares of all these variables. The Successful stop trials model included two regressors (Failed and Successful stop trials) and 36 nuisance regressors. We built a separate model for Successful stop trials, in which Go

trials were treated as an implicit baseline (given their high frequency). All task regressors were modeled by convolving with the canonical hemodynamic response function (HRF) and high pass filtered (128 s). We then conducted a gPPI analysis across the entire brain using the Shen atlas (Shen et al., 2013) for both Go and Successful stop trials. The gPPI analysis involved deconvolving the time series of each region of interest (ROI) with the hemodynamic response function, multiplying it by the psychological variables of interest to yield a neural level PPI term, and convolving the resulting PPI term with the HRF to obtain the BOLD level PPI effects (Di and Biswal, 2019). Separate GLM models were used to estimate the PPI effect of each ROI for Go trials and Successful stop trials, regressing the eigenvariate of the seed ROI. The GLM of the Go trials included 1 regressor of another ROI eigenvariate, 3 regressors of task condition, 3 regressors of the PPI effects, and one contrast term (Equation 1). The GLM of Successful stop trials included 1 regressor of another ROI eigenvariate, 2 regressors of task condition, 2 regressors of the PPI effects, and one contrast term (Equation 2), shown as follows:

$$Y = \beta_0 + \beta_1 * X_{\text{physio}} + \beta_2 * X_{\text{psycho(SS)}} + \beta_3 * X_{\text{psycho(FS)}} + \beta_4 * X_{\text{psycho(GO)}} + \beta_5 * X_{\text{physio}} * X_{\text{psycho(SS)}} + \beta_6 * X_{\text{physio}} * X_{\text{psycho(FS)}} + \beta_7 * X_{\text{physio}} * X_{\text{psycho(GO)}} + \varepsilon \quad (1)$$

$$Y = \beta_0 + \beta_1 * X_{\text{physio}} + \beta_2 * X_{\text{psycho(SS)}} + \beta_3 * X_{\text{psycho(FS)}} + \beta_4 * X_{\text{physio}} * X_{\text{psycho(SS)}} + \beta_5 * X_{\text{physio}} * X_{\text{psycho(FS)}} + \varepsilon \quad (2)$$

Note: SS, Successful stop trials; FS, Failed stop trials; GO, Go trials.

Where Y is the time series of seed ROI, $X_{physio}$is the time series of another ROI, $X_{psycho}$is the task design term, and ε is the residual term. The general PPI analysis was performed across the whole brain, and finally, we obtained a 268*268 PPI matrix for each subject derived from Go trials and Successful stop trials separately.

2.6 Connectome-based predictive modeling

2.6.1 ICV prediction

CPM is a data-driven method that can examine individual differences in brain connectivity (Shen et al., 2017). CPM identifies pairwise connections between brain regions most highly correlated with a given phenotype. Using the PPI matrix, we employed CPM to predict ICV, for ages 14, 19, and 23. The CPM analysis process includes feature selection, model building, and validation (Fig. S1). We applied cross-validation to divide all participants into training and testing sets. (i) First, we used partial correlation to calculate the relationship between each edge in the gPPI matrix and behavioural phenotype while controlling several covariates in the training set. These covariates included ages, genders, mode-centered PDS (at age 14 only), mean FD, and scan sites, regarded as a dummy variable. The r value with an associated *P* value for each edge was obtained, and a threshold $P = 0.01$ was set to select edges. The positive or negative correlated edges in feature selection were regarded as positive or negative networks. (ii) Second, we calculated network strength for each subject in the training set by summing the selected edges in the gPPI matrix for both positive and negative networks. We also estimated the network strength of a combined network by subtracting the strength of the negative from the strength of the positive network. (iii) Finally, we constructed predictive models based on the assumption of a linear relationship between network strength of the positive, negative, and combined networks, and behavioural phenotype in the training set. The covariates were also adjusted in this linear model. The network strengths for each subject in the testing set were calculated and input into the predictive model along with the covariates to predict each network's behavioural phenotypes.

2.6.2 Three cross-validation schemes

We used three CV schemes to test the robustness of predictive performance: k-fold (10-fold and 5-fold) and leave-site-out CV. For the k-fold CV, we randomly divided subjects into ten or five approximately equal-sized groups. For each fold, we trained the model on nine or four groups, respectively, and used it to predict the behavioural phenotype of the remaining group. We then assessed the predictive performance by comparing the predicted and observed values. For the leave-site-out CV, we divided subjects into eight groups based on their scan site. To account for the random splits of the k-fold CV, we repeated the process 50 times and calculated the average predictive performance for both the 10-fold and 5-fold CV (Lichenstein et al., 2021). In addition, we set a 95% threshold for selecting edges present in at least 48 out of 50 iterations to visualize the results. We also ran the CPM analysis with mean FD thresholds of 0.2, 0.3, and 0.4 mm to account for the influence of head motion on the predictive performance. The main text shows the results of the 10-fold CPM. The 5-fold CPM and leave-site-out CV results are shown in supplementary materials.

2.6.3 Prediction across timepoints and STRATIFY

To assess the ability of models developed at one timepoint to predict ICV at different timepoints, we applied predictive models developed at ages 14 and 19 to predict ICV at subsequent timepoints. Specifically, we used predictive models (including the parameters and selected edges) developed at age 14 to predict ICV at ages 19 and 23. We first calculated the network strength using the gPPI matrix at age 19 or 23 based on the selected edges identified from CPM analysis at age 14. We then used the linear model parameters (slope and intercept) from CPM analysis at age 14 to fit the network strength and predict ICV at age 19 or 23. Finally, we evaluated the predictive performance by calculating the correlation between the predicted and observed values at age 19 or 23. Similarly, we applied models developed at age 19 to predict ICV at age 23. In addition, we examined the generalizability of predictive models at age 23 by applying them to the STRATIFY dataset, which also includes subjects who were 23 years old. Furthermore, we estimated the predictive performances of ICV across patient groups in the STRATIFY. The correlation between the residual network strength of predictive networks and ICV was calculated across groups in the STRATIFY. The covariates, including age, sex, and mean FD, were regressed for network strength before the correlation analysis. It is worth noting that when applying models developed at one timepoint to predict at another timepoint or to generalize to a different dataset, the model was built using all subjects from the timepoint at which the model was developed.

2.7 Statistical analysis

2.7.1 Exploratory Factor Analysis

To explore the underlying structure of adolescent substance use, we performed an exploratory factor analysis using principal component extraction (Gaskin and Happell, 2014) on TLFB using Predictive Analytics Software (SPSS) version 20. Factor analysis explores the underlying structure of a set of observed variables without imposing a preconceived structure on the outcome. We used six items at age 14 and nine items at ages 19 and 23 of TLFB, including alcohol, tobacco, cannabis, cocaine, ecstasy, and ketamine (as shown in Table S21). We excluded items assessing the use of other drugs due to high proportions of missing data, standard deviations close to 0, or a Kaiser-Meyer-Olkin (KMO) statistic for individual variables below 0.5, considered the minimum value for a sample to be adequate. The KMO measure of sampling adequacy was 0.66 at age 14, 0.81 at age 19, and 0.77 at age 23. In addition, all Bartlett's tests of sphericity were significant (Age 14: $\chi^2(15) = 5137.067$, $P < 0.001$; Age 19: $\chi^2(36) = 5031.641$, $P < 0.001$; Age 23: $\chi^2(36) = 5106.265$, $P < 0.001$),

indicating that there was an underlying correlation structure and that factor analysis was appropriate. We rotated the factors using the varimax method with kaiser normalization to make it easier to discern the underlying measured constructs.

2.7.2 Linear mixed model

We constructed a linear mixed model to examine the change in ICV over time using the *lme4* and *lmerTest* packages in RStudio (version: 1.4; *http://www.rstudio.com/*) and R (version 4.1.1; *https://www.r-project.org/*). The timepoint was the fixed effect of interest in the model, while the subject was a random effect. Several covariates, including sex, scan sites, mode-center PDS, and age at 14, were also included as fixed effects in the models. The linear mixed model is shown as follows:

$$\text{ICV} \sim \text{Timepoint} + \text{Sex} + \text{Scan site} + \text{Mode\_center PDS} + \text{Age at 14} + (1|\text{Subject}) \quad (3)$$

2.7.3 Correlation between network strength and substance use

To examine the relationship between ICV/brain activity and substance use, we correlated the network strength of predictive networks with the factor scores of substance use at each timepoint and across all three timepoints separately. To control for potential confounders, we calculated residual network strength and residual factor scores by regressing the effects of age, sex, mean FD, scan sites, and mode-centered PDS for age 14. We used partial correlation to assess the association between residual network strength and residual TLFB and used a FDR correction ($q < 0.05$) for the multiple correlations.

Furthermore, we employed a three-wave bivariate latent change score model using the *lavvan* package in R and R studio to detect the linear change over time. This model allows us to quantify the longitudinal bidirectional influence between substance use and ICV over time (Nweze et al., 2023). Specifically, it facilitated an understanding of whether substance use predicted ICV and its brain activity, and vice versa. The key feature of this model is its ability to assess linear increases or decreases within the same construct across two adjacent waves. Change scores were calculated by regressing the observable score of a given timepoint from the previous timepoint (e.g., Δ Cig+CB in T1–T2 or Δ Cig+CB in T2–T3, where T1 = Timepoint 1, T2 = Timepoint 2, and T3 = Timepoint 3). Additionally, cross-lagged dynamic coupling (i.e., bidirectionality) was employed to explore individual differences in the relationships between substance use and linear changes in ICV/brain activity, as well as the relationship between ICV/brain activity and linear change in substance use. Covariates including age, sex, and scan sites were included in the model. For more details about the latent change score model, refer to the reference (Nweze et al., 2023).

As **Fig. 6** shows, the latent change score model was specifically applied to examine the association between substance use and behaviour and brain activity of sustained attention. We focused on the relationship between the network strength of positive and negative networks, derived from Go and successful stop trials, and two types of substance use (Cig+CB and alcohol use). Notably, drug use data were excluded as adolescents at age 14 have no drug score. A total of 10 models were performed, and all model fit indices met the predefined criteria: CFI > 0.92, RMSEA <0.05, and SRMR < 0.03. A FDR correction ($q < 0.05$) was applied for multiple correlations.

2.7.4 Permutation test

For the CPM analysis, we used a permutation test to assess the significance of the predictive performance, which is the correlation between the observed and predicted values. To generate a null distribution of these correlation values, we randomly shuffled the correspondence of the behavioural data and the PPI matrix of all subjects and reran the CPM pipeline with the shuffled data 1000 times. Based on this distribution, we set a threshold of $P < 0.05$ to determine the significance level at 95% for the predictive performance using 10-fold, 5-fold, and leave-site-out CV.

To estimate the significance of the predictive performance across timepoint and the external validation in the STRATIFY dataset, we shuffled the predictive values 1000 times. Then, we correlated the shuffled values with observed values to yield a null distribution of predictive correlation values. We also set a threshold of $P < 0.05$ to determine the significance level at 95% for the predictive performance across timepoints and generalization in STRATIFY.

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Author contributions

R.W., J.K., L.R., and K.R. conceptualized this study. T.B., G.J.B., A.L.W.B., C.B., F.M.C., P.J.C., H.F., M.F.-B., J.G., H.G., P.G., A.H., B.I., K.M., J.-L.M., F.N., T.P., M.R., C.L., Z.P., M.-L.P.-M., M.N.S., A.S., M.R. and T.W.R. acquired the data. Y.W. processed and analysed the data. R.B., L.F., J.K., E.S., T.N. and J.H. contributed to data analyses and interpreted the results with Y.W. and R.W.. Y.W. and R.W. wrote the manuscript. All authors edited the paper and gave final approval before submission.

Competing interests

Dr. Banaschewski served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Lundbeck, Medice, Novartis, Shire. He received conference support or speaker's fee by Lilly, Medice Novartis and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships. Dr Walter received a speaker honorarium from Servier (2014). The other authors report no biomedical financial interests or potential conflicts of interest.

Data and materials availability

IMAGEN data are available from a dedicated database: *https://imagen2.cea.fr*. Custom code that supports the findings of this study is available from the corresponding author upon request. All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

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Reviewer #1 (Public Review):

This study explored the relationship between sustained attention and substance use from ages 14 to 23 in a large longitudinal dataset. They found behaviour and brain connectivity associated with poorer sustained attention at age 14 predicted subsequent increase in cannabis and cigarette smoking from ages 14-23. They concluded that the brain network of sustained attention is a robust biomarker for vulnerability to substance use. The big strength of the study is a substantial sample size and validation of the generalization to an external dataset. In addition, various methods/models were used to prove the relationship between sustained attention and substance use over time.

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Reviewer #2 (Public Review):

Weng and colleagues investigated the relationship between sustained attention and substance use in a large cohort across three longitudinal visits (ages 14, 19, and 23). They employed a stop signal task to assess sustained attention and utilized the Timeline Followback self-report questionnaire to measure substance use. They assessed the linear relationship between sustained attention-associated functional connections and substance use at an earlier visit (age 14 or 19). Subsequently, they utilized this relationship along with the functional connection profile at a later age (age 19 or 23) to predict substance use at those respective ages. The authors found that connections in association with reduced sustained attention predicted subsequent increases in substance use, a conclusion validated in an external dataset. Altogether, the authors suggest that sustained attention could serve as a robust biomarker for predicting future substance use.

This study by Weng and colleagues focused on an important topic of substance use prediction in adolescence/early adulthood. While the study largely achieves its aims, several points merit further clarification:

(1) Regarding connectome-based predictive modeling, an assumption is that connections associated with sustained attention remain consistent across age groups. However, this assumption might be challenged by observed differences in the sustained attention network profile (i.e., connections and related connection strength) across age groups (Figures 2 G-I, Fig. 3 G_I). It's unclear how such differences might impact the prediction results.

(2) Another assumption of the connectome-based predictive modeling is that the relationship between sustained attention network and substance use is linear, and remains linear over development. Such linear evidence from either the literature or their data would be of help.

(3) Heterogeneity in results suggests individual variability that is not fully captured by group-level analyses. For instance, Figure 1A shows decreasing ICV (better-sustained attention) with age on the group level, while there are both increasing and decreasing patterns on the individual level via visual inspection. Figure 7 demonstrates another example in which the group with a high level of sustained attention has a lower risk of substance use at a later age compared to that in the group with a low level of sustained attention. However, there are individuals in the high sustained attention group who have substance use scores as high as those in the low sustained attention group. This is important to take into consideration and could be a potential future direction for research.

The above-mentioned points might partly explain the significant but low correlations between the observed and predicted ICV as shown in Figure 4. Addressing these limitations would help enhance the study's conclusions and guide future research efforts.

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Reviewer #3 (Public Review):

Summary:

Weng and colleagues investigated the association between attention-related connectivity and substance use. They conducted a study with a sizable sample of over 1,000 participants, collecting longitudinal data at ages 14, 19, and 23. Their findings indicate that behaviors and brain connectivity linked to sustained attention at age 14 forecasted subsequent increases in cigarette and cannabis use from ages 14 to 23. However, early substance use did not predict future attention levels or attention-related connectivity strength.

Strengths:

The study's primary strength lies in its large sample size and longitudinal design spanning three time-points. A robust predictive analysis was employed, demonstrating that diminished sustained attention behavior and connectivity strength predict substance use, while early substance use does not forecast future attention-related behavior or connectivity strength.

Weaknesses:

It's questionable whether the prediction approach (i.e., CPM), even when combined with longitudinal data, can establish causality. I recommend removing the term 'consequence' in the abstract and replacing it with 'predict'. Additionally, the paper could benefit from enhanced rigor through additional analyses, such as testing various thresholds and conducting lagged effect analyses with covariate regression.

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