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.

90 **MAIN TEXT**

91

92 Sustained attention is a critical cognitive process in daily life, playing a significant role in academic
93 achievement, social communication, and mental health (Esterman and Rothlein, 2019) and can be
94 defined as "the focus on performance on a single task over time, with the goal of explaining both the
95 fluctuations within an individual as well as the individual differences in overall ability to maintain stable
96 task performance" (p. 174)(Esterman and Rothlein, 2019). Sustained attention notably improves between
97 the ages of 9 and 16 years-old (Thomson et al., 2022), concomitant with cognitive maturation and brain
98 development during adolescence (Paus, 2005). The functional neuroanatomy of sustained attention
99 involves cingulate, prefrontal, and parietal cortices; supplementary motor area (SMA); frontal eye field;
100 and cerebellum (Bauer et al., 2020; Pinar et al., 2018). Key neurotransmitters associated with sustained
101 attention include dopamine (Marshall et al., 2019), noradrenaline (Greene et al., 2009), and acetylcholine
102 (Gill et al., 2000).

103 Cross-sectional studies suggest that substance use during adolescence, including cigarette
104 smoking (Treur et al., 2015), alcohol consumption (Ueno et al., 2022), and cannabis use (Wallace et al.,
105 2019), is associated with poorer sustained attention. For instance, adolescents (14-17 years-old) using
106 cannabis a minimum of 4 days per week for at least the last 6 months showed impaired sustained
107 attention in the Rapid Visual Information Processing Task (RVP), and in the Immediate Memory Task
108 versus non-users (Broyd et al., 2016; Figueiredo et al., 2020). Adolescents (12-17 years-old) in a high
109 tetrahydrocannabinol (THC; the primary psychoactive component in cannabis) group exhibited lower
110 accuracy on the RVP task than a low THC group (Shannon et al., 2010). Cigarette users aged 18-29 years-
111 old showed significant cognitive impairments in sustained attention than non-smokers in the RVP task
112 (Chamberlain et al., 2012). A systematic review of the next-day cognitive effects of heavy alcohol
113 consumption demonstrated impairments in sustained attention during alcohol hangovers using meta-
114 analysis (Yakir et al., 2007). These findings highlight the negative associations between substance use and
115 sustained attention.

116 Given the cross-sectional nature of the behavioural and neuroimaging studies above, it remains
117 unclear if impaired sustained attention predates the initiation of substance use and/or if it is a
118 consequence of substance use. Only one longitudinal study (Harakeh et al., 2012) has examined the
119 association between sustained attention and cigarette smoking, employing measurements across three-
120 waves and involving a large sample of 1,797 adolescents. Poor sustained attention; unlike other
121 neurocognitive functions such as working memory, attention flexibility, or perceptual sensitivity; was

122 associated with the increased probability of adolescents subsequently initiating cigarette smoking
123 between ages 11 and 13 and with a higher chance of being a daily smoker by age 16.

124 Harakeh and colleagues' findings suggest that poor sustained attention may precede the onset of
125 cigarette smoking. However, as their study was based on a behavioural level, the neural correlates
126 underlying these associations remain untested. It is biologically plausible that poorer sustained attention
127 predates substance use. Nicotine and THC increase availability of the neurotransmitters such as
128 dopamine, noradrenaline, and acetylcholine in the prefrontal cortex and striatum (Bloomfield et al., 2016;
129 Fitzgerald, 2013; McGehee and Role, 1995; Narayanaswami et al., 2013; Wise and Robble, 2020).
130 Furthermore, reducing these neurotransmitters via pharmacological challenges has been associated with
131 impaired sustained attention (Thiele and Bellgrove, 2018). Similar to a "self-medication hypothesis" in
132 schizophrenia, where substance use has been related to low striatal dopamine (Awad and Voruganti,
133 2015), it is plausible that there is a link between lower sustained attention and later substance use.

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

144 Functional brain networks can predict various behavioural traits, such as substance use (Yip et al.,
145 2019) and sustained attention (Rosenberg et al., 2016). Previous studies (e.g., (Rosenberg et al., 2018))
146 have used brain connectivity to develop predictive models of sustained attention that can be generalized
147 to healthy and clinical populations. However, while behavioural changes in sustained attention have been
148 documented and functional brain networks that predict substance use have been identified (Yip et al.,
149 2019), the underlying change in sustained attention brain networks from adolescence to adulthood and
150 their relation to substance use are relatively less well described. Lower sustained attention has been
151 accompanied by both stronger reductions in neural activity in the visual cortex, as well as stronger
152 recruitment of the right supramarginal gyrus with increasing time on a sustained attention task with
153 central cues in cigarette smokers as opposed to non-smokers (Vossel et al., 2011). In a resting-state

154 functional magnetic resonance imaging (fMRI) paradigm, cannabis users aged 16-26 had stronger
155 connectivity between the left posterior cingulate cortex and the cerebellum, correlated with poorer
156 performance on sustained attention/working memory and verbal learning measures (Ritchay et al., 2021).
157 While most brain connectomic research has utilized resting-state fMRI data, it has been shown that
158 functional connectivity (FC) during task performance, especially task-related FC (Zhao et al., 2023),
159 outperforms typical task-based and resting-state FC at predicting individual differences over time, in
160 addition to having the potential to capture more behaviourally relevant information (Dhamala et al.,
161 2022; Greene et al., 2018; Yoo et al., 2018).

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

175 **Results**

176 ***1. Behavioural changes over time***

177 Participants' demographic information for all analyses is shown in Table 1 (see also Tables S1-S2).
178 We used the intra-individual coefficient of variation (ICV) from Go trials to index sustained attention.
179 Lower ICV indicates better sustained attention. A linear mixed model analysis showed significant fixed
180 effects of age (i.e., timepoint) on ICV ($F_{1895.3} = 51.14$, $P < 0.001$) (Fig. 1A). Post-hoc analysis showed that
181 ICV decreased with age: ICV at age 14 was significantly higher than ICV at ages 19 ($t = 6.535$, $P < 0.001$)
182 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
183 < 0.001). The full results of the linear mixed model analysis are shown in Tables S3-S4. In addition, we
184 found that individual differences in each ICV were significantly correlated between the three timepoints
185 (Fig. 1B and Table S5, all $P < 2.8e^{-7}$).

186 *Place Table 1. about here*

187 *Place Fig. 1 about here*

188 ***2. Cross-sectional brain connectivity***

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

196 Positive, negative, and combined networks derived from Go trials significantly predicted ICV: at
197 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 =
198 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 $P <$
199 0.001) (Fig. 2C). The connectome patterns of predictive networks are shown in Figs. 2D-I. Fig. S2
200 summarizes the connectivity within and between functional networks and depicts their respective
201 contribution to the predictive network. The above results were validated using 10-fold cross validation
202 (CV); similar results were obtained when using 5-fold CV and leave-site-out CV (Table S6). The predictive
203 networks had similar connectome patterns when different exclusion criteria for head motion were used
204 (mean framewise displacement, mean FD < 0.2 - 0.4 mm) (Figs. S4-S6A).

205 *Place Fig. 2 about here*

206 Positive, negative, and combined networks derived from Successful stop trials significantly
207 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.
208 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
209 at age 23 (r = 0.24, r = 0.21, and r = 0.23, respectively, all $P < 0.001$) (Fig. 3C). The connectome patterns of
210 predictive networks are shown in Figs. 3D-I. Fig. S3 summarizes the connectivity within and between
211 functional networks and the proportion of brain networks involved in the predictive network. We
212 obtained similar results using a 5-fold CV and leave-site-out CV (Table S6). The predictive networks had
213 similar connectome patterns when different exclusion criteria for head motion were used (mean FD < 0.2
214 - 0.4 mm) (Figs. S4-S6B).

215 *Place Fig. 3 about here*

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, 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).

Place Fig. 4 about here

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

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

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

253 We calculated the Spearman correlation between ICV/sustained brain activity and TLFB factor
254 score per timepoint and across timepoints. Brain activity was measured by the strength of positive and
255 negative networks predicting sustained attention. The *P* values were corrected by false-discovery rate
256 (FDR) correction ($q < 0.05$). Figs. 5A-C summarizes the results showing the correlation between ICV and
257 brain and Cig+CB. The correlations between ICV and Cig+CB per timepoint and across timepoints are
258 shown in Fig. 5A (Tables S13-14). The correlations between sustained attention network strength derived
259 from Go trials and Cig+CB per timepoint and across timepoints are shown in Fig. 5B. In addition, the
260 correlations between sustained attention network strength during Successful stop and Cig+CB use per
261 timepoint and across timepoints are shown in Fig. 5C (Tables S17-18). No correlation between alcohol
262 use and ICV and brain activity was found after FDR correction. Detailed results on the correlation
263 between ICV/brain activity and substance use can be found in the supplementary materials (Tables S13-
264 20).

265 *Place Fig. 5 about here*

266 ***7. Bivariate latent change score model***

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

273 *Place Fig. 6 about here*

274 ***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 $P > 0.172$).

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.* $\beta = 0.12$, $P < 0.001$). 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.* $\beta = 0.09$, $P = 0.006$). 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.* $\beta = -0.09$, $P = 0.006$). 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).

Place Fig. 7 about here

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 $P > 0.011$).

Place Table 2. about here

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,

305 our results indicate that behaviour and brain connectivity associated with poorer sustained attention at
306 age 14 predicted a larger increase in cannabis and cigarette smoking from ages 14-23. Furthermore, our
307 findings highlight the robustness of the brain network associated with sustained attention over time,
308 making the latter a potentially useful biomarker for vulnerability to substance use.

309 ***Substance use and the sustained attention network***

310 Our study applied a latent change score model on a large longitudinal dataset, testing the
311 precedence between substance use and sustained attention. In contrast to prior research suggesting that
312 substance use impaired sustained attention (Broyd et al., 2016; Figueiredo et al., 2020), our results
313 indicate that lower sustained attention also predates substance use. A link between substance use and
314 sustained attention is plausible, given the underlying neurobiology of this sustained attention. Substantial
315 evidence from neuropharmacological studies in rats and humans has shown the modulatory role of
316 neurotransmitters in sustained attention (Bloomfield et al., 2016; Granon et al., 2000; Marshall et al.,
317 2019). Elevated dopamine and noradrenaline levels in the prefrontal cortex lead to improved sustained
318 attention in a dose-dependent manner (Marshall et al., 2019). In humans, methylphenidate, a
319 psychostimulant commonly used to treat ADHD, increases both noradrenaline and dopamine signaling
320 and improves sustained attention (Dockree et al., 2017). Thus, poorer sustained attention may reflect a
321 lower basal level of dopamine and noradrenaline. More importantly, studies in primates (Morgan et al.,
322 2002; Nader et al., 2006), rodents (Dalley et al., 2007; Trifilieff et al., 2017), and humans (Casey et al.,
323 2014; Trifilieff and Martinez, 2014; Volkow et al., 2006) have indicated that low basal dopamine levels are
324 markers of vulnerability for increased drug administration. For example, Casey et al. (2014) demonstrated
325 that blunted dopamine release may precede the development of addiction in humans. Nader et al. (2006)
326 found a negative correlation between baseline D2 receptor availability and rates of cocaine self-
327 administration in monkeys. Thus, these findings collectively suggest that sustained attention and its brain
328 network could serve as a biomarker of vulnerability to substance use.

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

337 ***Neural associations between cigarette and cannabis use***

338 We constructed composite scores of substance use. An exploratory factor analysis identified
339 cigarettes and cannabis items as a common factor, aligning with previous studies (Ferland and Hurd, 2020;
340 Hindocha et al., 2016; Weinberger et al., 2018) that indicate concurrent cannabis and cigarette use
341 among users. A national survey in America indicated that 18–23% of cigarette smokers aged 12–17 met
342 the criteria for cannabis use disorder, in contrast to only 2% of non-smoking youth (Weinberger et al.,
343 2018). Another national online survey in the UK reported that 80.8% of cigarette smokers engage in
344 cannabis consumption, indicating a prevalent practice of co-administering cannabis and tobacco through
345 smoking (Hindocha et al., 2021). Shared genetic factors (Agrawal et al., 2010; Stringer et al., 2016) and
346 similar neural associations (Wetherill et al., 2015) contribute to the co-use of cannabis and cigarettes.
347 Stringer et al. (2016) demonstrated a strong and significant genetic correlation between lifetime cannabis
348 use and lifetime cigarette smoking within a large cohort of 32,330 subjects, suggesting a high degree of
349 genetic sharing between the two. Using neuroimaging techniques, Wetherill et al. (2015) indicated that
350 individuals who used cannabis, smoked tobacco, or engaged in co-use exhibited larger gray matter
351 volumes in the left putamen compared to healthy controls. Both nicotine and cannabis have similar
352 effects on mesolimbic dopaminergic pathways engaged, modulating dopamine release in the striatum
353 (Bossong et al., 2009; Dongelmans et al., 2021). Collectively, these findings suggest a similar neural
354 association between cigarette and cannabis use.

355 ***Specificity and robustness of sustained attention networks***

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

363 We also replicated and extended the developmental pattern of sustained attention and its
364 networks from mid-adolescence to young adulthood. A notable enhancement in sustained attention (i.e.,
365 decreased ICV) was observed from ages 14 to 23, as expected (Fortenbaugh et al., 2015; Williams et al.,
366 2005). Sustained attention networks derived from Go and Successful stop trials predicted behaviour at
367 different timepoints, implying that individual differences in sustained attention and associated networks
368 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

399 ms later in unpredictable stop trials. To adjust task difficulty dynamically, we used a tracking algorithm on
400 the delay between the Go signal and stop signal (stop signal delay, SSD, 250-900 ms in 50 ms increments)
401 (Verbruggen et al., 2019), to produce 50% successful and 50% unsuccessful inhibition trials. The task at
402 age 14 included 400 Go trials and 80 variable delay stop trials, with 3 and 7 Go trials between successive
403 stop trials. The task at ages 19 and 23 consisted of 300 Go trials and 60 variable delay stop trials. Before
404 the MRI scan, subjects also performed a practice session with a block of 60 trials to become familiar with
405 the task. ICV is used to assess sustained attention in this task for each subject. ICV reflects short-term
406 within-person variations in task performance (Verbruggen et al., 2019). Specifically, ICV is computed by
407 dividing the standard deviation of mean go RT by the mean go RT. Lower ICV indicates better sustained
408 attention.

409 ***2.3 Self-Report Questionnaires***

410 ***2.3.1 Puberty development scale (PDS)***

411 The PDS, an 8-item self-report assessment, measures the pubertal development of adolescents
412 (Petersen et al., 1988). The PDS evaluates physical development using a 5-point scale where 1
413 corresponds to prepubertal, 2 to beginning pubertal, 3 to mid-pubertal, 4 to advanced pubertal, and
414 5 to postpubertal. In addition, the items are adapted for sex, such as voice changes for males or
415 menarche for females.

416 ***2.3.2 Timeline Followback (TLFB)***

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

421 ***2.4 MRI acquisition and pre-processing***

422 Functional MRI data of the stop-signal task in the IMAGEN study were collected at eight scan sites
423 (London, Nottingham, Dublin, Mannheim, Dresden, Berlin, Hamburg, and Paris), and data in STRATIFY
424 were collected at three scan sites (Berlin, two scanners in London) with 3T MRI scanners. The MR
425 scanning protocols, cross-site standardization, and quality checks are further described in (Whelan et al.,
426 2012). All images were obtained using echo-planar imaging (EPI) sequence with the following parameters:
427 repetition time (TR) = 2.2s, echo time (TE) = 30ms, flip angle = 75°, field of view (FOV) = 224 mm × 224
428 mm, data matrix = 64 × 64, slice thickness = 2.4 mm with 1 mm slice gap, voxel size = 3.5 × 3.5 × 4.38 mm,

429 40 transversal interleaved slices. The MRI data has 444 volumes at age 14 and 320-350 volumes at ages
430 19 and 23. Standardized hardware was used for visual stimulus presentation (Nordic Neurolab, Bergen,
431 Norway) at all scan sites.

432 All fMRI data from the IMAGEN study were pre-processed centrally using SPM12 (Statistical
433 Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/) with an automated pipeline. The images were
434 corrected for slice timing and then realigned to the first volumes to correct head motions. Subjects were
435 excluded from the study if they had a mean framewise displacement (mean FD) > 0.5mm. Subsequently,
436 the data were non-linearly transformed to the Montreal Neurological Institute Coordinate System (MNI)
437 space using a custom EPI template with the voxels resampled at $3 \times 3 \times 3$ mm resolution. Finally, the
438 images were smoothed with a Gaussian kernel at a full-width-at-half-maximum (FWHM) of 5 mm.

439 ***2.5 General psychophysiological interaction (PPI) analysis***

440 PPI is an approach for describing task-dependent FC between brain regions. Generalized PPI
441 analysis (gPPI) generates task-related FC matrices across the whole brain instead of just a single region. In
442 this study, we adopted gPPI analysis to produce a task-related FC matrix and connectome predictive
443 modeling (CPM) to investigate the predictive brain network from adolescents to young adults. First, we
444 conducted a general linear model (GLM) analysis on the pre-processed fMRI data to examine brain
445 activity during the stop signal task. Two separate GLMs were created for Go trials and Successful stop
446 trials. The Go trials model included three regressors (Go trials, Failed stop trials, and Successful stop trials)
447 and 36 nuisance regressors, which accounted for factors such as head motion and the signal from white
448 matter and cerebrospinal fluid. The 36 nuisance regressors are 3 translations, 3 rotations, mean white
449 matter signal, mean cerebrospinal fluid signal, mean matter signal, their derivatives, and the squares of
450 all these variables. The Successful stop trials model included two regressors (Failed and Successful stop
451 trials) and 36 nuisance regressors. We built a separate model for Successful stop trials, in which Go trials
452 were treated as an implicit baseline (given their high frequency). All task regressors were modeled by
453 convolving with the canonical hemodynamic response function (HRF) and high pass filtered (128 s). We
454 then conducted a gPPI analysis across the entire brain using the Shen atlas (Shen et al., 2013) for both Go
455 and Successful stop trials. The gPPI analysis involved deconvolving the time series of each region of
456 interest (ROI) with the hemodynamic response function, multiplying it by the psychological variables of
457 interest to yield a neural level PPI term, and convolving the resulting PPI term with the HRF to obtain the
458 BOLD level PPI effects (Di and Biswal, 2019). Separate GLM models were used to estimate the PPI effect
459 of each ROI for Go trials and Successful stop trials, regressing the eigenvariate of the seed ROI. The GLM
460 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 two behavioural phonotypes, 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.

523 ***2.7 Statistical analysis***

524 ***2.7.1 Exploratory Factor Analysis***

525 To explore the underlying structure of adolescent substance use, we performed an exploratory
526 factor analysis using principal component extraction (Gaskin and Happell, 2014) on TLFB using Predictive
527 Analytics Software (SPSS) version 20. Factor analysis explores the underlying structure of a set of
528 observed variables without imposing a preconceived structure on the outcome. We used six items at age
529 14 and nine items at ages 19 and 23 of TLFB, including alcohol, tobacco, cannabis, cocaine, ecstasy, and
530 ketamine (as shown in Table S21). We excluded items assessing the use of other drugs due to high
531 proportions of missing data, standard deviations close to 0, or a Kaiser-Meyer-Olkin (KMO) statistic for
532 individual variables below 0.5, considered the minimum value for a sample to be adequate. The KMO
533 measure of sampling adequacy was 0.66 at age 14, 0.81 at age 19, and 0.77 at age 23. In addition, all
534 Bartlett's tests of sphericity were significant (Age 14: $\chi^2(15) = 5137.067$, $P < 0.001$; Age 19: $\chi^2(36) =$
535 5031.641, $P < 0.001$; Age 23: $\chi^2(36) = 5106.265$, $P < 0.001$), indicating that there was an underlying
536 correlation structure and that factor analysis was appropriate. We rotated the factors using the varimax
537 method with kaiser normalization to make it easier to discern the underlying measured constructs.

538 ***2.7.2 Linear mixed model***

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

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

544 ***2.7.3 Correlation between network strength and substance use***

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

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

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

571 ***2.7.4 Permutation test***

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

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

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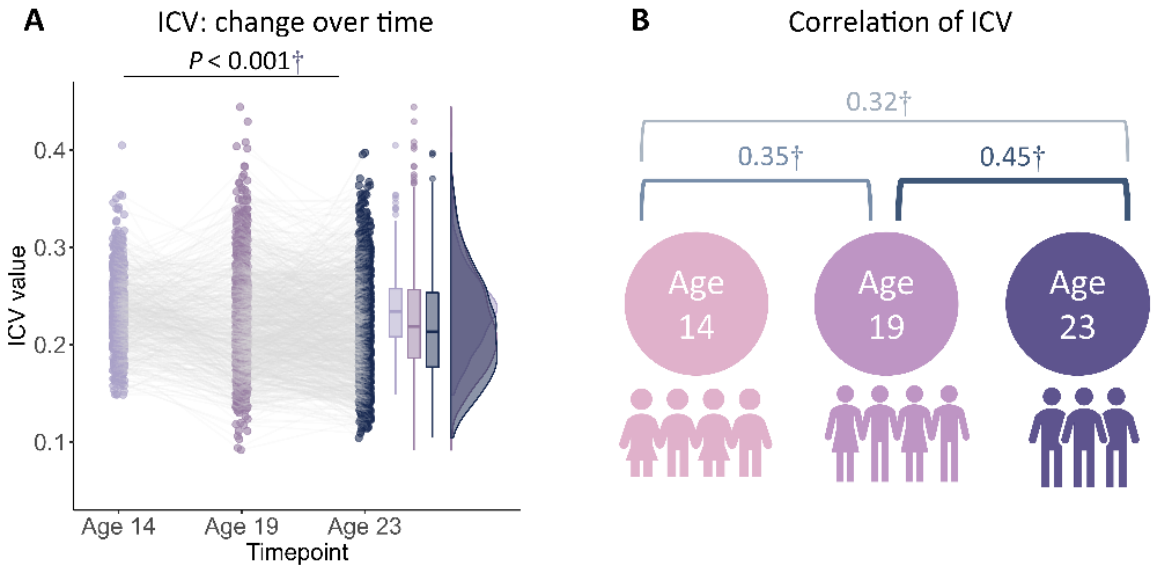
Author contributions:

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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874 **Fig. 1 Intra-individual coefficient of variation (ICV) changes over time. (A)** ICV changes over time. **(B)** Correlation
875 of ICV between timepoints within subjects. †, $P < 0.001$.

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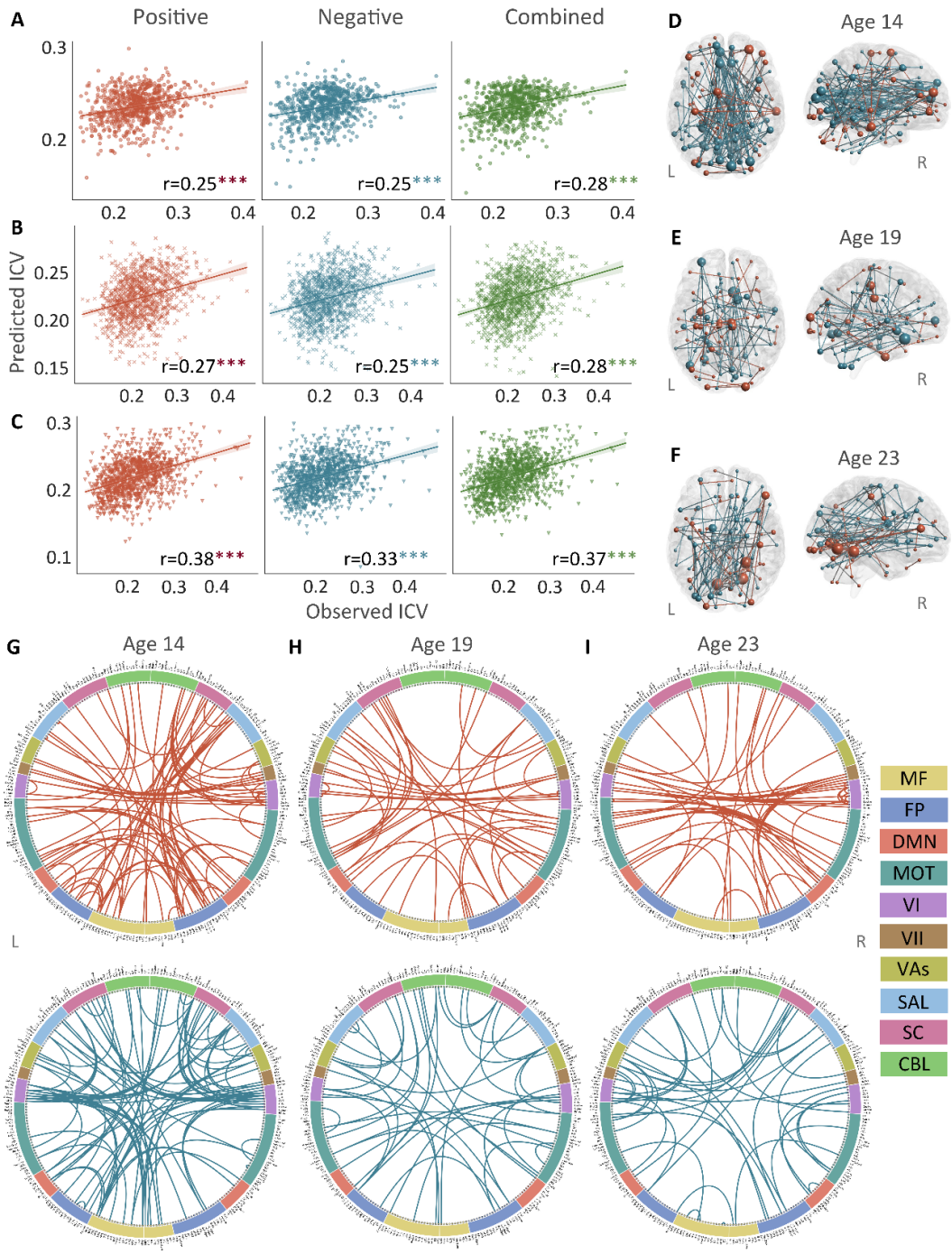


Fig. 2 The predictive performances and networks of intra-individual coefficient of variation (ICV) per timepoint derived from Go trials. Correlation between observed and predicted ICV in positive, negative, and combined networks at **(A)** age 14, **(B)** age 19, and **(C)** age 23. Predictive networks 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. ***, $P < 0.001$.

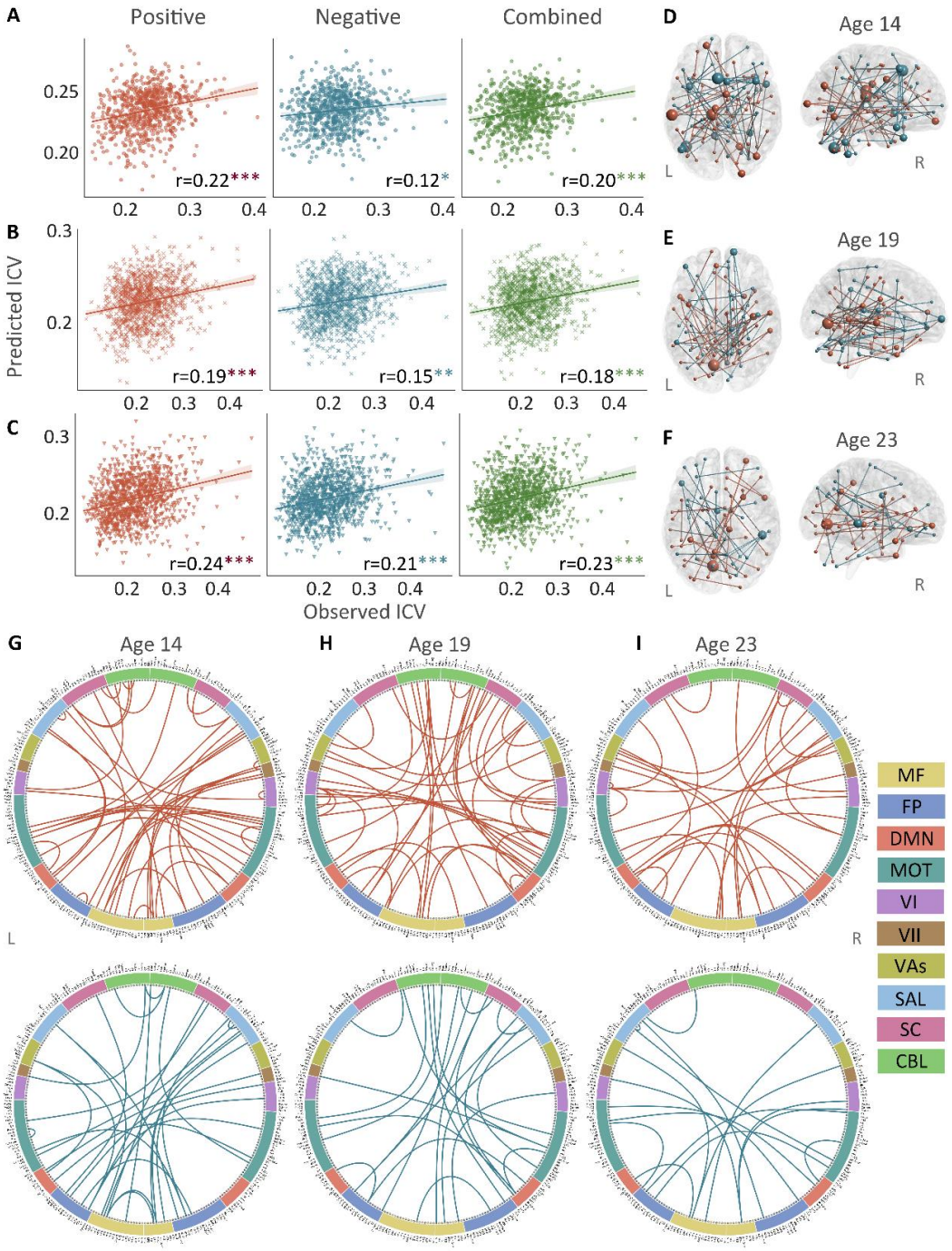


Fig. 3 The predictive performances and networks of intra-individual coefficient of variation (ICV) per timepoint derived from Successful stop trials. Correlation between observed and predicted ICV in positive, negative, and combined networks at **(A)** age 14, **(B)** age 19, and **(C)** age 23. Predictive 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. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

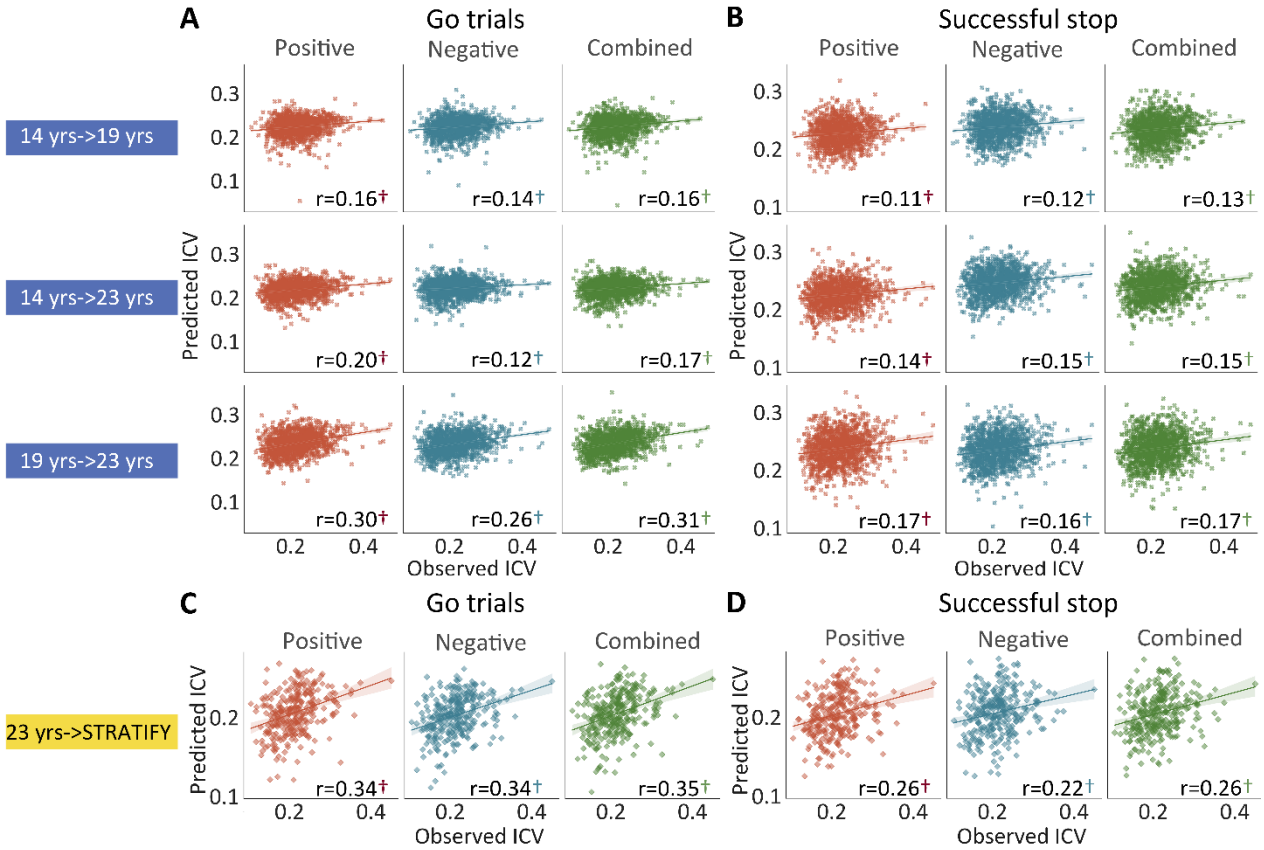


Fig. 4 The predictive performances of intra-individual coefficient of variation (ICV) across timepoints and generalization in STRATIFY. Predictive performances of ICV **(A)** derived from Go trials and **(B)** derived from Successful stop trials. The top, middle, and bottom rows of (A) and (B) panels 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. †, $P < 0.001$.

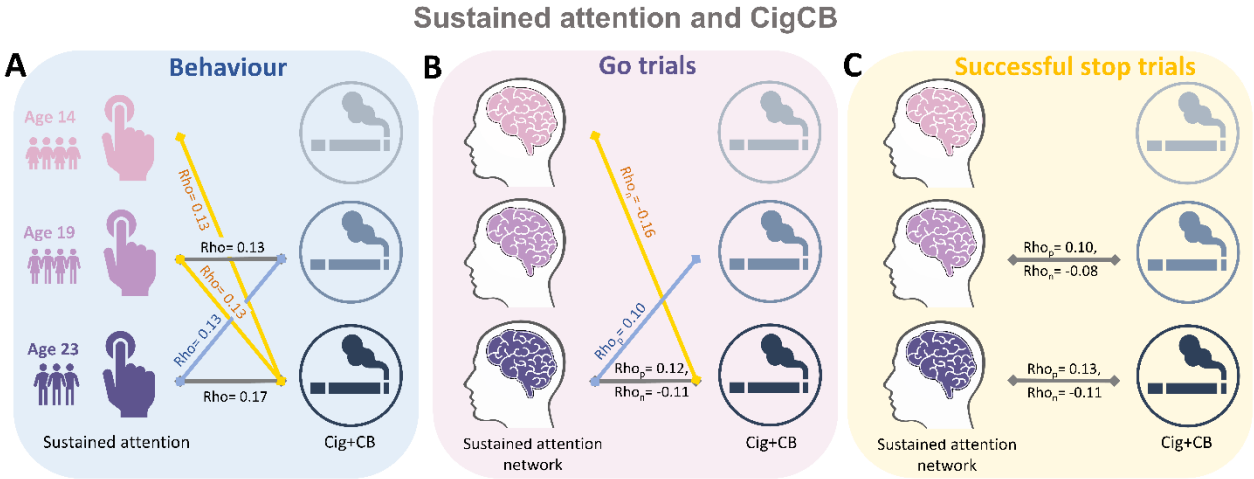


Fig. 5 Significant correlations between sustained attention and substance use across timepoints (FDR correction, q<0.05). (A) Correlations between the intra-individual coefficient of variation (ICV) and Cigarette and cannabis use (Cig+CB) across timepoints. Correlations between sustained attention network 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.

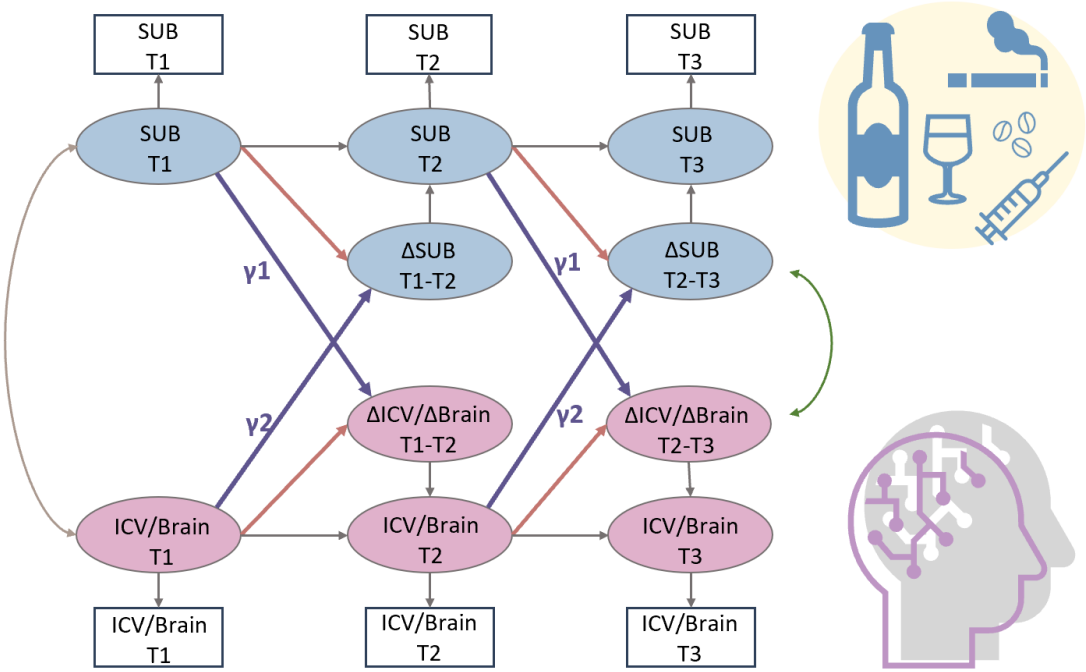


Fig. 6 A simplified bivariate latent change score model for substance use and ICV/brain activity. SUB, substance use (alcohol, cigarette and cannabis use); Brain, brain network strength of positive/negative network of sustained attention derived from Go trials/Successful stop trials. ICV, intra-individual 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.

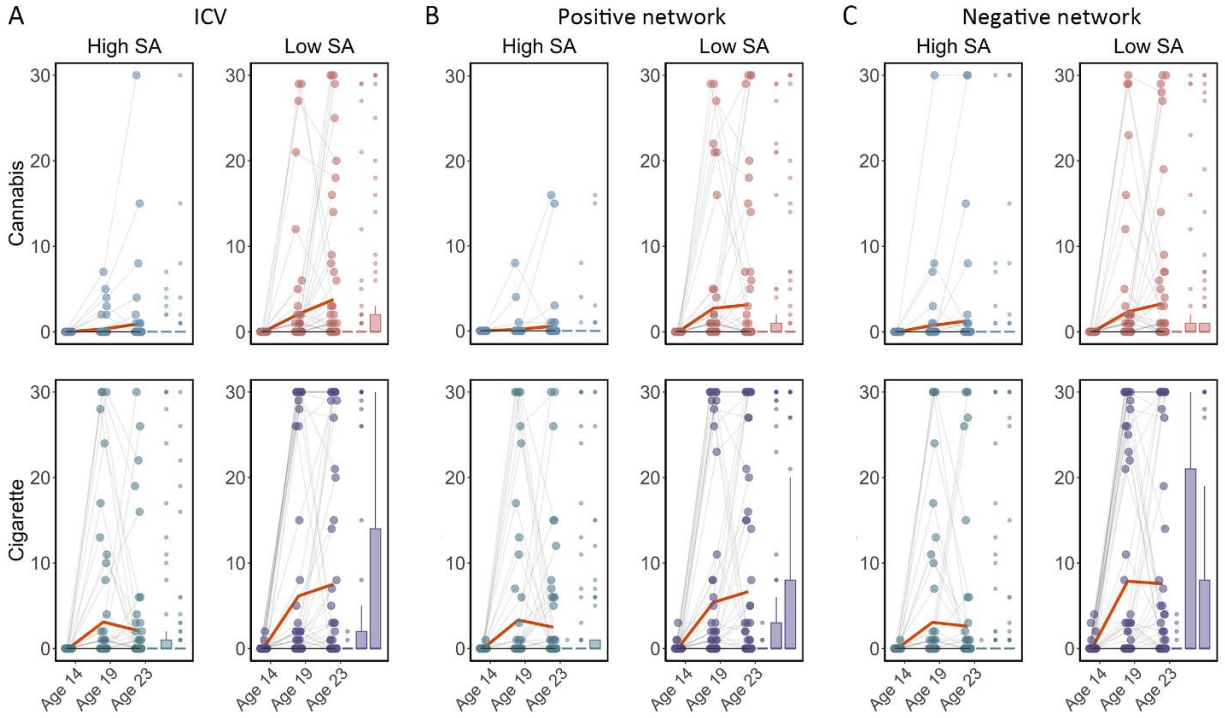


Fig. 7 Cigarette and cannabis score in Timeline Followback changes in individuals with high sustained attention (High SA) and low sustained attention (Low SA) from ages 14 to 23. Participants were categorized into five equal groups based on the intra-individual coefficient of variation (ICV), strength 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.

934 **Table 1. Demographic information of adolescents in the linear mixed model across three timepoints.**

	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

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

940

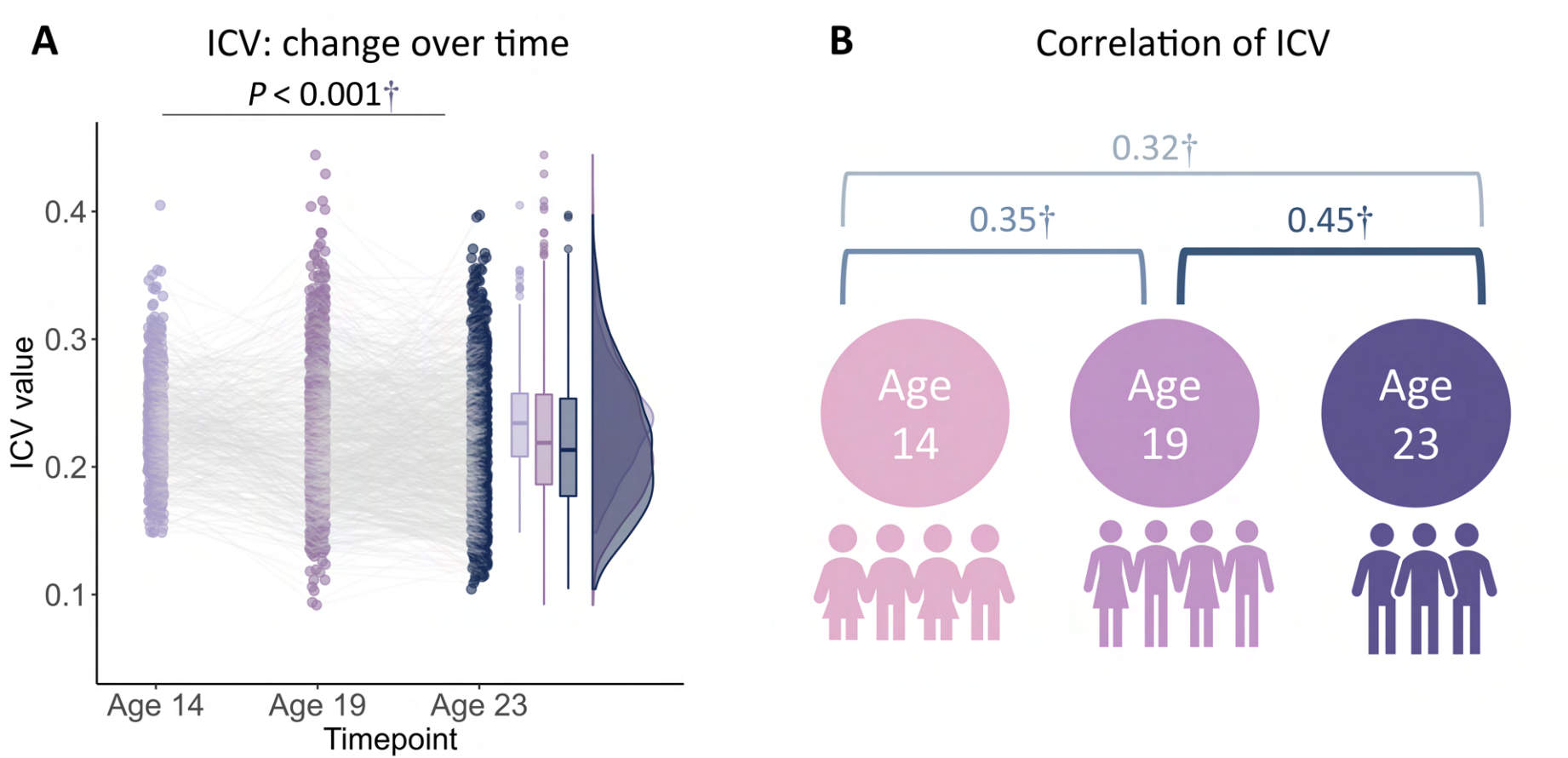
941 **Table 2. Bivariate latent change score model showing the bi-directional association between substance**
942 **use and ICV/brain networks (False Discovery Rate corrected).**

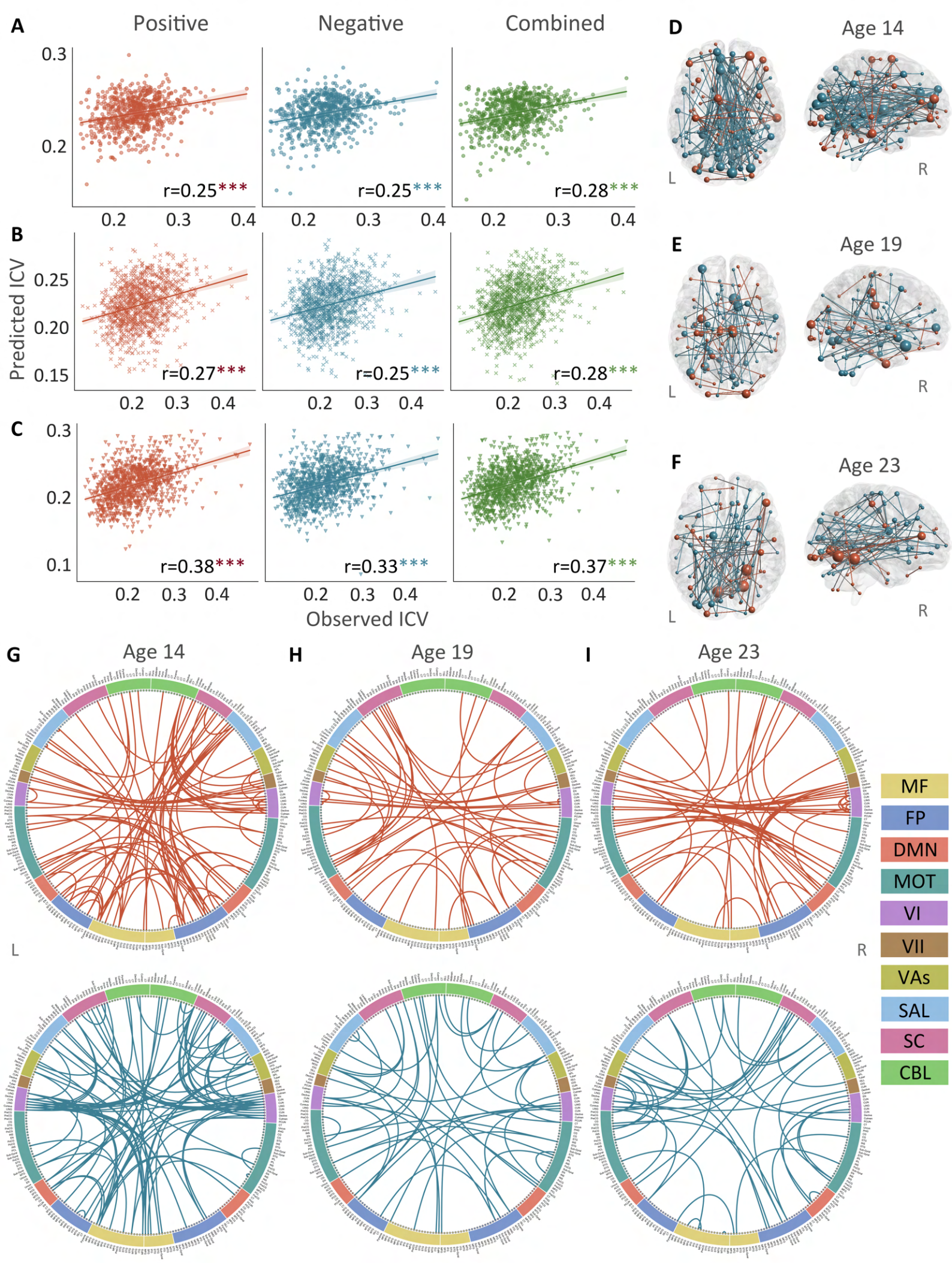
	Cig+CB		Alcohol use	
	Lagged effects of Cig+CB (γ1)	Lagged effects of ICV/brain networks (γ2)	Lagged effects of alcohol use (γ1)	Lagged effects of ICV/brain networks (γ2)
	Std. *β* (SE)	Std. *β* (SE)	Std. *β* (SE)	Std. *β* (SE)
ICV	0.017 (0.039)	**0.117 (0.031)*** **	0.005 (0.029)	0.057 (0.030)
SA GT 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)

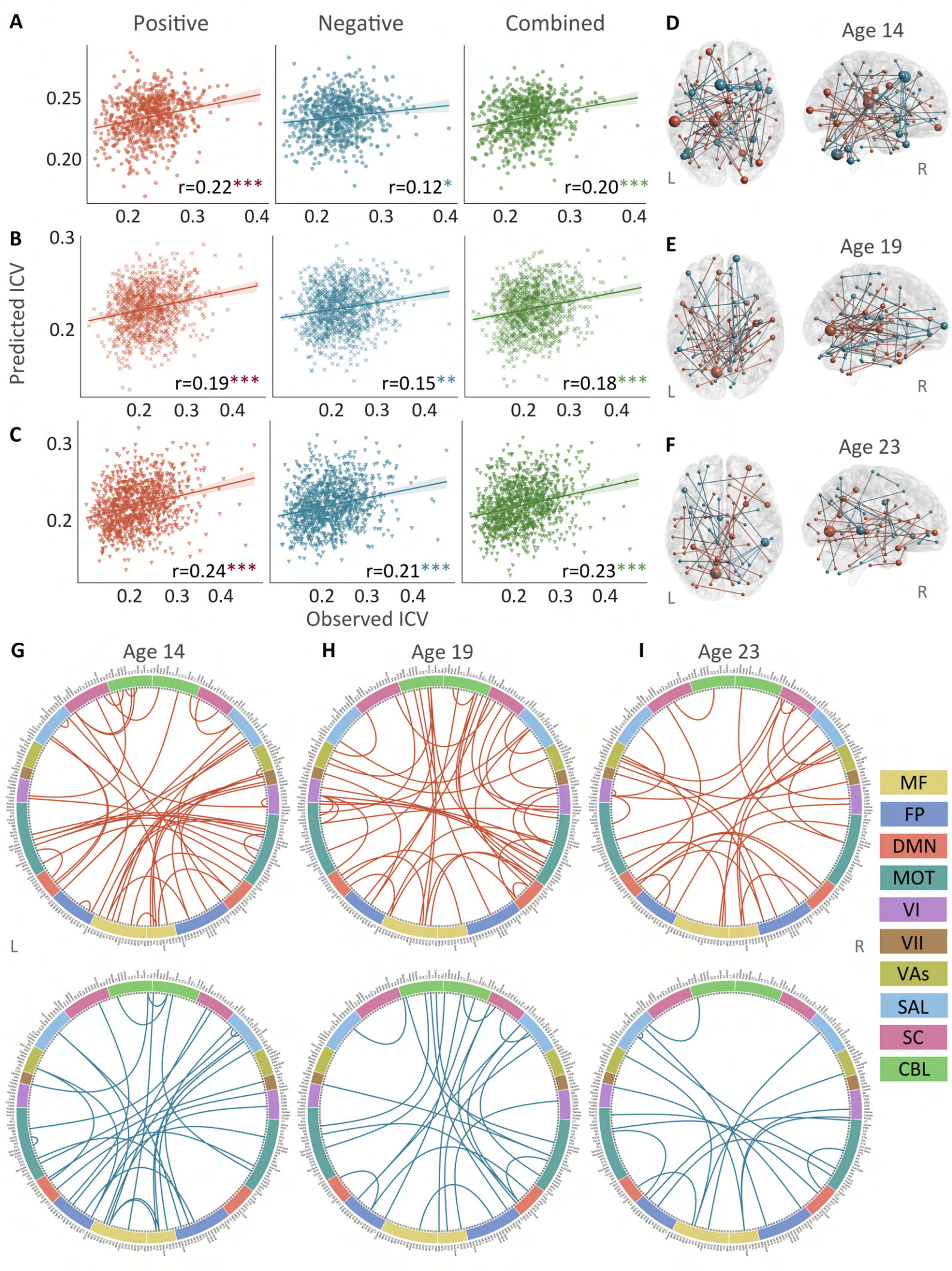
943 **Note:** SA GT, sustained attention network derived from Go trials; SA SS, sustained attention network derived from
944 Successful stop trials; PosNet/NegNet, positive/negative network strength; ICV, intra-individual coefficient of
945 variation; Cig+CB, Cigarette and cannabis use. Bold fonts represent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

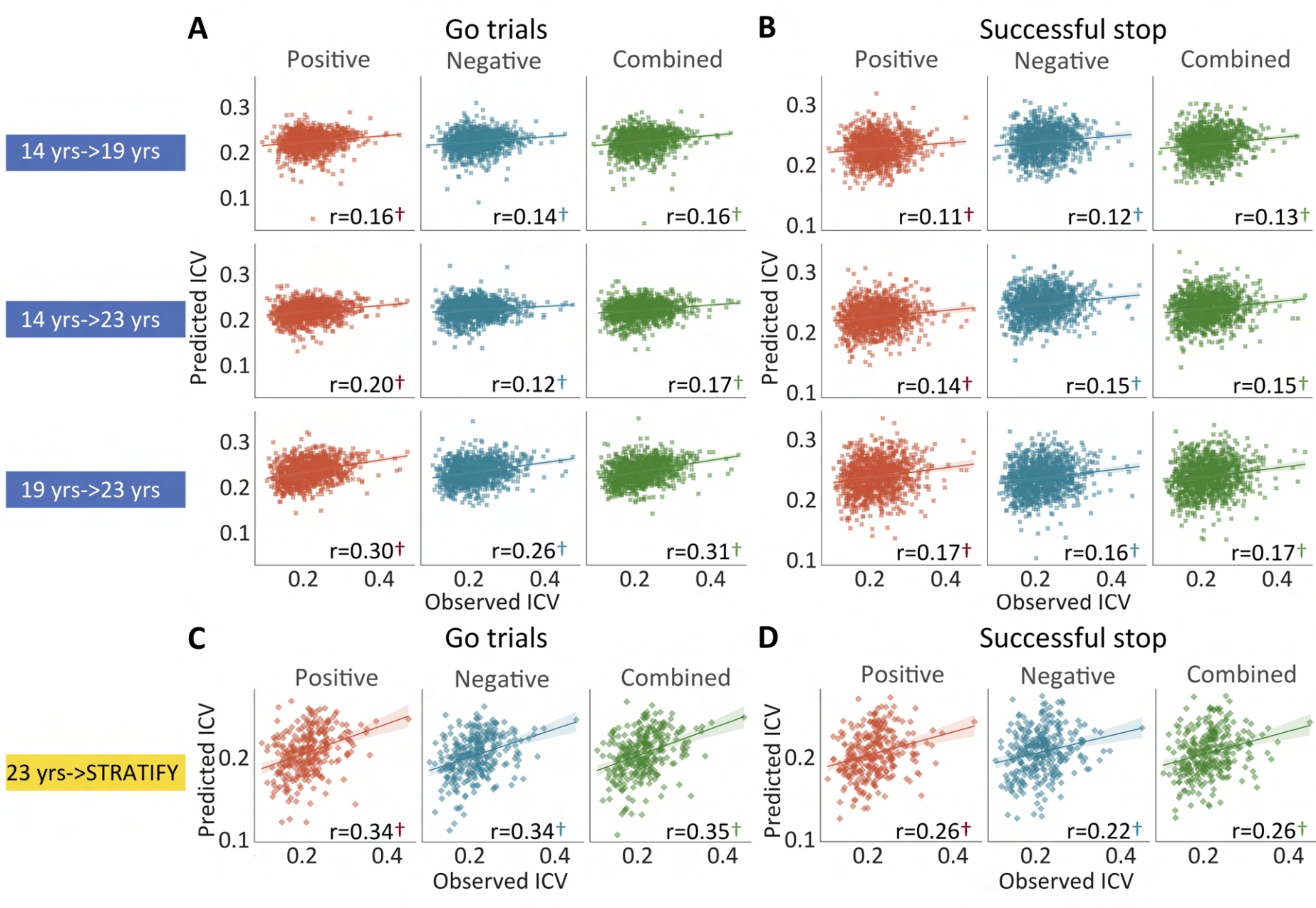
947

948

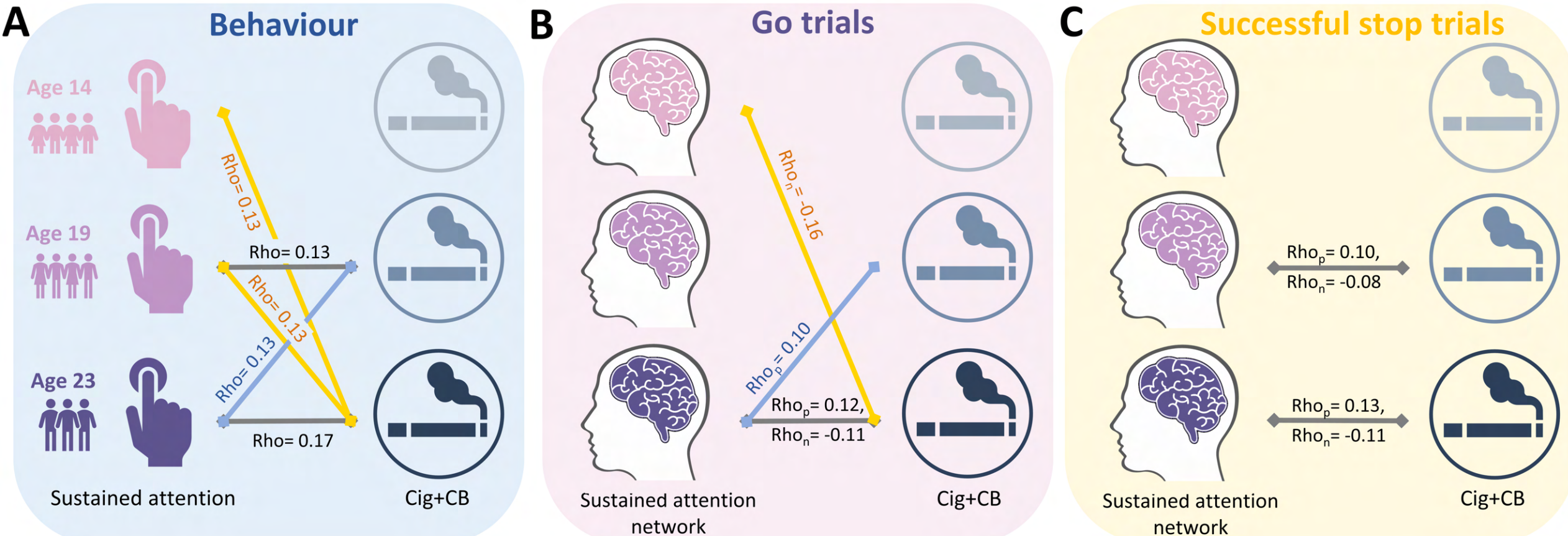

A
ICV: change over time
P < 0.001†
ICV value
0.4
0.3
0.2
0.1
Age 14
Age 19
Age 23
Timepoint
B
Correlation of ICV
0.32†
0.35†
0.45†
Age 14
Age 19
Age 23

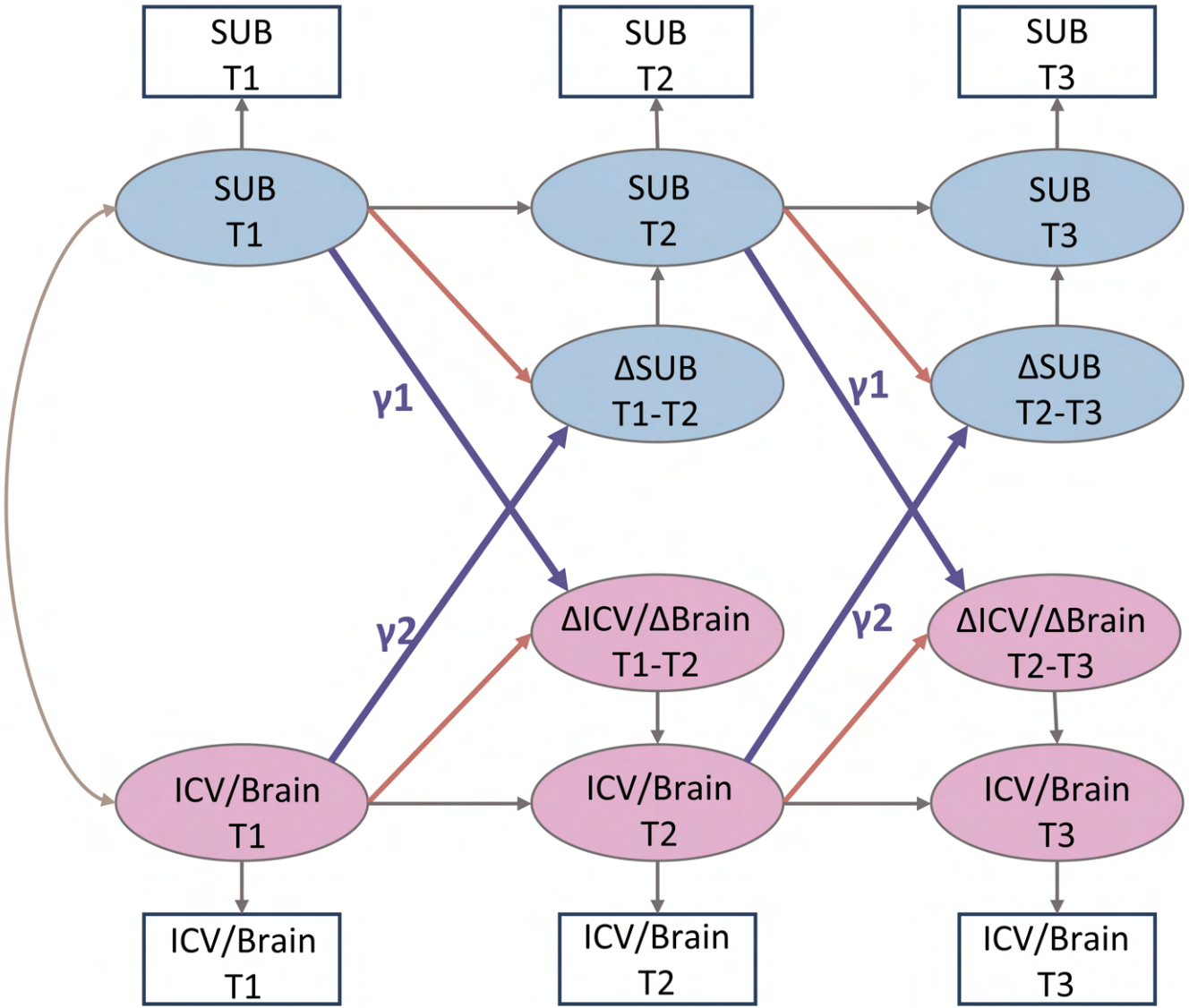

A
Positive
Negative
Combined
r=0.25***
r=0.25***
r=0.28***
B
Predicted ICV
r=0.27***
r=0.25***
r=0.28***
C
r=0.38***
r=0.33***
r=0.37***
Observed ICV
D
Age 14
E
Age 19
F
Age 23
L
R
G
Age 14
H
Age 19
I
Age 23
MF
FP
DMN
MOT
VI
VII
VAs
SAL
SC
CBL

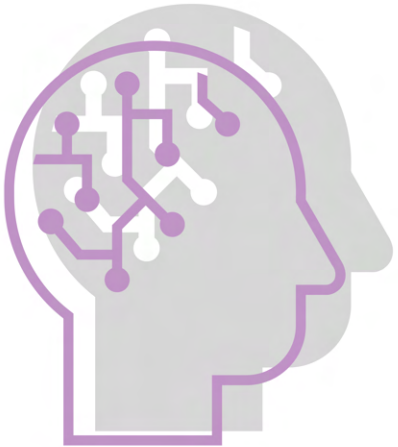

A
Positive
Negative
Combined
0.25
0.20
r=0.22***
r=0.12*
r=0.20***
0.2
0.3
0.4
B
0.3
0.2
Predicted ICV
r=0.19***
r=0.15**
r=0.18***
C
r=0.24***
r=0.21***
r=0.23***
Observed ICV
D
Age 14
L
R
E
Age 19
F
Age 23
G
Age 14
H
Age 19
I
Age 23
MF
FP
DMN
MOT
VI
VII
VAs
SAL
SC
CBL

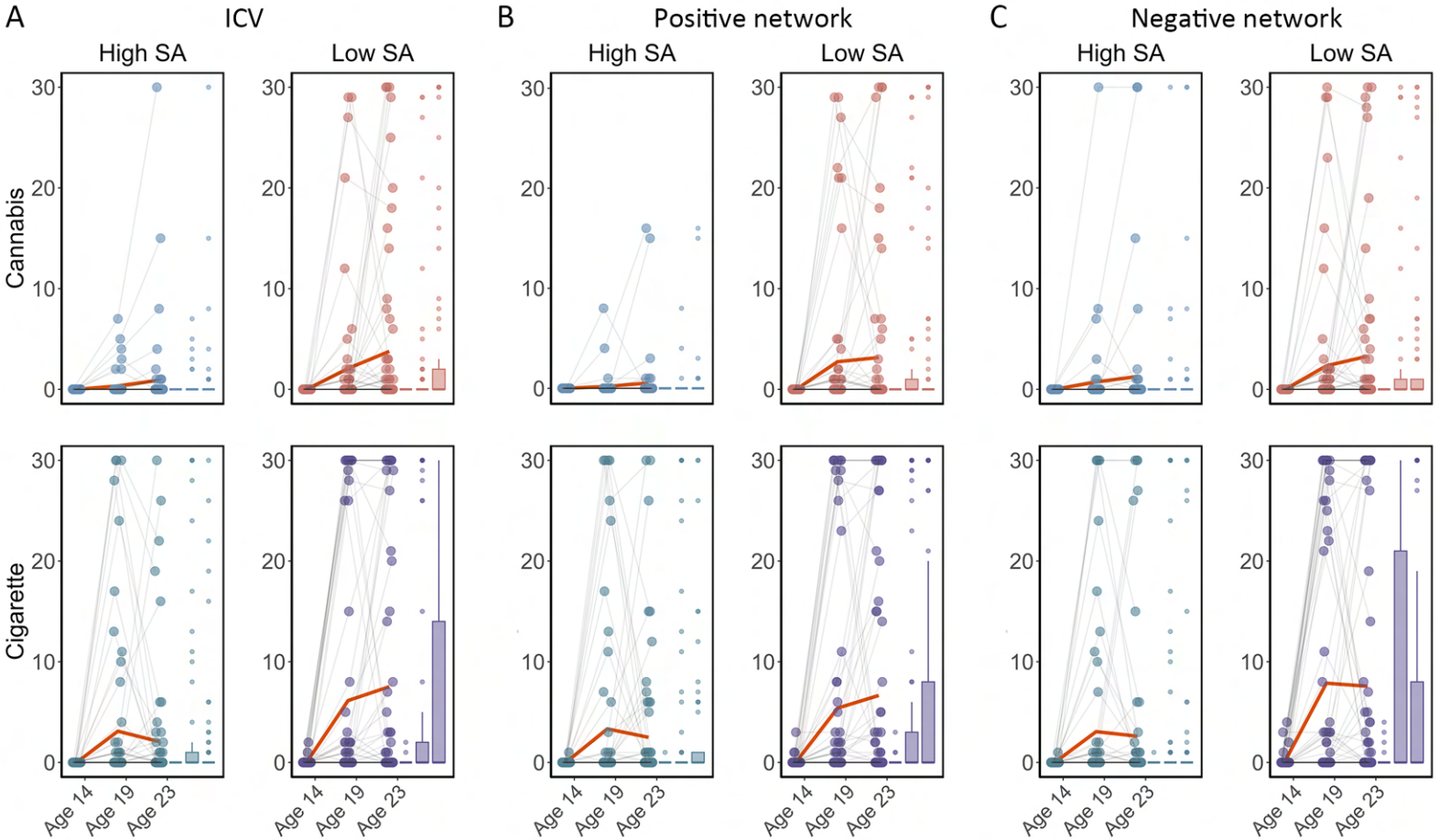

A
Go trials
Positive
Negative
Combined
B
Successful stop
Positive
Negative
Combined
14 yrs->19 yrs
14 yrs->23 yrs
19 yrs->23 yrs
Predicted ICV
Observed ICV
0.1
0.2
0.3
0.2
0.4
r=0.16†
r=0.14†
r=0.16†
r=0.11†
r=0.12†
r=0.13†
r=0.20†
r=0.12†
r=0.17†
r=0.14†
r=0.15†
r=0.15†
r=0.30†
r=0.26†
r=0.31†
r=0.17†
r=0.16†
r=0.17†
C
Go trials
D
Successful stop
23 yrs->STRATIFY
r=0.34†
r=0.34†
r=0.35†
r=0.26†
r=0.22†
r=0.26†

Sustained attention and CigCB




SUB T1
SUB T2
SUB T3
SUB T1
SUB T2
SUB T3
ΔSUB T1-T2
ΔSUB T2-T3
γ1
γ1
γ2
γ2
ΔICV/ΔBrain T1-T2
ΔICV/ΔBrain T2-T3
ICV/Brain T1
ICV/Brain T2
ICV/Brain T3
ICV/Brain T1
ICV/Brain T2
ICV/Brain T3




A
ICV
B
Positive network
C
Negative network
High SA
Low SA
Cannabis
Cigarette
0
10
20
30
Age 14
Age 19
Age 23