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Neural Signatures of Cognitive Control Predict Future Adolescent Substance Use Onset and Frequency

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ABSTRACT

BACKGROUND: Adolescent substance use is a significant predictor of future addiction and related disorders. Understanding neural mechanisms underlying substance use initiation and frequency during adolescence is critical for early prevention and intervention.

METHODS: The current longitudinal study followed 91 substance-naïve adolescents annually for 7 years from ages 14 to 21 years to identify potential neural precursors that predict substance use initiation and frequency. Cognitive control processes were examined using the Multi-Source Interference Task to assess functional neural connectivity. A questionnaire was used to assess substance use frequency.

RESULTS: Stronger connectivity between the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (dlPFC) at time 1 predicted a delayed onset of substance use, indicative of a protective effect. A notable decline in this dACC–dlPFC connectivity was observed 1 year prior to substance use initiation. Conversely, lower connectivity of the dACC with the supplementary motor area and heightened connectivity of the anterior insula with the dorsal medial prefrontal cortex and angular gyrus were predictive of greater frequency of future substance use. These findings remained after controlling for demographic and socioeconomic covariates.

CONCLUSIONS: This study highlights the critical role of cognitive control–related neural connectivity in predicting substance use initiation and frequency during adolescence. The results imply that efforts to strengthen and monitor the development of the top-down cognitive control system in the brain from early adolescence can be protective and deter progression into problematic substance use. Furthermore, for adolescents with heightened frequency of substance use, interventions may prove more effective by targeting interoceptive processes in cognitive control training.

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Adolescence is an important period characterized by heightened susceptibility to risk-taking behaviors, which have implications for substance use (1,2). Research indicates that early initiation and frequent use of substances during this developmental stage can be particularly serious given the rapid changes in the brain. This early substance use is associated with increased risk of developing substance use disorders in adulthood (3) and is often accompanied by significant challenges in both social and professional lives (4,5). National data indicate that approximately 68% of individuals ages 12 to 17 years in the United States reported initiating the use of substances such as cigarettes, alcohol, or marijuana during the past year (6). Given these statistics, identifying neurodevelopmental precursors linked to the risk of early substance use and heavy use during adolescence is crucial (7). In the current study, we analyzed brain data at baseline and within-subject changes over 7 years to identify neural-level precursors that predict substance use onset and frequency upon onset, paving the way for innovative early prevention and intervention strategies.

Previous studies found that adolescents who engaged in substance use showed significant differences in neural activity in several brain regions, including the prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, and parietal cortex (8–11), compared with adolescents who never engaged or engaged at less severe levels. Recent research suggests that substance use during adolescence is linked to imbalanced functional development (12,13), particularly between top-down control and bottom-up limbic networks (14,15). However, it is not clear whether such altered neural activity or functional connectivity among people who use substances reflect predisposing neural vulnerabilities in adolescents or neurotoxic consequences resulting from substance use (16). This uncertainty arises because most studies are based on cross-sectional data or utilize resting-state functional magnetic resonance imaging (fMRI) and lack information on whether and which underlying brain mechanisms may prospectively predict substance use and frequency of use upon onset across development.

To clarify the brain mechanisms that prospectively predict initiation and progression of substance use (16), in the current study, we examined the trajectories of functional connectivity during cognitive control linked to substance use. A growing body of imaging research highlights the crucial role of the dorsal ACC (dACC) and anterior insula (aINS) in substance use and addiction (17,18) because they are important in initiating cognitive control processes in the brain as a part of the salience network (19–21). They play important roles, particularly in sensory gating (21) and conflict resolution (22), by prioritizing relevant information over other sensory inputs. This allows subsequent cognitive control processes to occur appropriately. Therefore, we focused on the connectivity changes of the dACC and aINS to test how the functional connectivity changes of these 2 seed regions are related to substance use onset and frequency. Specifically, we examined whether functional connectivity mechanisms between these 2 regions could effectively predict substance use initiation and frequency upon onset in adolescents who had not previously used substances. Our longitudinal functional connectivity approach not only offers a comprehensive perspective on the evolving neural configurations of the adolescent brain but also enhances the precision of predictions regarding substance use patterns during this crucial developmental phase.

To this end, we used the Multi-Source Interference Task (MSIT), a cognitive control task that consistently activates the dACC and aINS (19,23). We performed generalized psychophysiological interaction (gPPI) analyses with the dACC and aINS seeds to examine whole-brain connectivity during the MSIT and tested the predictability over 7 years for substance use initiation and frequency upon onset in substance-naïve adolescents. Drawing from contemporary theories on brain function and prior studies on substance use involvement, we hypothesized that stronger connectivity of salience network regions (dACC and aINS) with cognitive control–centric regions, such as the dorsolateral PFC (dlPFC), might predict delayed substance use onset and reduced frequency of substance use (8,24).

METHODS AND MATERIALS

Participants

The 91 substance-naïve participants (53% male) at time 1, drawn from the full sample of 138 adolescents (52% male), were included in the analyses. Participants were 14 years at time 1 (mean = 14.06, SD = 0.54; time 7: mean = 21.25, SD = 0.65) (see Table S1 for more information). The criteria for exclusion encompassed conditions such as claustrophobia, a previous head injury causing unconsciousness lasting more than 10 minutes, orthodontic treatments that hindered image capture, and any other factors that would make MRI inappropriate or unsafe.

These adolescents were recruited through e-mail announcements, flyers, and snowball sampling. Data collection took place at university offices where participants completed questionnaires, tasks, and interviews. The study lasted around 5 hours, and participants received monetary compensation. The research was approved by the university's review board, and written consent/assent was obtained from all participants.

Measures

Cognitive Control. Cognitive control processing in the brain was measured by the MSIT (23) at each time point (Figure 1A), with participants performing the task in the MRI scanner. The MSIT has been reported to consistently activate key regions within the salience network such as the dACC and aINS (19,23). In the MSIT, participants view 3 digits and are instructed to identify the unique digit by pressing a corresponding button. In the neutral condition, the position of the distinct digit aligns with its identity. Conversely, in the interference condition, the position and identity of the digit are mismatched, demanding the suppression of task-irrelevant responses to prioritize the goal-directed task (23). By contrasting the interference condition with the neutral condition, neural connectivity associated with the detection of and response to cognitively demanding conflict is assessed, capturing a person's cognitive control ability (25,26). The design of the MSIT in the current study included 4 blocks with 24 trials in each block. Each condition was 42 seconds, with the sequence of conditions being intermittent and alternating between the neutral block and the interference block. The total duration of the task was approximately 5.6 minutes, and the total scan time was 6.5 minutes.

Substance Use Measure. Substance use was evaluated annually using a substance use index (27), from time 1 to time 7. Adolescents rated the typical frequency of smoking cigarettes, using tobacco, consuming alcohol, and using marijuana (e.g., "Which is the most true for you about smoking cigarettes?") on a 6-point scale as follows: 1 (never used), 2 (tried once–twice), 3 (used 3–5 times), 4 (usually use a few times a month), 5 (usually use a few times a week), and 6 (usually use every day). The reliability (Cronbach's α) ranged from 0.60 to 0.75. The substance use score was calculated by summing across nicotine (i.e., maximum score between cigarette and tobacco), alcohol, and marijuana, resulting in a range of 3 to 18. Substance-naïve participants were those with a time 1 substance use score of 3, indicating no prior or current exposure to any of the listed substances. Two variables related to substance use, onset time and frequency upon onset, were entered separately into the general linear model (GLM) for the MRI analysis. The onset time was defined as the first instance when the substance use score exceeded 3, whereas the frequency upon onset referred to the substance use score at that time.

Imaging Acquisition and Analysis

Data Acquisition and Preprocessing. See the Supplement.

GLM for Cognitive Control Task. The preprocessed MRI data underwent analysis by being entered into a first-level GLM. In this GLM, interference and neutral blocks were modeled using boxcars convolved with the canonical hemodynamic response function alongside 6 motion regressors and framewise displacement (FD) regressors. To calculate FD, rotational displacement was converted to millimeters using a sphere's surface with a radius of 50 mm. Volumes with FD $>$ 0.9 mm were modeled by incorporating a volume-specific regressor for each flagged volume in the GLM. This

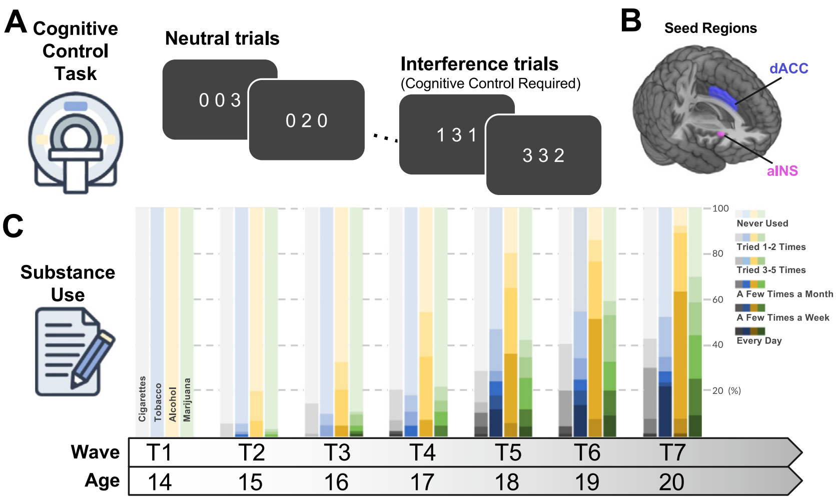

Figure 1. Overview of the current study design and substance use frequency in adolescents. The figure presents an overview of the experimental design utilized to examine the relationship between functional connectivity and substance use in adolescents over 7 consecutive years (T1–T7). **(A)** The top panel illustrates the Multi-Source Interference Task (MSIT) that participants underwent in a magnetic resonance imaging scanner, which is composed of neutral trials and interference trials that require cognitive control. **(B)** Regions of interest: dorsal anterior cingulate cortex (dACC) and anterior insula (aINS). **(C)** The bottom panel depicts the substance use patterns in participants, ages 14 to 20 years, with color-coded frequencies indicating usage from never used to used every day. The study tracks the evolution of these variables across time, revealing neural signatures of future substance use onset and frequency in adolescents.

approach allowed simultaneous analysis of repeated-measures data. The GLM generated an "interference greater than neutral" contrast map by subtracting the neutral beta map from the interference beta map.

gPPI Analysis. gPPI was used to investigate whether cognitive control task–dependent connectivity with the dACC and aINS seeds could predict the future onset time and frequency of substance use during adolescence. The gPPI functional connectivity analyses were conducted using the gPPI toolbox v.13 (28) in SPM8. Two separate models were created at the individual subject level, focusing on 2 seed regions, i.e., the dACC and aINS. The dACC seed region was defined based on a 50% probability threshold from the Harvard-Oxford cortical structural atlas (https://neurovault.org/collections/262/) and Neuromorphometrics atlas[1] distributed with SPM (Figure 1B). The bilateral aINS region was functionally defined based on the interference effect (interference minus neutral) during the MSIT using a longitudinal group-level model from our previous study, which demonstrated measurement invariance across development (29). The coordinates [−30, 14, 13] and [33, 20, 7] in Montreal Neurological Institute (MNI) space, with each defined as a 5-mm sphere, were derived from this prior work (Figure 1B).

The first-level gPPI GLM included psychological regressors for task conditions (interference and neutral conditions), time-series data from the seed region, and interaction terms for the task conditions. The contrast between the interference and neutral conditions was then analyzed in a second-level GLM to perform group analysis. The onset time and frequency upon onset of substance use in individuals were included as a covariate in two separate second-level GLMs to identify potential neural indicators predicting the onset year and frequency of substance use. Given that these are seed-based whole-brain analyses, we applied a voxel-level threshold of $p < .01$ and a familywise error (FWE) cluster-level correction at $p < .05$ at the whole-brain level.

[1]The Neuromorphometrics tissue labels are derived from MRI scans in the OASIS project (https://www.oasis-brains.org/) and are provided by Neuromorphometrics Inc. Available at: https://neuromorphometrics.com/ under academic subscription (also see https://github.com/neurodebian/spm12/blob/master/spm_templates.man).

RESULTS

Transition of Substance Use Across 7 Years

Of the 91 substance-naïve adolescents at time 1, 78 reported varying levels of substance use over the following 6 years. A substantial portion of substance use onset time occurred during time 2 and time 3, collectively representing 24% of the sample (Figure 1C). Upon onset, the frequency of substance use was at the "try" level (i.e., once or twice) for a single substance (i.e., substance use score = 4, 37% of the sample), and the substance use score increased over time across all substances.

dACC Seed Connectivity Predicting Future Substance Use Onset Time and Frequency Upon Onset

Predicting Future Substance Use Onset Time From Time 1 Connectivity. The whole-brain connectivity analysis revealed that substance use onset time was significantly predicted by dACC-dlPFC connectivity (Table 1, Figure 2A, and Figure S1; $p_{FWE} = .010$, $k = 255$, $\beta = 0.423$). That is, higher dACC-dlPFC connectivity at time 1 predicted a delayed onset of substance use over the following 6 years. The prediction remained significant after controlling for demographic and socioeconomic covariates (i.e., sex, age, race, ethnicity, and income-to-needs ratio) ($\beta = 0.418$, $p < .001$) (Table S2).

A Decline in dACC-dlPFC Connectivity Prior to Substance Use Onset Time. In the analysis described above, a robust association was observed between stronger dACC-dlPFC connectivity at time 1 and delayed onset of substance use during the subsequent 6 years, suggesting protective effects (i.e., protective against early onset during adolescence) of the functional connectivity between dACC and dlPFC. To

Table 1. Regions With Significant Connectivity to dACC Seed in Substance-Naïve Brains at Time 1 Predicting Substance Use Onset Time

Seed	Cluster No.	Region	*k*	p_{FWE}	β	MNI [X, Y, Z]	*t*
dACC	1	R middle frontal gyrus, BA 9	255	.010	0.423	[36, 32, 25]	4.09
		R middle frontal gyrus, BA 6	–	–	–	[30, 14, 49]	3.45

β refers to standardized coefficients of the significant connectivity that predicted future substance use initiation, *k* indicates the number of voxels in the cluster, and *t* indicates the *t* value reported for peak voxels. Pick-defining threshold: $p_{uncorrected} < .01$. Cluster-defining threshold $p_{FWE} < .05$.

BA, Brodmann area; dACC, dorsal anterior cingulate cortex; FWE, familywise error; MNI, Montreal Neurological Institute; R, right.

explore whether alterations in this connectivity could predict substance use initiation, we compared the dACC-dlPFC connectivity change between substance-naïve brains at time 1 and each year before or after any reported substance use. We recentered the time variables to the year of substance use onset rather than chronological age to compare changes in dACC-dlPFC connectivity between time 1 and each of the 4 years prior to onset, the onset year, and 1 year after onset (6 time points). The results revealed a significant decline in dACC-dlPFC connectivity strength between time 1 and 1 year prior to substance use initiation, $t_{44} = -2.819$, Cohen's $d = -0.420$, $p = .007$ (Figure 2B, C), even with Bonferroni adjustment ($p < .008$). Notably, 71.11% of participants (32 of 45) showed this decline in connectivity. Except for the 1 year prior to substance use onset, all other connectivity changes from time 1 were not significant (*p*s $>$ .607). This finding demonstrates that a decrease in dACC-dlPFC connectivity strength during the preceding year of substance use onset may be a significant precursor to the initiation of substance use. To ensure that the result was not due to chronological age effects, a series of paired *t* tests comparing time 1 with each subsequent time point were conducted, but they yielded no significant differences (Table S3).

Predicting Future Substance Use Frequency Upon Onset From Time 1 Connectivity. Using dACC as a seed, the results revealed a significant inverse prediction of the frequency of future substance use by supplementary motor area (SMA) regions (Table 2, Figure 3A, and Figure S2A) ($p_{FWE} = .003$, $k = 323$, $\beta = -0.468$). This finding suggests that stronger dACC-SMA connectivity at time 1 is associated with lower frequency of substance use upon onset during the subsequent years. This association persisted even when we controlled for participants' demographic and socioeconomic characteristics ($\beta = -0.438$, $p < .001$) (Table S4).

aINS Seed Connectivity Predicting Future Substance Use Onset Time and Frequency Upon Onset

Predicting Future Substance Use Onset From Time 1 Connectivity. No significant clusters were identified using the aINS seed.

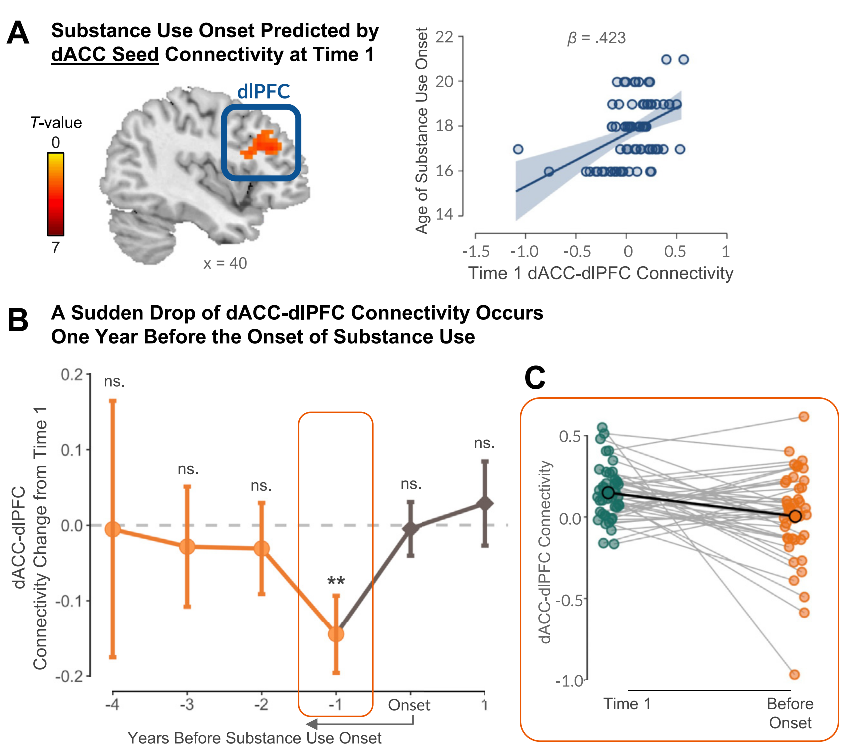

Figure 2. Dorsal anterior cingulate cortex (dACC)–dorsolateral prefrontal cortex (dlPFC) connectivity as a predictor of substance use onset time. The figure illustrates the role of the dACC to dlPFC connectivity in relation to the onset of substance use. **(A)** Whole-brain regression analysis shows an association between higher dACC-dlPFC connectivity at time 1 and a delay in the age at first substance use. The scatter plot is presented solely for illustrative purposes, displaying a positive association between dACC-dlPFC connectivity and the age at first substance use. The translucent area surrounding the fit line indicates the 95% CI. **(B)** The data points in orange depict the trajectory of dACC-dlPFC connectivity before the onset of substance use, showing a decline 1 year prior. The data points in gray depict dACC-dlPFC connectivity at and after substance use onset. Error bars represent the standard error. **(C)** A spaghetti plot shows individual trajectories of dACC-dlPFC connectivity from time 1 to 1 year before substance use onset. $^{**}p < .01$. ns., nonsignificant.

Table 2. Connectivity of Time 1 Substance-Naïve Brain Predicting Future Substance Use Frequency Upon Onset

Seed	Cluster No.	Region	*k*	p_{FWE}	β	MNI [X, Y, Z]	*t*
dACC	1	R middle frontal gyrus, BA 6	323	.003	−0.466	[33, −4, 49]	−4.26
		R subgyral, BA 6	–	–	–	[30, −4, 58]	−3.83
Insula	1	R medial frontal gyrus, BA 9	311	.004	0.441	[9, 41, 31]	4.67
		R medial frontal gyrus, BA 8	–	–	–	[12, 35, 46]	3.81
		R superior frontal gyrus, BA 9	–	–	–	[18, 56, 34]	3.46
	2	R precuneus, BA 19	320	.003	0.422	[42, −73, 40]	4.44
		R inferior parietal lobule, BA 40	–	–	–	[45, −55, 40]	4.05
		R supramarginal gyrus, BA 40	–	–	–	[57, −46, 37]	3.78

β indicates standardized coefficients of the significant connectivity that predicted future substance use frequency, *k* indicates the number of voxels in cluster, and *t* indicates the *t* value reported for peak voxels. Pick-defining threshold: $p_{uncorrected} < .01$. Cluster-defining threshold $p_{FWE} < .05$.

BA, Brodmann area; dACC, dorsal anterior cingulate cortex; FWE, familywise error; MNI, Montreal Neurological Institute; R, right.

Predicting Future Substance Use Frequency Upon Onset From Time 1 Connectivity. Analyses with the aINS seed demonstrated significant positive prediction of the frequency of future substance use by the connectivity from aINS to the dorsal medial PFC (dmPFC) (Table 2, Figure 3B, and Figure S2B) (p_{FWE} = .004, *k* = 311, β = 0.440) and angular

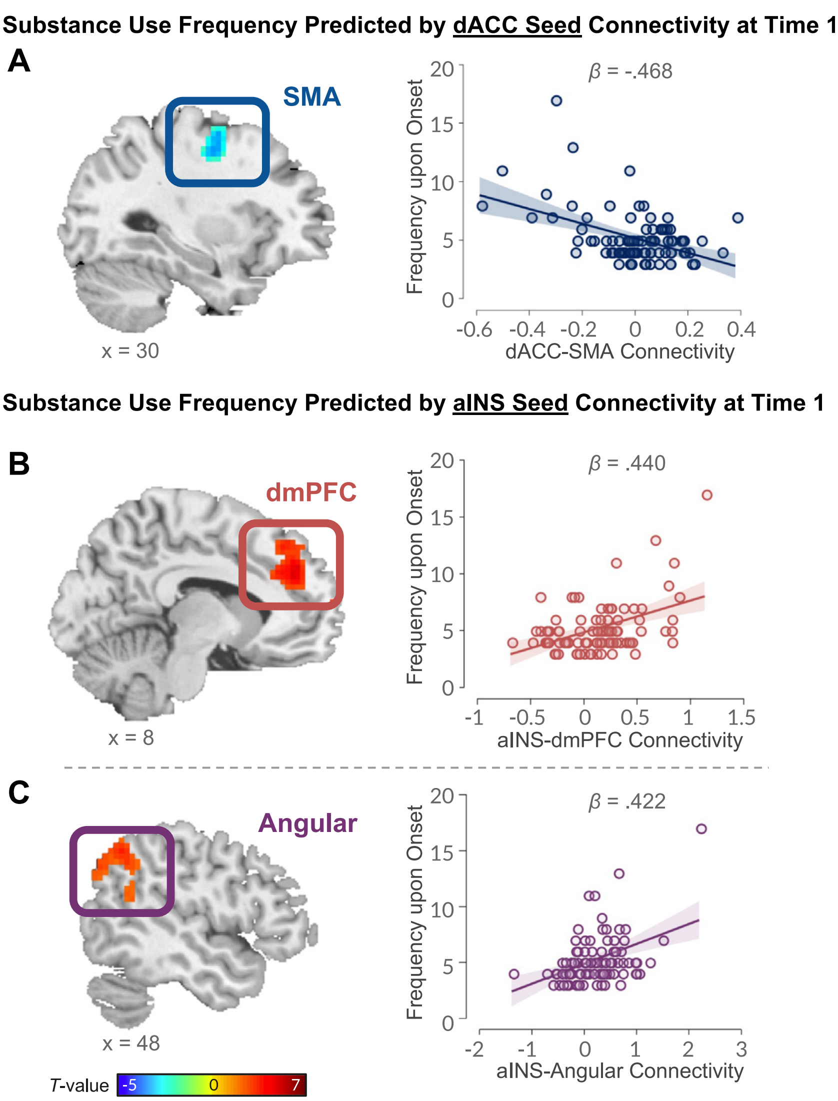

Figure 3. Predictive correlations between time 1 connectivity and future substance use frequency upon onset. The figure illustrates the role of the dorsal anterior cingulate cortex (dACC) and anterior insula (aINS) seeds connectivity in predicting substance use frequency upon onset. **(A)** Whole-brain regression analysis showed that the higher dACC connectivity to the supplementary motor area (SMA) at time 1 is associated with lower substance use frequency upon onset. **(B)** Whole-brain regression analysis showed that higher aINS connectivity to the dorsomedial prefrontal cortex (dmPFC) at time 1 is associated with higher substance use frequency upon onset. **(C)** Whole-brain regression analysis showed that higher aINS connectivity to the angular gyrus at time 1 is associated with higher substance use frequency upon onset. Note: The scatter plot is presented solely for illustrative purposes. The translucent area surrounding the fit line indicates the 95% CI.

gyrus regions (Table 2, Figure 3C, and Figure S2B) (p_{FWE} = .003, k = 320, β = 0.422). These findings indicate that higher aINS-dmPFC connectivity and higher aINS–angular connectivity at time 1 predicted higher frequency of substance use upon onset in the following 6 years. These correlations remained significant after adjusting for demographic and socioeconomic covariates (βs = 0.403 to 0.440, $ps < .001$) (Tables S5 and S6).

Robustness Check

We validated the robustness of predictability of the identified connectivity using bootstrap with replicates and leave-one-out cross-validation (Table S7 and the Supplement).

Supplementary Analyses of Individual Substance Use Behaviors

Analyses examining the predictive association between the identified connectivity at time 1 and individual substance use behaviors (nicotine, alcohol, and marijuana) showed that the most specific subtypes of substance use behaviors remain predictably associated in the same direction with the identified connectivity patterns (Tables S8 and S9 and the Supplement).

Sensitivity Analysis Using Resting-State fMRI

We examined whether the predictability of the functional connectivity identified in the main analysis was intrinsic or task dependent by conducting a sensitivity analysis using resting-state fMRI. Results revealed that none of the resting-state connectivity values predicted future substance use onset time or frequency upon onset (Figure S3 and the Supplement).

Cognitive Control Behavioral Performance

Our data suggest a decline prior to the onset in neural connectivity but not in behavioral performance (Tables S10 and S11 and the Supplement for correlations and age-related changes).

DISCUSSION

This study elucidates the critical role of functional connectivity derived from cognitive control processes in predicting adolescent substance use, a known risk factor for later addiction. Our findings suggested that stronger dACC-dlPFC connectivity at time 1 predicted delayed substance use onset, indicating a protective role. Furthermore, there was evidence that a marked decline in this dACC-dlPFC connectivity 1 year prior to substance use onset might have served as a precursor to initiation. Additionally, lower dACC-SMA connectivity and heightened aINS-dmPFC and aINS–angular connectivity at time 1 were linked to higher future substance use frequency upon onset. These findings were specific to connectivity patterns during the cognitive control task because resting-state connectivity did not significantly predict substance use outcomes. The results underscore the significant role of cognitive control–related brain functioning underlying risky substance use during adolescence.

Our findings highlight the important role of strong dACC-dlPFC connectivity in substance-naïve adolescents. This connectivity strength predicted delayed substance use onset, whereas its notable decline marked a potential risk for substance use initiation within a year. The dACC is implicated in modulating cognitive resources, especially when a task demands enhanced control (30). The dlPFC is known for its involvement in cognitive control such as top-down adjustment of response inhibition (31) and is also known as a regulator of adolescent risky decision making (32). Furthermore, the coactivation of the dACC and dlPFC has been proposed by the theoretical model regarding the top-down control of the prefrontal cortex, as suggested by Miller and Cohen (33). Research has supported this model by showing that the dACC detects conflict signals that are resolved by biased allocation of top-down control in the dlPFC (34,35). Although they did not examine functional connectivity directly, recent meta-analyses also indicate that dACC and dlPFC coactivation is crucial in risk-taking behaviors (36,37). Additionally, a systematic review on neural correlates of risk-taking in substance-related behaviors found that dlPFC activation decreases and dACC activity increases during risk-taking (38). Extending those prior findings and supporting the proposed model of top-down control of the prefrontal cortex (33), our research clarifies that strengthened functional connectivity of the dACC with the dlPFC may serve as a signature protective factor of cognitive control against early substance use initiation.

A sudden decline in dACC-dlPFC connectivity during the year preceding substance use onset predicted initiation during the following year. There is evidence that dACC-dlPFC connectivity decreases with cognitive fatigue (39), suggesting that the decline in our study may reflect the peak of cognitive strain prior to the onset of substance use, potentially signaling an impending failure in controlling substance use initiation. Interestingly, we also observed a restoration of this connectivity to baseline levels at the onset of use, which could be due to the dissipation of cognitive fatigue once substance use begins. It is also possible that this restoration may reflect a shift between the initiation and progression phases, engaging different neural circuits. Similar patterns were observed in a previous study of adolescents, where frontal activation returned to baseline after substance use began, suggesting adaptive changes in brain circuitry (9). However, further research is needed to explore how these connectivity patterns evolve as substance use progresses.

The study also highlights the role of strong dACC-SMA connectivity in predicting lower substance use frequency upon onset. This finding is consistent with previous research on the role of the SMA in cognitive control, particularly its function in regulating internal states together with its role in motor control (40). In studies of adolescent substance use, reduced activation of the SMA during cognitive control tasks has been linked to heavier smoking (41), whereas higher SMA activation during cognitive control has been associated with heavy drinking and alcohol-related blackouts, indicating functional compensation (11). Furthermore, our finding suggests that enhanced dACC to SMA connectivity during cognitive control may serve as a neural protective factor, predicting reduced frequency of future substance use during adolescence.

Conversely, our data indicate that increased insular connectivity may significantly influence substance use progression, consistent with theories that the insula gates and integrates sensory signals to direct motivated behavior (20).

This involves processing interoceptive cues such as cravings and pain, which is crucial in developing drug addiction (18,42,43). Specifically, heightened insula connectivity with regions implicated in sensory and social-emotional processing—the dmPFC, which is involved in self-referential thought and emotional processing (22,44), and the angular gyrus, which is involved in integrating sensory information and social cognition (45,46)—predicted heightened substance use frequency upon onset. This finding is corroborated by previous research showing that insula lesions often led to addiction remission (47) and that alterations in connectivity involving the dmPFC and the angular region tend to result in relapse in substance use disorders (48). To our knowledge, our findings present the first evidence that heightened insula connectivity with the dmPFC and the angular gyrus in substance-naïve adolescents represents a neural risk factor associated with higher frequency of future substance use at initiation.

Behavioral studies have posited that heightened reward sensitivity during adolescence may underlie substance use tendencies, while also highlighting the potential of cognitive control as an early prevention strategy, suggesting that cognitive control could modulate reward sensitivity to deter adolescent substance use (49,50). However, existing behavioral research demonstrates that the direct predictions of adolescent substance use from cognitive control have often been nonsignificant or shown weak effect sizes (51). A review of neuroimaging studies indicated hyperactivation in reward-processing regions (e.g., striatum), rather than cognitive control–related activation in prefrontal regions, as a brain vulnerability factor for substance use (52). This review primarily included studies of young people with a family history of substance use disorders, with only a subset using cognitive control tasks. This heterogeneity in task types and sample likely contributed to the discrepancies in findings. Complementarily, the current prospective analyses, which focused on within-person changes during the crucial developmental period of adolescence, bring cognitive control neural mechanisms into the spotlight. They revealed that dACC-dlPFC connectivity serves dual roles: as a protective factor, where its stronger connectivity predicts delayed substance use onset, and as a risk factor, where its sudden decline predicts substance use onset within a year. These results highlight that both the level and change in neural connectivity underlying cognitive control could be important and direct predictors of risky substance use behaviors.

From a theoretical perspective, our research elaborates on the triple network model by underscoring the role of the salience network in initiating cognitive control (53). Specifically, our findings demonstrate how the dACC and aINS within the salience network, known for conflict monitoring and sensory integration, respectively (19–21), interact with the central executive network (i.e., dlPFC) and the default mode network (i.e., dmPFC and angular) to influence cognitive control. In addition, our findings reveal functional distinctions between the dACC and aINS: the dACC, by recruiting the dlPFC, is more sensitive in predicting behaviors related to substance use, demonstrating how the salience network collaborates with the central executive network to support top-down regulatory control (33–35). In contrast, the aINS, in coupling with the dmPFC and angular, is associated with bottom-up emotional processing (22,44). Although aINS connectivity does not directly predict the onset of substance use, it suggests a potential circuit through which the salience network interacts with the default mode network, offering important insights for predicting substance use frequency. This functional connectivity analysis deepens our understanding of the interactions of the salience network with other neural networks and offers new insights into adolescent substance use development.

From a methodological perspective, the study underscores the importance of integrating cognitive control in predicting substance use onset and frequency. Adolescence is a particularly vulnerable period of neurodevelopment characterized by increased risk-taking behavior, including substance use. However, the link between adolescent substance use and aberrant brain function, whether due to neurotoxic effects or preexisting neural vulnerabilities, remains unclear (29). Research reported to date, which has often been limited by cross-sectional designs (7) or a focus on adult populations (54), has not fully explored these developmental dynamics. This study's longitudinal design, which tracked substance-naïve adolescents over 7 years, facilitated a comprehensive analysis. It assessed not only between-person differences at baseline but also within-person changes, predicting future substance use initiation within the developmental window of adolescence. This supports the hypothesis of preexisting neural vulnerabilities.

Additionally, this study used robust statistical methods (leave-one-out cross-validation and bootstrapping) to ensure the reliability of its predictions (55). Despite these strengths, although we used longitudinal data, the correlational nature of our analyses prevents us from inferring causality. This study also provides a framework for exploring similar questions in larger datasets, such as the ABCD (Adolescent Brain Cognitive Development) Study (https://abcdstudy.org), where distinct cognitive and reward-related tasks, together with a larger sample size, could test whether the task-specific connectivity patterns that we observed are consistent across different tasks and populations.

Conclusions

Our findings highlight that cognitive control–related neural connectivity may play an important role in forecasting substance use initiation and frequency during adolescence. The data presented here imply that efforts to strengthen and monitor the development of the top-down cognitive control system in the brain from early adolescence may be protective and help deter progression into problematic substance use. Furthermore, for adolescents with heightened frequency of substance use, interventions may prove more effective by targeting interoceptive processes in cognitive control training to deter the progression into problematic substance use.

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Y-YC was responsible for conceptualization, investigation, methodology, formal analysis, and writing the original draft of the article. ML was responsible for investigation, methodology, formal analysis, and writing the original draft of the article. T-HL was responsible for conceptualization, investigation, methodology, reviewing and editing the article, and supervision. JL was responsible for data curation. BC was responsible for supervision, project administration, and funding acquisition. JK-S was responsible for conceptualization, investigation, methodology, reviewing and editing the article, supervision, project administration, and funding acquisition.

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The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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