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In Vivo Neuroimaging Evidence of Prefrontal Cortex Dysfunction in Adolescents With Substance Use: A Systematic Review

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Abstract

Background. Adolescence marks a critical phase for neurodevelopment, particularly in the prefrontal cortex (PFC), which underpins executive function and impulse control. This period coincides with the vulnerability to substance use, which has a significant impact on brain maturation. In vivo neuroimaging techniques provide valuable insights into the structural and functional alterations in the PFC associated with adolescent substance use. This review aims to synthesize the available literature focusing on the PFC dysfunction in adolescent substance users. **Methods.** A comprehensive search was conducted across peer-reviewed, Scopus-indexed databases, including PubMed, Web of Science, and Google Scholar. Eligible studies included adolescents aged 10–19 years with reported substance use like alcohol, nicotine, cannabis, opioids, stimulants, or polysubstance use, assessed via structural or functional neuroimaging techniques (MRI, fMRI, DTI, PET). Data were extracted on study design, sample characteristics, imaging modalities, and findings related to PFC dysfunction. **Results.** Sixteen studies met the inclusion criteria. Structural MRI studies reported reduced cortical thickness and gray matter volume in the dorsolateral and orbitofrontal regions among the cannabis and alcohol users. Functional imaging studies consistently showed the hypoactivation of PFC circuits during executive function tasks, along with the altered resting-state connectivity within the default mode and reward networks. **Conclusion.** This evidence suggests that adolescent substance use is linked with structural, functional, and neurochemical alterations in the PFC, which may further affect executive functioning and impulse control. Thus, it highlights the need for longitudinal studies to understand the neurodevelopmental vulnerabilities and highlight the importance of early prevention and intervention strategies targeting adolescent substance users.

Keywords: adolescents; substance use; prefrontal cortex; neuroimaging methods; PRISMA

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Introduction

Adolescence is a critical developmental period characterized by rapid brain development and maturation, particularly in regions involved in cognitive and emotional processing (Clark et al., 2008). During this time, significant neuronal growth occurs, resulting in both structural and functional changes in the brain. This period also marks behaviors such as social interaction, exploration, novelty seeking, and mostly high-risk-taking behaviors (Boer et al., 2024). Thus, often these periods of heightened neuroplasticity also represent a vulnerability to substance use, including early exposure to alcohol, nicotine, cannabis or marijuana, and other psychoactive substances. Such exposure has been shown to disrupt the typical neurodevelopmental trajectories, particularly affecting the prefrontal cortex (PFC) region, which is primarily responsible for executive functions such as planning, decision-making, impulse control, and reward regulation. These alterations in the PFC functioning during adolescence not only hinder cognitive control but also hint at the risk of

developing substance use disorders in adulthood (Ferdous, 2022). In 2019, the prevalence of alcohol consumption among 15- to 19-year-olds remained high worldwide (22%) with very little gender differences and a tendency to increase from initially low levels in some regions (World Health Organization, 2024).

The field of addiction research has long focused on impairments in self-regulation and maladaptive processing, both of which are closely linked to PFC dysfunction. Studies have shown that drug use increases activity in the PFC regions when related to drug cues, and decreases non-drug-related activity, especially during the episodes of binging and periods of craving in addiction (Goldstein & Volkow, 2011). Advancements in in vivo neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and diffusion tensor imaging (DTI), have thus provided compelling evidence for these dysfunctions marked by the consumption of such psychoactive substances. These methods consistently report hypoactivation of the PFC during cognitive control tasks, followed by disruptions in limbic-striatal connectivity and various other structural abnormalities (Li et al., 2009). These neurobiological alterations are thought to contribute to the continued and compulsive use of substances. Other cognitive domains, including memory (10% lower recall in heavy drinkers), attention, and processing speed, also show significant decline with the involvement of substance use like alcohol. Some studies also show that even after 4 weeks of abstinence, regular adolescent marijuana users showed deficits in learning, working memory, cognitive flexibility, and error monitoring (Squeglia et al., 2009).

Given the context of growing technological access and social influence, adolescent substance use continues to rise, which further links early use to later-life addiction (Silveri et al., 2016). It is therefore essential to synthesize the neuroimaging findings that illuminate the neural mechanisms underlying this vulnerability. Despite a growing body of neuroimaging research investigating the neural correlates of adolescent substance use, findings remain scattered and inconsistent. Methodological issues in these studies are important to consider, such as variability in imaging techniques and defining of abstinent periods (Squeglia et al., 2009). Some studies report structural deficits (Goldstein & Volkow, 2011), others highlight functional hypoactivation or disrupted connectivity (Goldstein & Volkow, 2011) within the PFC, while others report no significant change. This inconsistency limits our understanding of the precise neural alterations associated with adolescent substance use and impedes the development of targeted interventions. Hence, this review aims to (a) consolidate the present evidence of PFC dysfunction in adolescents with substance use, (b) examine how these alterations contribute to addiction risk, and (c) identify the methodological limitations for prevention and treatment research.

Methods

This systematic review was performed under the 2020 PRISMA guidelines, where the data were retrieved and compiled to understand, identify, describe, and characterize various structural and functional changes in the PFC, one of which is the main focus of the study.

Information Sources

An initial pool of information was collected using a serial search of articles, performed using various electronic databases like Google Scholar, Semantic Scholar, PubMed, BASE (Bielefeld Academic Search Engine), Web of Sciences, and ResearchGate. This was done to identify the relevant studies for the review. Additionally, reference search from other studies was manually conducted. Data limit of 2010 to 2025, a 15-year boundary was considered to ensure good quality, with extensive findings culminating access to the width and breadth of the data. The selection of these took place between August 11–20, 2025.

Search Strategy

The keywords search used the free-text keywords using Boolean operators in various database searches which included (“Adolescents”) AND (“substance use” OR “drug use” OR “cannabis” OR “nicotine” OR “alcohol” OR “marijuana”) AND (“prefrontal cortex dysfunction” OR “PFCD” OR “executive function dysfunction” OR “impulse control difficulties”) AND (“In-Vivo neuroimaging” OR “MRI” OR “fMRI" OR “DTI” OR “PET” OR “MRS”).

Study Selection and Categorization Process

The inclusion criteria included all the studies involving adolescents whose ages ranged between 10–19 years (as per World Health Organization); participants with current or past substance use; participants using one or more of the following substances: alcohol, cannabis, nicotine, opioids, stimulants, inhalants, substance use as defined by diagnostic criteria (DSM-5, ICD-10) or validated screening tools, or any self-reported usage evidence of PFC dysfunction based on in vivo neuroimaging

findings; neuroimaging modalities may include fMRI, structural MRI, DTI, PET, etc., both structural and functional outcomes of PFC dysfunction. All cross-sectional, longitudinal, Masters dissertation, doctoral theses, and book chapters were extensively considered.

All identified records were imported into Mendeley/Zotero reference manager, and duplicates were removed. All animal studies were also removed. They were further screened for title and abstract screening. Of those which were retrieved, full text screening was conducted using the inclusion criteria. The study selection process, including the identification, screening, eligibility assessment, and inclusion of studies, is presented in Figure 1.

Data Extraction

A standardized data extraction sheet was done using Microsoft Excel to collect details on author(s) and year of study; theoretical or conceptual framework; research questions, hypotheses, and objectives; methodology (sample, research design, neuroimaging modality); analysis and major findings with respect to structural or functional PFC outcomes, conclusion, limitations, and suggestions for future research methods.

Data Synthesis

A narrative synthesis was used because of the heterogeneity in neuroimaging techniques, outcome measures, and types of substance use. The studies were categorized on the basis of structural (e.g., cortical thickness, gray matter volume) abnormalities, task-based and resting-state fMRI functional activation patterns, changes in connectivity (DTI, functional connectivity), and neurochemical or metabolic (MRS, PET). Patterns across studies were compared where there was enough homogeneity and converging evidence pointed out.

Results

Theme 1: Structural Brain Alterations in Adolescent Substance Use

Studies have shown several neurostructural differences in adolescents who often engage in early substance use. Lopez-Larson et al. (2011) found that the cortical thickness in the prefrontal and insular regions had significantly reduced among the adolescent marijuana users, which shows that these regions are crucial for decision-making and interoceptive awareness (see Figure 2). A study by Cheetham et al. (2012) reported that reduced orbitofrontal volumes predicted future initiation of cannabis use during a 4-year follow-up, indicating that adolescents may be vulnerable to experimentation due to preexisting vulnerabilities in neural structure. Further studies by Cheetham et al. (2014) found volumetric dissimilarities in the anterior cingulate cortex related to alcohol consumption, which again supports structural brain predictors of risk trajectories.

Another study by Sultan et al. (2021), which examined adolescents with bipolar disorder, shows that cannabis use was highly linked to changes in the neural structures, underscoring the combination of psychiatric vulnerability and changes in the brain structure due to substance use. Interestingly, Orr et al. (2019) demonstrated that already very low amounts of cannabis use were correlated with differences in gray matter volumes, which provokes concern that even low exposure during adolescence can be measured.

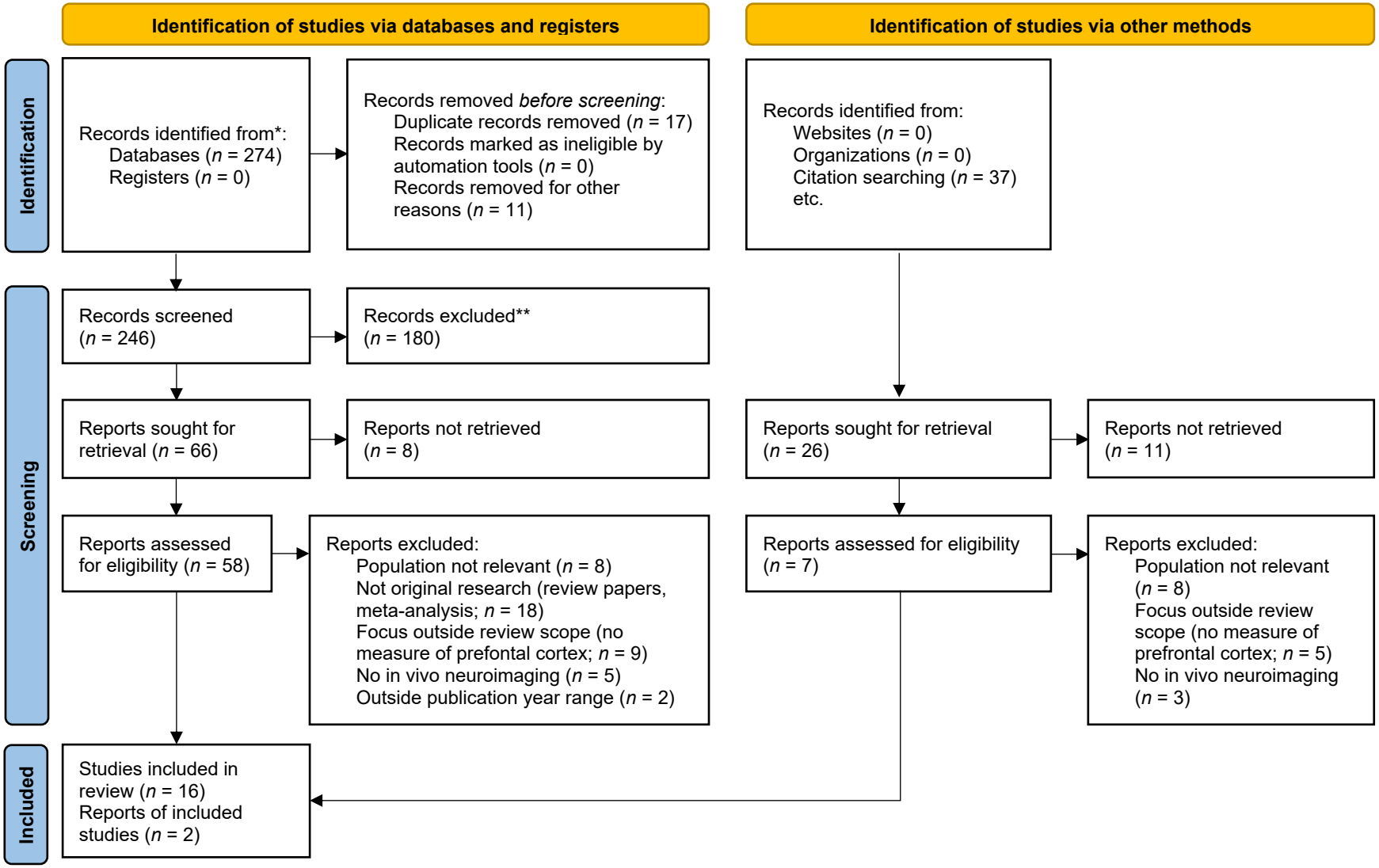
In more recent studies, Miller et al. (2024) showed that neuroanatomical variability is a significant predictor of substance use initiation. Yet, brain differences are not only a consequence of substance use but also may be a precursor of it. Overall, these results indicate a two-way interaction, which shows structural abnormalities can be both prone to substance use and aggravated by early exposure.

Theme 2: Reward Processing and Cue Reactivity

Another predominant theme involves changes in reward circuitry and a heightened sensitivity to substance-related cues. Brumback et al. (2015) demonstrated that heavy consumption of alcohol in adolescence amplified brain responses to alcohol cues, which later decreased with a period of abstinence, highlighting the plasticity of reward-associated neural activity. Swartz et al. (2020) showed that increased reward-related brain activity is predictive of future alcohol consumption, suggesting that increased reactivity can serve as a biomarker of future risk.

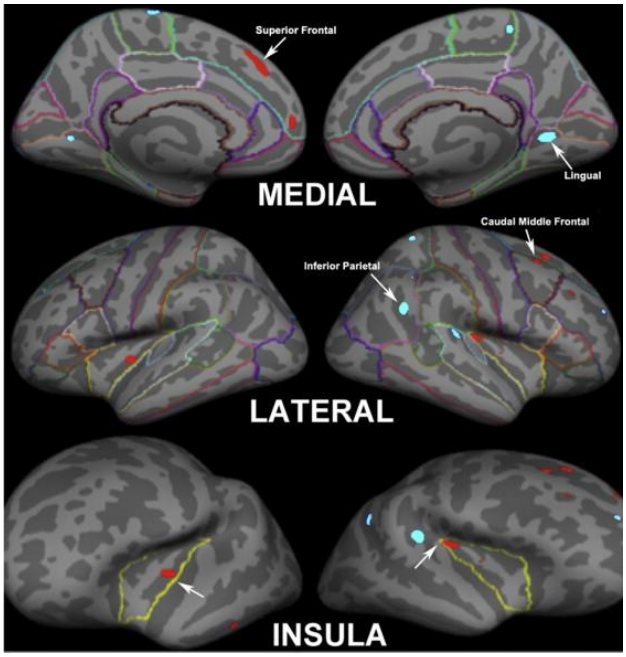
Weissman et al. (2015) found that an earlier onset of substance use was linked to strong connectivity between reward and cognitive control networks, possibly due to compensatory mechanisms that might later become destabilized. Similarly, Stanger et al. (2013) attributed neuroeconomic insights into risky substance abuse to individual differences in neural activities during delay discounting tasks, and these results were incorporated into the field of addiction research.

Figure 1. *PRISMA 2020 Flow Diagram for New Systematic Reviews Which Included Searches of Databases, Registers and Other Sources.*



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
Source: Page et al., (2021).

Figure 2. *Altered Prefrontal and Insular Cortical Thickness in Adolescent Marijuana Users.*



Note. Reproduced from Lopez-Larson et al. (2011). Altered prefrontal and insular cortical thickness in adolescent marijuana users. Reproduced under the terms of the Creative Commons Attribution License (CC BY).

In a large multicenter study, Whelan et al. (2014) identified neuropsychosocial profiles that differentiated current and future alcohol misusers, predominantly in the adolescent population, which shows consistent results with other studies that find that aberrant reward processing underpins both initiation and escalation of use. Collectively, these studies underscore the importance of altered sensitivity to reward cues as a predictor of future direction as well as present use.

Theme 3: Cognitive Control and Neuropsychological Outcomes

Substance use during adolescence also overlaps with cognitive development, mainly executive functioning. Squeglia et al. (2012) identified that the onset of moderate to severe alcohol consumption predicted deterioration in neuropsychological functioning across the domains of memory and attention, with varied effects on boys and girls. Additionally, Lisdahl et al. (2013) found that earlier initiation of alcohol and marijuana consumption disrupts cognition, brain structure, and functional connectivity, which showcases the long-term risks of development.

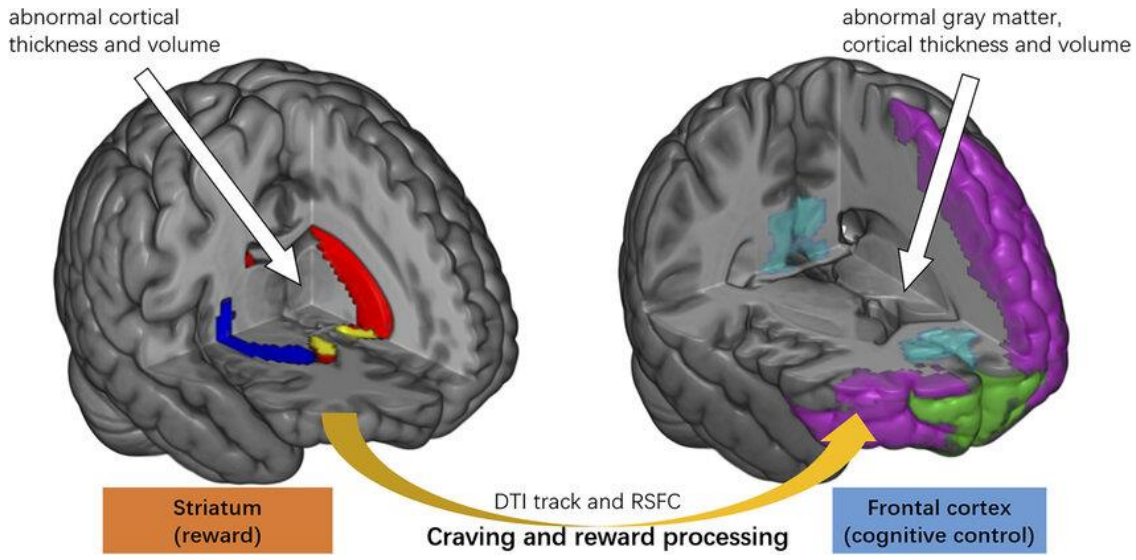
Tervo-Clemmens et al. (2018) offered narrower results, indicating that adolescent cannabis use impacts the brain systems involved in adult working memory encoding and retrieval and further indicated long-term changes in cognitive circuitry. Deneen et al. (2022) compared frontostriatal circuits between adolescent nicotine addiction and internet gaming disorder which showed similarities in the cognitive control disturbance across both behavioral and substance-related addictions (see Figure 3). Overall, these results emphasize the idea that substance use in adolescence is not confined to instant reward-driven mechanisms but has broader implications on higher-order executive functioning and long-term cognitive health.

New research emphasizes the importance of connectivity-based mechanisms in explaining adolescent substance use. Ewing et al. (2017) identified orbitofrontal cortex connectivity as a potential mechanism of behavior change, showing how functional links between prefrontal and limbic regions shape risk-taking and adaptability. Sultan et al. (2021) extended this by linking cannabis use in adolescents with bipolar disorder to neurostructural connectivity differences, underscoring the interplay between psychiatric conditions and substance-related neural pathways.

Theme 4: Connectivity and Mechanisms of Change

Likewise, Weissman et al. (2015) highlighted strengthened connectivity between the reward and control networks in early initiators and indicated neurodevelopmental changes that might mediate vulnerability. The studies collectively suggest that connectivity-based changes can mediate between structural weaknesses and functional differences in reward processing and provide a more dynamic conceptualization of adolescent addiction outcomes.

Figure 3. *Comparison of Frontostriatal Circuits in Adolescent Nicotine Addiction and Internet Gaming Disorder.*



Note. Reproduced from Deneen et al. (2022). Comparison of frontostriatal circuits in adolescent nicotine addiction and internet gaming disorder. Licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0).

Table 1

Characteristics and Major Findings of the Studies Examining Prefrontal Cortex Dysfunction in Adolescents With Substance Use

Author (Year)	Theoretical/ Conceptual Framework	Research Question / Hypotheses / Objectives	Methodology (Sample, Research Design)	Analysis and Major Findings	Conclusion/ Limitations	Suggestions for Future Research	Reviewer's Observation
Lopez-Larson et al. (2011)	Neurodevelop-mental disruption framework	To assess cortical thickness in adolescent marijuana users	MRI: adolescent, marijuana users vs controls	Reduced PFC and insula thickness	Structural deficits associated with adolescent cannabis use	Longitudinal studies needed	Very relevant, structural PFC evidence in youth
Brumback et al. (2015)	Cue-reactivity and abstinence	Does brain responses to alcohol cues change after abstinence?	fMRI; heavy-drinking adolescents; repeated at 1 month	Cue-related PFC activation decreased after abstinence	PFC may recover with abstinence	Longer abstinence follow-up	Recovery-focused inclusion
Cheetham et al. (2012)	Neurodevelop-mental risk: orbitofrontal cortex role	Do OFC volumes predict initiation of cannabis use in adolescents?	Longitudinal MRI; 4-year follow-up; adolescents	Smaller OFC volumes predicted earlier cannabis initiation	PFC structural differences may precede substance use	Replicate in larger, diverse cohorts	Strong fit. Prospective, PFC-focused
Cheetham et al. (2014)	Anterior cingulate risk model	Do ACC volumes predict alcohol-related problems in adolescence?	MRI; prospective cohort study	Smaller ACC predicted alcohol-related problems	Structural deficits precede alcohol misuse	Larger, longer-term prospective studies	Good fit. ACC/PFC link

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Deneen et al. (2022)	Frontostriatal circuit models	To compare circuits in adolescent nicotine addiction vs. internet gaming disorder	fMRI studies of adolescents with nicotine addiction and IGD	Shared and distinct frontostriatal abnormalities in both disorders	Limited sample sizes; cultural context: China	Broader cross-cultural comparisons	Interesting comparative angle but secondary to substance use focus
Ewing et al. (2017)	Neurocircuitry of behavior change	Is OFC connectivity linked to adolescent behavior change?	fMRI; adolescents during behavior tasks	Increased OFC connectivity related to reduced risk behaviors	Connectivity may underlie adaptive changes	Explore substance-specific pathways	Relevant conceptual support
Lisdahl et al. (2013)	Delay hypothesis – onset age matters	To explore effect of early onset on brain and cognition	Review of MRI and cognitive tests	Early use associated with reduced PFC volume and function	Timing of use matters more than total exposure	Emphasize developmental timing in future designs	Directly aligned with your study
Miller et al. (2024)	Neurodevelop-mental variability in early adolescence	To examine whether neuroanatomical variability predicts initiation of substance use in late childhood/early adolescence	JAMA Network Open dataset; large community-based cohort	Structural MRI showed variability in brain morphology (esp. PFC, striatum) associated with risk for early substance initiation	Neuroanatom-ical variability may predispose youth to early substance use; causality not established	Longitudinal and genetically informed designs	Very relevant, directly links neurodevelop mental variability and risk pathways
Orr et al. (2019)	Neurodevelop-mental vulnerability	Are there GM differences with very low cannabis use in adolescence?	MRI (IMAGEN dataset); n>1500 adolescents	Low-level cannabis use associated with reduced PFC gray matter	Even minimal use affects PFC development	Examine dose-response and reversibility	Directly relevant, structural PFC findings
Squeglia et al. (2012)	Developmental trajectories + substance use	To observe working memory brain activation over time in adolescents	Longitudinal fMRI (3-year follow-up); heavy drinkers vs. controls	Initiating heavy drinking is associated with less efficient PFC activation	Working memory impaired even before dependence sets in	Use pre-use baselines and track over time	Strong longitudinal PFC-focused study
Stanger et al. (2013)	Neuroeconomics and delay discounting	To investigate neural correlates of delay discounting in adolescent substance abusers	fMRI; adolescents with substance abuse vs. controls	Greater discounting and altered PFC–striatal activation in users	Neuroeco-nomic models explain impulsivity in adolescent substance use	Explore interventions targeting decision-making processes	Directly relevant links PFC to risky choices and use
Sultan et al. (2021)	Neurostructural abnormalities in comorbidity (cannabis + bipolar disorder)	To study cannabis use and brain structure in adolescents with bipolar disorder	MRI study. adolescents with bipolar disorder with/without cannabis use	Cannabis use associated with altered PFC volumes in bipolar adolescents	Small clinical sample, comorbidity complicates results	Larger samples needed, examine clinical outcomes	Novel clinical angle, comorbidity, shows stronger PFC vulnerability

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Author (Year)	Theoretical/ Conceptual Framework	Research Question / Hypotheses / Objectives	Methodology (Sample, Research Design)	Analysis and Major Findings	Conclusion/ Limitations	Suggestions for Future Research	Reviewer's Observation
Swartz et al. (2020)	Reward processing and adolescent alcohol use	To test whether reward-related brain activity predicts increases in alcohol use	fMRI reward task, longitudinal adolescent cohort	Stronger ventral striatum activation predicted higher future alcohol use	Reward hypersen-sitivity is a risk factor	Examine moderators like environment and stress	Good fit prospective evidence linking reward system activity to alcohol trajectories
Tervo-Clemmens et al. (2018)	Cannabis effects on working memory circuitry	To assess adolescent cannabis use effects on adult working memory processes	Longitudinal, fMRI of WM tasks	Adolescent cannabis use predicted poorer WM encoding and altered PFC-hippocampal activation in adulthood	Early cannabis use disrupts brain systems supporting WM	Larger longitudinal samples needed	Relevant, long-term cognitive conse-quences of early cannabis use
Weissman et al. (2015)	Connectivity between reward and control networks	To test whether earlier substance onset predicts altered connectivity	fMRI connectivity analyses in adolescents	Earlier onset predicted stronger reward–control network connectivity	Altered connectivity may reinforce risky behaviors	Longitudinal causal tests needed	Strong prospective evidence for timing of onset
Whelan et al. (2014)	Neuropsycho-social risk framework	Can neuropsycho-social profiles predict adolescent alcohol misuse?	IMAGEN longitudinal, multi-site	Identified PFC dysfunction as predictor of alcohol misuse	PFC dysfunction precedes problem drinking	Apply predictive models clinically	Landmark Nature study, highly relevant

Discussion

The overall findings from these literature imply that substance use during adolescence is closely connected to structural and functional impairments in the PFC, a key area responsible for executive functions, including decision-making, impulse control, and reward processing. Multiple studies have found that adolescent users of substances such as cannabis, alcohol, and nicotine have lower cortical thickness and volume in PFC subregions such as the orbitofrontal cortex and anterior cingulate cortex, regions used to regulate emotions and inhibit inappropriate behaviors (Cheetham et al, 2014). These neuroanatomical alterations not only indicate the effects of early substance use but also significantly predict subsequent substance use initiation and escalation, showing a bidirectional relationship between PFC dysfunction and substance use vulnerability.

Functionally, neuroimaging research has indicated that adolescent substance users exhibit overactive brain activity to substance cues and reduced activity to nondrug rewards, with dysregulated reward processing systems. The imbalance agrees with addiction models that focus on the inhibition of responses and abnormal salience attribution within the PFC circuits. Longitudinal studies confirm the hypothesis that premature dysfunction of the PFC is predictive of the neuropsychological deficits, including working memory and decision-making, which in turn lead to the compulsiveness of substance use during this developmental period.

In sum, these results support the role of dysfunction in the PFC of adolescent users of substances as an indicator of both vulnerabilities to substance-related addiction and the consequences of substance-induced neurodevelopmental discontinuity, which

highlights the importance of early detection and intervention strategies among adolescents, including a focus on PFC-function rehabilitation to prevent vulnerability to substance-related addictions.

Conclusion

Overall, all the reviewed studies provide clear evidence that adolescent substance use is closely associated with significant changes in the PFC, including the loss of cortical thickness and volume in regions such as the orbitofrontal and anterior cingulate cortices. These morphological alterations are not only a result of substance use onset but also outcomes of neurodevelopmental derailment through early exposure. Neuroimaging data show that connectivity within frontostriatal circuits is disrupted, reducing executive functions such as impulse control and choice-making and exaggerating reward reactions to drug-related stimuli. This lack of regulation in neural networks explains why adolescent substance users cannot regulate their behaviour and challenge substance cues.

In practice, the patterns of aberrant activation observed in these adolescents are indicative of an overbalance between increased sensitivity to drug rewards and decreased sensitivity to nondrug rewards, as is expected in the models of addiction as impaired response inhibition and abnormal salience attribution. Longitudinal evidence also indicates that brain dysfunction` in the PFC at a young age is a predictor of future cognitive impairment and increasing substance use problems.

Clinically, these findings support developing cognitive training and behavioral therapies specifically aimed at strengthening prefrontal cortical control and reducing reward sensitivity to substance cues to curb addictive behaviors. Functional imaging can also guide pharmacological treatments by revealing neurotransmitter system dysregulations in PFC networks. Additionally, neuroimaging advances contribute to public health by informing educational programs on the neurodevelopmental risks of adolescent substance use, encouraging policies prioritizing early screening and intervention. Ultimately, integrating neuroimaging evidence into clinical and community practice promises improved outcomes by addressing the neural underpinnings of addiction vulnerability during this crucial developmental period.

Author Disclosures

The authors declare no conflicts of interest. No AI tools were used to generate the core content of this manuscript. However, minimal assistance was utilized for grammar correction and refinement of sentence structure.

References

Boer, O. D., El Marroun, H., & Muetzel, R. L. (2024). Adolescent substance use initiation and long-term neurobiological outcomes: Insights, challenges and opportunities. *Molecular Psychiatry, 29*(7), 2211–2222. https://doi.org/10.1038/s41380-024-02471-2

Brumback, T., Squeglia, L. M., Jacobus, J., Pulido, C., Tapert, S. F., & Brown, S. A. (2015). Adolescent heavy drinkers' amplified brain responses to alcohol cues decrease over one month of abstinence. *Addictive Behaviors, 46*, 45–52. https://doi.org/10.1016/j.addbeh.2015.03.001

Cheetham, A., Allen, N. B., Whittle, S., Simmons, J. G., Yücel, M., & Lubman, D. I. (2012). Orbitofrontal volumes in early adolescence predict initiation of cannabis use: A 4-year longitudinal and prospective study. *Biological Psychiatry, 71*(8), 684–692. https://doi.org/10.1016/j.biopsych.2011.10.029

Cheetham, A., Allen, N. B., Whittle, S., Simmons, J. G., Yücel, M., & Lubman, D. I. (2014). Volumetric differences in the anterior cingulate cortex prospectively predict alcohol-related problems in adolescence. *Psychopharmacology, 231*(8), 1731–1742. https://doi.org/10.1007/s00213-014-3483-8

Clark, D. B., Thatcher, D. L., & Tapert, S. F. (2008). Alcohol, psychological dysregulation, and adolescent brain development. *Alcoholism: Clinical and Experimental Research, 32*(3), 375–385. https://doi.org/10.1111/j.1530-0277.2007.00601.x

Deneen, K. M., Hussain, H., Waheed, J., Xinwen, W., Yu, D., & Yuan, K. (2022). Comparison of frontostriatal circuits in adolescent nicotine addiction and internet gaming disorder. *Journal of Behavioral Addictions, 11*(1), 26–39. https://doi.org/10.1556/2006.2021.00086

Ewing, S. W. F., Chung, T., Caouette, J. D., Ketcherside, A., Hudson, K. A., & Filbey, F. M. (2017). Orbitofrontal cortex connectivity as a mechanism of adolescent behavior change. *NeuroImage, 151*, 14–23. https://doi.org/10.1016/j.neuroimage.2016.12.076

Ferdous, N. (2022). Examining neurocognitive markers in adolescence as predictors of changes in later substance use. San Diego State University.

Goldstein, R. Z., & Volkow N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*(11), 652–669. https://doi.org/10.1038/nrn3119

Li, C. S., Luo, X., Yan, P., Bergquist, K., & Sinha, R. (2009). Altered impulse control in alcohol dependence: Neural measures of stop signal performance. *Alcoholism: Clinical and Experimental Research, 33*(4), 740–750. https://doi.org/10.1111/j.1530-0277.2008.00891.x

Lisdahl, K. M., Gilbart, E. R., Wright, N. E., & Shollenbarger, S. (2013). Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. *Frontiers in Psychiatry, 4*, Article 53. https://doi.org/10.3389/fpsyt.2013.00053

Lopez-Larson, M. P., Bogorodzki, P., Rogowska, J., McGlade, E., King, J. B., Terry, J., & Yurgelun-Todd, D. (2011). Altered prefrontal and insular cortical thickness in adolescent marijuana users. *Behavioural Brain Research, 220*(1), 164–172. https://doi.org/10.1016/j.bbr.2011.02.001

Miller, A. P., Baranger, D. A. A., Paul, S. E., Garavan, H., Mackey, S., Tapert, S. F., LeBlanc, K. H., Agrawal, A., & Bogdan, R. (2024). Neuroanatomical variability and substance use initiation in late childhood and early adolescence. *JAMA Network Open, 7*(12), Article e2452027. https://doi.org/10.1001/jamanetworkopen.2024.52027

Orr, C., Spechler, P., Cao, Z., Albaugh, M., Chaarani, B., Mackey, S., D'Souza, D., Allgaier, N., Banaschewski, T., Bokde, A. L. W., Bromberg, U., Büchel, C., Burke Quinlan, E., Conrod, P., Desrivières, S., Flor, H., Frouin, V., Gowland, P., Heinz, A., … Garavan, H. (2019). Grey matter volume differences associated with extremely low levels of cannabis use in adolescence. *Journal of Neuroscience, 39*(10), 1817–1827. https://doi.org/10.1523/jneurosci.3375-17.2018

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., ... Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ, 372*, n71. https://doi.org/10.1136/bmj.n71

Silveri, M. M., Dager, A. D., Cohen-Gilbert, J. E., & Sneider, J. T. (2016). Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. *Neuroscience and Biobehavioral Reviews*, *70*, 244–259. https://doi.org/10.1016/j.neubiorev.2016.06.042

Squeglia, L. M., Jacobus, J., & Tapert S. F. (2009). The influence of substance use on adolescent brain development. *Clinical EEG and Neuroscience, 40*(1), 31–38. https://doi.org/10.1177/155005940904000110

Squeglia, L. M., Spadoni, A. D., Infante, M. A., Myers, M. G., & Tapert, S. F. (2012). Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. *Psychology of Addictive Behaviors, 26*(3), 427–437. https://doi.org/10.1037/a0016516

Stanger, C., Elton, A., Ryan, S. R., James, G. A., Budney, A. J., & Kilts, C. D. (2013). Neuroeconomics and adolescent substance abuse: Individual differences in neural networks and delay discounting. *Journal of the American Academy of Child & Adolescent Psychiatry, 52*(7), 747–755. https://doi.org/10.1016/j.jaac.2013.04.013

Sultan, A. A., Kennedy, K. G., Fiksenbaum, L., MacIntosh, B. J., & Goldstein, B. I. (2021). Neurostructural correlates of cannabis use in adolescent bipolar disorder. *International Journal of Neuropsychopharmacology, 24*(3), 181–190. https://doi.org/10.1093/ijnp/pyaa077

Swartz, J. R., Weissman, D. G., Ferrer, E., Beard, S. J., Fassbender, C., Robins, R. W., Hastings, P. D., & Guyer, A. E. (2020). Reward-related brain activity prospectively predicts increases in alcohol use in adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry, 59*(3), 391–400. https://doi.org/10.1016/j.jaac.2019.05.022

Tervo-Clemmens, B., Simmonds, D., Calabro, F. J., Day, N. L., Richardson, G. A., & Luna, B. (2018). Adolescent cannabis use and brain systems supporting adult working memory encoding, maintenance, and retrieval. *NeuroImage, 169*, 496–509. https://doi.org/10.1016/j.neuroimage.2017.12.041

Weissman, D. G., Schriber, R. A., Fassbender, C., Atherton, O., Krafft, C., Robins, R. W., & Guyer, A. E. (2015). Earlier adolescent substance use onset predicts stronger connectivity between reward and control networks. *Developmental Cognitive Neuroscience, 16*, 121–129. https://doi.org/10.1016/j.dcn.2015.07.002

Whelan, R., Watts, R., Orr, C. A., Althoff, R. R., Artiges, E., Banaschewski, T., Barker, G. J., Bokde, A. L. W., Büchel, C., Carvalho, F. M., Conrod, P. J., Flor, H., Fauth-Bühler, M., Frouin, V., Gallinat, J., Gan, G., Gowland, P., Heinz, A., Ittermann, B., … the IMAGEN Consortium (2014). Neuropsychosocial profiles of current and future adolescent alcohol misusers. *Nature, 512*(7513), 185–189. https://doi.org/10.1038/nature13402

World Health Organization. (2024). Adolescent mental health. https://www.who.int/news-room/fact-sheets/detail/adolescent-mental-health

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