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Adolescent substance use initiation and long-term neurobiological outcomes: insights, challenges and opportunities

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Abstract

The increased frequency of risk taking behavior combined with marked neuromaturation has positioned adolescence as a focal point of research into the neural causes and consequences of substance use. However, little work has provided a summary of the links between adolescent initiated substance use and longer-term brain outcomes. Here we review studies exploring the long-term effects of adolescent-initiated substance use with structural and microstructural neuroimaging. A quarter of all studies reviewed conducted repeated neuroimaging assessments. Long-term alcohol use, as well as tobacco use were consistently associated with smaller frontal cortices and altered white matter microstructure. This association was mostly observed in the ACC, insula and subcortical regions in alcohol users, and for the OFC in tobacco users. Long-term cannabis use was mostly related to altered frontal cortices and hippocampal volumes. Interestingly, cannabis users scanned more years after use initiation tended to show smaller measures of these regions, whereas those with fewer years since initiation showed larger measures. Long-term stimulant use tended to show a similar trend as cannabis in terms of years since initiation in measures of the putamen, insula and frontal cortex. Long-term opioid use was mostly associated with smaller subcortical and insular volumes. Of note, null findings were reported in all substance use categories, most often in cannabis use studies. In the context of the large variety in study designs, substance use assessment, methods, and sample characteristics, we provide recommendations on how to interpret these findings, and considerations for future studies.

Introduction

Adolescence is a transitional phase between childhood and early adulthood, roughly corresponding to the onset of puberty until young adulthood[1], and is accompanied by physical growth, changes in body composition, the appearance of secondary sex characteristics[2], and changes in cognitive and socioemotional functioning[3]. For example, individuals traversing adolescence show marked improvement in reasoning, information processing[4], and forming new relationships[5]. Importantly, this developmental period is also characterized by behaviors that include social interaction, exploration, novelty and sensation seeking, and in particular high levels of risk-taking behavior[6].

One common risk-taking behavior that adolescents exhibit is substance use initiation (SUI). During adolescence, alcohol, cannabis, and tobacco are the most frequently used substances[7]. In 2018, the prevalence of lifetime substance use among adolescents in the US was approximately 26% for alcohol, 15% for cannabis, and 13% for tobacco[7]. Patterns of substance use among adolescents vary, for example use of alcohol only, combined alcohol and smoking (cannabis and/or tobacco), and polysubstance use[8]. The high prevalences observed are concerning for several reasons, among which are that early SUI in adolescence (i.e. prior to 14 years of age) increases the risk of substance use disorder (SUD) later in life significantly[9]. In addition, earlier ages of initiation have also been shown to leave adolescents more vulnerable to faster transitions into SUDs[7].

The short-term negative effects of substance use during adolescence are well known, for example intoxication or overdose[10], accidents due to driving under the influence[11, 12], as well as unprotected sex and unintended pregnancies[13]. Prolonged substance use has also been implicated in adverse health consequences across multiple systems, for example cardiovascular, digestive, and respiratory [14]. Several key aspects of brain health and performance have been implicated with long-term exposure, including cognitive performance (e.g., executive function), and mental health (e.g., attention-deficit/hyperactivity disorder, depression and anxiety)[15, 16]. Prior work has also suggested that long-term excessive alcohol use may contribute to accelerated aging and age-related diseases, for example cognitive decline, dementia, Alzheimer disease and Parkinson's disease[17, 18].

In order to better understand these cognitive, neurological, and mental health-related consequences of early SUI and SUDs, it is crucial to gain additional insights into the underlying neurobiological sequelae. This knowledge not only improves our understanding of SUD from an

etiological perspective, but can also play a pivotal role in providing information which is helpful in aiding public health policy. Therefore, here we provide an overview of both retrospective and prospective studies that investigated SUI in adolescence in relation to long-term structural and microstructural brain outcomes. We investigated multiple groups of substances, including alcohol, tobacco, cannabis, and other illicit drugs. In this overview, we focused on studies with detailed information on timing of SUI during adolescence (from age 10 to 21 years), with outcomes measured in late adolescence and adulthood (ages 12 to 66 years). Finally, this review aims to provide a comprehensive overview of the existing literature, pinpoint research gaps and challenges, and offer recommendations for future directions in SUD-related neuroimaging research.

Cause, consequence and study design

The substance use neuroimaging literature can be broadly divided into two general categories: understanding the neurobiological substrates which predict or even cause SUI, and uncovering the neurobiological consequences after short and long-term exposure to substance use and abuse. As noted above, this review focuses on the latter. However, one of the more challenging tasks for understanding SUD from a neurobiological perspective is disentangling the different *causes* and resulting *consequences* of substance use; the classic 'chicken or the egg' problem. For example, the increase of risk-taking behavior in adolescence specifically may be due to remodeling of dopaminergic brain networks underlying affective and motivational processes leading to increased reward-seeking, especially in the presence of peers[19]. Between adolescence and adulthood, risk-taking behavior decreases and coincides with the later maturing cognitive control system (i.e. the dorsolateral prefrontal cortex, anterior and posterior cingulate, and temporo-parietal cortices), which strengthens the capacity for self-regulation[19]. While these neurobiological characteristics could be correlated with a given SUD, our ability to make causal inferences on observed associations is heavily dependent on the design of a study. In the context of human studies, prospectively collected, repeated-measures longitudinal data are the best option for delineating the potentially causal substrates of use and use initiation from the downstream consequences of long-term use. However, despite being accompanied by more assumptions and challenges in making etiological interpretations, cross-sectional studies without question provide important insights into the links between substance use and the brain. In the

context of study design, it is worth highlighting three general classifications of research depending on the goal of the work: descriptive, predictive, and etiological (causal)[20]. While these classifications are not always explicitly attached to the studies included in this review, we consider the vast majority likely fall implicitly under the category of etiological. We assign this general classification primarily because of the general study designs and research questions employed (early use initiation with long-term follow-up) and the tendency to adjust effect estimates for confounding factors (either statistically in models, or via case-control matching).

Structural and microstructural neuroimaging

The SUD literature utilizes a broad repertoire of neuroimaging techniques, including electroencephalography, positron emission tomography, and (functional) magnetic resonance imaging (MRI). One of the first, and still most widely-used, modalities leveraged within the MRI family is traditional structural MRI. Though several different contrasts are available, T_1 and T_2-weighted imaging remain the most commonly-used for describing brain structure and morphology. These contrasts make it possible to delineate global brain volumes (e.g., total brain, gray matter, etc.), as well as regionally-specific focal volumes (e.g., hippocampal, cingulate gyrus). Several automated images analysis software packages allow for such volumes of subcortical and cortical brain regions to be quantified, and also allow for additional morphological information to be derived, such as the thickness or surface area of the cortical mantle, and also indicators of the complex folding structure of the brain (e.g., gyrification). Going beyond describing brain morphology on a macrostructural level, diffusion weighted imaging has been widely used to extract detailed information on the underlying microstructure of (primarily myelinated) neuronal tissue by measuring water diffusion. Given axonal packing structure, diameter, and myelination status are all known to influence water diffusion, these diffusion profiles offer clues as to how the underlying white matter (and also gray matter) neural tissue are organized at a microstructural level. The diffusion tensor is the most commonly utilized model, however more complex and accurate descriptors of the diffusion profile have been developed and are increasingly utilized given advances in more comprehensive diffusion imaging acquisitions[21]. Fractional anisotropy (ranging from 0 to 1, the degree of which diffusion is preferential along a single axis) and mean diffusivity (describing the average amount of diffusion) are two of the more widely used indicators of white matter microstructure. For both

morphological and white matter microstructural analyses, analyses are typically conducted using predefined regions (or tracts) of interest (ROIs), or using all voxels/vertices in the image (i.e., hundreds of thousands of data points per individual) within an exploratory framework. In order to remain complete yet concise, this review focuses on structural and microstructural MRI techniques only.

Brain Development and Aging

Before we review how SUI in adolescence can impact the brain over time, it is important to first discuss the trajectories of neurodevelopment and aging in the absence of substance use. Nearly three decades of *in vivo* neuroimaging have shown that the cognitive, socioemotional and behavioral changes observed during adolescence also coincide with morphological, functional and metabolic changes in the human brain[22-24]. From a lifespan perspective, several morphological features of the cortex, for example cortical thickness, volume, and surface area, have been shown to undergo measurable remodeling during neurodevelopment and aging. While cortical thickness increases nonlinearly during childhood, the process of cortical thinning begins during adolescence and persists across the lifespan. While the precise underlying physiological processes still are not fully understood, cortical thinning is thought to result from both regressive processes such as naturally occurring cell death and systematic synaptic pruning, and progressive processes, such as the increase of myelination, in part depending on the timing (i.e., during development and aging)[25, 26]. In parallel, cortical surface area increases from childhood, reaches a maximum area in adolescence and then decreases modestly until the age of 45 years[27, 28]. White matter volumes increase throughout childhood and adolescence and reach a peak volume in young adulthood [29]. These cortical maturational processes typically start in sensory areas, and continue in regions that subserve higher-order cognitive processes[30]. In middle and late adulthood, this development continues with small decreases in grey matter, stabilization of white matter and subcortical volumes, and an increase in ventricular volumes over time [29].

Early substance use initiation and long-term structural brain outcomes

In the review below, we offer an overview of structural neuroimaging studies which report either prospective or retrospective ascertainment of SUI during adolescence and also make

a distinction between studies with ≥10 years since initiation (YSI) and those with <10 years. All studies described here were selected based on an average use initiation below age 20 years. As such, studies on adult samples that did not report on average use initiation, were excluded in the review. Although this review was not systematic, we used an inclusive approach in which we used search outcomes of a previous systematic review on brain-substance use relationships[31], followed by extensive snowball sampling (focused on including more types of substance use and longer follow-up durations) and notifications for new relevant publications, resulting in the inclusion of 103 studies.

The adjustable **Supplemental Table 1** offers a comprehensive overview of the literature reviewed, and contains information on the type of study, demographic characteristics, YSI, and the primary findings. Studies reporting a YSI of ≥10 years are presented in bold, and studies employing a sample size of N < 100 are presented in italics. **Figure 1** and **Figure 2** provide a visual representation of long-term (sub)cortical brain outcomes associated with alcohol, cannabis and tobacco use.

Alcohol

Studies with alcohol-related structural brain outcomes are shown in Supplemental Table 1 (yellow labeled). All listed studies reported an average alcohol use initiation below age 20 years. Of these studies, one fifth reported a YSI of ≥10 years, with the rest reporting a YSI <10 years.

Across several studies, long-term alcohol use was mostly associated with thinner cortex, smaller gray matter volumes, and altered white matter microstructure (i.e., lower FA, higher MD) of frontal brain regions. Specifically, these associations were mostly found in the orbitofrontal cortex (OFC)[32, 33], the anterior cingulate cortex (ACC)[32, 33], the prefrontal cortex (PFC)[34] and the frontopolar cortex[33]. Importantly, these associations remained present after controlling for cannabis and tobacco use. Moreover, in studies with repeated neuroimaging alcohol users (usually defined as heavy or binge drinkers) displayed a steeper decline of frontal gray matter volume or cortical thickness over time as compared to non- or light users. Specifically, accelerated reductions of the ACC, middle frontal gyrus (MFG) and OFC were reported across multiple longitudinal cohorts [35-42]. In the largest study with repeated neuroimaging (N = 1,387), Seo and colleagues reported smaller ACC, OFC and PFC volumes in

heavy alcohol users at their final neuroimaging measurement (age 19 years)[43]. Similarly, studies with single timepoint neuroimaging and up to 7 years retrospectively ascertained alcohol use found smaller ACC[44] and altered PFC structures in binge drinkers[45, 46]. In the insular cortex, alcohol use was related to smaller volume, cortical thickness and surface area across multiple longitudinal cohorts with a YSI up to 10 years[33, 37, 41-43], of which three had repeated neuroimaging[41-43]. Alcohol-related group differences in temporal and parietal regions have also been reported. For the temporal lobe, alcohol use was related to a steeper decline of volume and cortical thickness over time in multiple studies with repeated neuroimaging[36, 42, 47, 48], and to smaller volume of temporal regions 10 years after initiation[33]. For the parietal lobe, smaller volume and thinner parietal cortex were detected in alcohol users[32, 39, 42, 44]. Specifically, the posterior cingulate cortex (PCC) was implicated in studies with repeated neuroimaging[39, 42] as well as in studies with single timepoint neuroimaging[44].

Subcortical structures have been implicated in alcohol-related brain findings as well. In studies with repeated neuroimaging, greater volume reduction of various subcortical regions was consistently observed in alcohol users, particularly for the hippocampus[38, 40, 49], amygdala, and thalamus[43]. Similarly, retrospective studies with single timepoint neuroimaging reported smaller hippocampus volume[50], variations in thalamus volume[34], but larger nucleus accumbens (NAcc) volume[51] in alcohol users.

DTI studies with a YSI up to 11 years reported a link between moderate to heavy drinking and altered white matter microstructure in various tracts, including the corpus callosum[52, 53] and the anterior thalamic radiation (ATR)[54]. These findings were partly sex-specific: one study reported lower FA in men and higher FA in women[53], while another study found white matter alterations in men only[52].

When exploring global brain structure measures, the study with the longest YSI (approximately 27 years) of alcohol use that was ascertained prospectively (N = 400, Dunedin longitudinal study) reported a lower mean cortical thickness, smaller total brain volume and lower average fractional anisotropy in long-term alcohol users[55]. Interestingly, the findings of Knodt et al.[55] suggest an association with polysubstance use rather than alcohol use only, as the findings did not remain when adjusting for other substance use. Of the studies reviewed, only one study reported an overall thicker cortex in the context of long-term alcohol use[32].

In summary, long-term alcohol use initiated in adolescence has been consistently associated with morphological and microstructural characteristics in the frontal cortex, ACC, insula and subcortical brain areas. Findings for YSI < 10 years and YSI ≥10 years were similar, although longer term alcohol-related brain differences may tend to show a stronger association with polysubstance use. Studies with repeated neuroimaging outcomes had an average YSI between 2 and 5 years, which has several implications: first, it may be more difficult to disentangle reverse causality (i.e., antecedents from consequences), and second it is possible more follow-up time would enable for delineating more wide-spread neurobiological correlates. Importantly, several studies reported no association between 2-to-3 years of heavy drinking or binge drinking and structural brain variations[40, 56, 57]. However, the vast majority of studies implicate the involvement of key frontal, insular and limbic areas in the long-term outcomes of early-onset SUI.

Cannabis

Studies with cannabis-related structural brain outcomes are shown in Supplemental Table 1 (green labeled). All listed studies reported an average cannabis use initiation below age 20 years. Of these studies, roughly a third reported a YSI of ≥10 years, with the rest reporting a YSI <10 years.

Gray matter structure of the frontal cortex (i.e., volume, cortical thickness) has been implicated in several studies of cannabis use, mostly in studies with a YSI < 10. The largest study with repeated neuroimaging (N= 799, employing the IMAGEN cohort) reported that more lifetime cannabis use was related to a steeper decline of PFC thickness over time in adolescents aged 16-to-19 years[58]. Smaller or thinner frontal regions were also reported in another study where cannabis use was prospectively ascertained for 8 years[59], and in studies that assessed up to 10 years of cannabis use retrospectively[60-63]. However, in several young adolescent samples, cannabis use has also been linked to *thicker* frontal cortices[59, 61, 64]. DTI studies with a YSI up to 17 years reported altered white matter microstructure, mostly lower FA, in frontal brain regions of cannabis users[65-68]. In one study, repeated neuroimaging showed frontal decreases in FA over time were related to cannabis use[68].

Several single timepoint neuroimaging studies with a YSI ≥ 10 showed that regular cannabis use (i.e., weekly) was associated with smaller subcortical volumes and lower

subcortical connectivity, particularly in the hippocampus [55, 69-72]. After controlling for alcohol and/or tobacco use, these associations mostly remained, and were reported for both current[70, 72], as well as former heavy cannabis users (average 29 years abstinent)[69]. Moreover, several single timepoint neuroimaging studies with a YSI < 10 reported smaller volume[73] and lower FA[74] of the hippocampus and other subcortical regions[75-77], as well as smaller volume of the parahippocampal gyrus[78] in heavy cannabis users. A meta-analysis from 2013 that included some of these studies reported a consistent smaller hippocampal volume in cannabis users compared to non-users[79]. Conversely, in several samples, particularly in young adolescent samples, cannabis use has also been associated with larger subcortical volumes (e.g., hippocampus and amygdala) [61, 77, 80, 81]. When examining white matter microstructure, cannabis-related alterations were mostly reported in the corpus callosum[66, 71, 82, 83].

Although to a lesser extent, cannabis use has been associated with variations of temporal and parietal brain structure. In young adolescent samples (up to 17.8 years old), larger volume[81] and thicker cortex[61] of temporal and parietal regions was reported in cannabis users, while in older samples (up to 23 years old) with higher YSI, smaller volume[78] and thinner cortex[75] of temporal regions was reported. Furthermore, cannabis use has been related to smaller[78] and thinner[61] insular regions. Finally, DTI studies with a YSI up to 12.5 years that assessed cannabis use retrospectively reported altered white matter microstructure across the brain[54, 62, 74, 84-86], sometimes specifically in early-onset users[87]. Two studies with repeated neuroimaging reported a steeper decrease of FA over time in several large association tracts such as the superior and inferior longitudinal fasciculi (SLF and ILF) in cannabis-dependent individuals[68, 88].

Alongside this literature, several studies with large samples present null findings when examining the association between cannabis use and brain structure (e.g., N = 622 and N = 474[89], N = 181[90], N = 261[91]). For example, no associations were observed between cannabis use frequency patterns over time and subcortical brain structure[89, 90, 92]. Furthermore, studies employing a whole-brain, voxel-wise approach for both gray matter[93] and white matter structure[87] showed no associations with cannabis use. Given these null findings in larger sample studies, it is important to consider the possibility of inflated effect sizes[94] and an increased risk of false-positive findings[95, 96] in several small sample studies (N < 100) reporting an association between cannabis use and brain morphology.

In summary, studies with a YSI of up to 48 years reported a relationship between long-term cannabis use initiated in adolescence and structural brain differences, mostly in regions that show high concentrations of cannabinoid receptors such as frontal brain regions and the hippocampus. Although direction of the effect estimates (i.e., smaller or larger) was somewhat inconsistent, overall findings of studies with repeated measures and high YSI suggest smaller volumes and thinner cortices in long-term cannabis users. However, in some samples of young adolescent cannabis users, increases in thickness and volumes were reported. Importantly, null findings on the relationship between long-term cannabis use and brain structure were reported in several well-powered studies of adolescent and adult samples.

Co-use of alcohol and cannabis

Co-use of alcohol and cannabis is highly common in adolescence and young adulthood, and several studies have explored the association of co-use when initiated in adolescence (see Supplement 1, labeled striped yellow/green). The largest study with repeated neuroimaging (N = 724, NCANDA cohort) showed that use of both alcohol and cannabis, but not alcohol use or cannabis use alone, was associated with a steeper decline in volume in frontal, temporal and parietal brain regions over time[97]. Alcohol and cannabis co-use has also been related to a steeper decline in surface area over time in frontal brain regions, although this decline was even more pronounced for alcohol use only[41]. Contrastingly, 2-5 years of heavy alcohol-cannabis co-use was associated with thicker frontal, temporal and parietal cortices in two studies, one of which included repeated neuroimaging[98, 99]. Extensive co-use of alcohol and cannabis (often defined as 100+ episodes of use) has also been associated with altered white matter microstructure across cohorts with repeated neuroimaging, in particular lower FA of the superior and inferior longitudinal fasciculus, internal capsule, and corpus callosum[54, 56, 100-102]. It is noteworthy that all included studies on alcohol with cannabis co-use had a YSI < 10 (range 1.38-6.90 years), and the oldest average age at the neuroimaging assessment was 21.7 years, which limits our interpretations beyond young adulthood. Furthermore, several of the above-mentioned studies made use of one specific cohort. Thus, comparisons with other populations are needed in the future to examine the generalizability of these results.

In summary, the combined use of alcohol and cannabis may have specific associations with brain structure and microstructure, as compared to alcohol or cannabis use only. This idea is

demonstrated through findings on midlife brain structure in long-term cannabis users, that may mostly reflect a broader pattern of polysubstance use[55]. Alcohol and cannabis co-use has been associated with altered white matter microstructure and smaller volume and surface area in various brain regions. In contrast, thicker frontal, temporal and parietal cortices have also been reported.

Tobacco/Nicotine

Only few studies examined the associations between long-term tobacco use initiated in adolescence and neuroimaging outcomes later in life. Five studies with a YSI ≥ 10 and 7 studies with a YSI < 10 years were reviewed (see Supplement 1, labeled dark teal). Overall, daily tobacco use was primarily associated with thinner cortices, smaller surface area and smaller volume of frontal, subcortical and insular regions, although brain variations were reported widespread across the brain as well[55, 103].

When studying the frontal lobe of tobacco users, smaller measures of the ACC, PFC, OFC were reported most consistently across retrospective studies with a YSI ≥ 10, also after controlling for alcohol and cannabis use[55, 103-105]. Furthermore, in two studies with repeated neuroimaging, 2 to 3 years of tobacco use was related to thinner[106] and smaller OFC[107].Several studies also reported smaller volumes of the thalamus[103, 105] and insula[105, 108].

Interestingly, individuals with a smoking history up to 10 years (assessed retrospectively) mainly showed higher FA in the SLF, corona radiata, internal capsule and corpus callosum[109-112]. Frequency of early initiated tobacco use, specifically greater tobacco use per smoking day, has been associated with higher MD of the SLF and ILF as well[113]. The largest longitudinal study on tobacco-related brain outcomes in this review[107] (N=6,806), that employed the Adolescent Brain Cognitive Development study (ABCD) sample, investigated very early tobacco use (initiated at age 9-10 years) and brain outcomes at a 2-year follow-up. The authors found smaller volume and surface area of frontal, temporal and parietal regions in young adolescent smokers.

In summary, long-term tobacco use seems to be associated with smaller gray matter measures across the brain, particularly in frontal areas such as the OFC, as well as altered white matter microstructure (mostly higher FA). Interestingly, smaller gray matter structures were reported both in young adolescent smokers after relatively few years since initiation, as well as in adult smokers with as many as 27 years since initiation. As most DTI studies included

individuals only roughly 10 years since initiation, future studies are needed to elucidate white matter characteristics in longer-term adult smokers.

Other substances

In this section, we review long-term structural brain outcomes of other substances, categorized into phenethylamine (e.g., amphetamine, cocaine, MDMA), opioid (heroin) and ketamine use. (see Supplement 1, labeled dark blue for phenethylamines and dark purple for opioids and ketamine).

All but one study[114] had single timepoint neuroimaging and retrospective use assessment. Of note, several studies were not considered in this review, as the average age of substance use initiation in these studies was later in adulthood (at age >23 years)[115-121]. To some extent, this is not unexpected considering the higher average age of stimulant and opioid use initiation (17.0-18.0 years, respectively, in the US)[122] compared to the average age of alcohol, cannabis and tobacco use initiation (16.5, 16.4 and 16.6 years, respectively, in the US)[122].

Several studies investigated brain outcomes in long-term phenethylamine users (YSI range 1.3-14.3), whose use mostly consisted of amphetamine, methamphetamine or 3,4-methylenedioxymethamphetamine (MDMA) use. Noticeably, phenethylamine-related brain variations in the putamen, insula and frontal regions were reported across multiple cohorts, albeit not consistently either smaller or larger for the insula and frontal regions. In heavy users as well as in occasional users of phenethylamines, larger left volume of the putamen was reported[123, 124]. Interestingly, more frequent use of amphetamines was associated with larger left insula volume[123], while methamphetamine dependence was related to lower gray matter density (GMD) [125] and smaller volume[126], but thicker cortex in the insula[127]. A similar picture emerges in the frontal lobe, where more frequent use of amphetamines was linked to larger frontal volume[123], while methamphetamine dependent users showed smaller volumes[126] and lower GMD[125] of frontal regions. One study with a single neuroimaging measure at age 38 reported that combined amphetamine and alcohol use, but not amphetamine dependence alone, was associated with thinner frontal cortices, suggesting that polysubstance use might explain part of the long-term brain findings[128].

DTI studies on phenethylamine use showed both higher FA[114] and higher diffusivity[129] in the putamen. For frontal white matter, lower FA was reported[129]. Differences in results

(lower/higher FA, smaller/larger structures) might be explained by the age of the outcome assessment, which ranged from 16 to 41 years.

The relation between cocaine use and structural brain measures was also investigated in studies with a YSI > 10 (range: 10-21 years). These studies consistently reported smaller regional brain volume in cocaine dependent individuals, particularly in the SFG [130, 131], temporal [130, 131], occipital [130, 132] and subcortical [131-133] regions. Similar to amphetamine-related findings, cocaine dependence was associated with both smaller volume[132] as larger volume[131] of the right putamen.

Opioid use for up to 14 years after initiation, which primarily consisted of heroin use, was related to smaller volume[132] and lower gray matter density[134] of the insula. Other implicated regions were the PFC, ACC, fusiform gyrus and cerebellum, which were lower in GMD in opioid users[134]. One study with a YSI of 14 reported more total cerebrospinal fluid (CSF) in a sample of opioid users[135].

In the largest study on ketamine (N=126), use over the course of almost 10 years was associated with larger volume of the caudate nuclei and larger white matter volume throughout the brain[136]. However, ketamine use was also associated with smaller volume of the left precuneus 5 years after initiation[137], and altered white matter microstructure 7 years after initiation[138]. Specifically, ketamine users, compared to polydrug users that did not use ketamine, showed lower AD primarily in prefrontal white matter tracts.

Summarized, long-term use of phenethylamine drugs such as amphetamines and cocaine was primarily associated with larger volume and altered white matter microstructure of the putamen. Furthermore, larger volumes of the frontal and insular cortices were reported in adolescent samples, while smaller volumes of these regions were reported in adult samples, possibly suggesting differential brain outcomes for continuation of use into adulthood. Long-term opioid use initiated in adolescence was linked to smaller volume and altered white matter microstructure in subcortical regions, the insula, and various frontal regions, although larger subcortical volume was reported in the largest study included. As none of the above-mentioned studies explored the relationship between opioid use and brain outcomes longitudinally, it is yet unclear if and how the reported structural brain variations might change over time.

A note on sample size

In light of a recent influential study that suggested that sample sizes of over 1,000 participants are needed to examine reproducible brain-behavior associations[139], concerns can be raised about the generalizability of the reported findings in this review. This can be particularly relevant given some of the heterogeneity of findings across studies. However, it is unlikely such large sample sizes are needed for all human neuroimaging research. For example, a study by Makowski et al.[140] indicated that a sample size of 100 participants can be sufficient, and likely the sample size depends more on the research question and methods employed. Nevertheless, despite the inclusion of many studies that included hundreds to thousands of participants, generalizability limitations of studies with modest sample sizes[94, 95] in this review should be taken into account.

Sex differences

As the literature generally suggests that males and females differ in neurodevelopmental trajectories[141], it is also of interest to understand how such differences in brain morphology relate to sex differences in substance use and risk of developing SUD[142]. Examining potential sex differences is of added value as it can offer insight into how several systems potentially play a role in the development of SUD, including endocrine, metabolic and immune system function in men and women. In the current review of the literature surveyed (Supplemental Table 1), very few studies examined whether sex-specific associations between substance use and brain structure/microstructure existed [46, 52, 53, 101]. In most studies which did explore this, sex differences were detected. Furthermore, in many of the studies reviewed, women were substantially underrepresented in the sample (a proportion of less than 20% was not uncommon). Future work should continue to explore the potential for differential neurobiological correlates between males and females, in addition to gender differences, but care should be taken to ensure sufficiently-powered statistical inferences are possible.

Study Design & Temporality

In order to fully disentangle the neurobiological precursors and consequences of substance abuse, prospective, repeated measures data collections are crucial. Understanding whether neural features exist *prior* to use improves our ability to make inferences on the longer-term outcomes of substance use. However, given the complexity in procuring these exceptional

datasets, it is not surprising that this study design was relatively rare in the literature surveyed. Of the available data, studies with neuroimaging estimates prior to initiation were most common when examining alcohol and cannabis use. Interestingly, prior to any alcohol use initiation, smaller right ACC, pars triangularis, isthmus cingulate, parahippocampal gyrus and left postcentral gyrus volumes have been observed [47, 143]. Thus, as the cingulate cortex is routinely observed in studies several years after use initiation, it is possible that at least part of the association linking alcohol use to longer term accounts can be accounted for by neural features which predate use initiation. However, importantly, not all prospective studies that investigated alcohol use reported pre-existing structural brain variations [36, 39, 43]. Likewise, in one large (N=6,806) longitudinal study examining tobacco-related brain outcomes, the authors reported smaller volume and surface area of frontal, temporal and parietal regions in young adolescent tobacco smokers, with some of these differences detectable already at the baseline MRI [107]. Such pre-existing differences have been less frequently observed in cannabis use studies that enrolled participants prior to cannabis use initiation [58, 81, 93]. In a recent systematic review, several consistent findings emerged from studies examining brain morphological predictors of substance use initiation in adolescents, with the ACC and frontal cortex predictive of future alcohol, cannabis or tobacco use [31].

Co-morbid psychopathology

Apart from understanding whether there are neural correlates which precede (or predispose one to) substance use initiation, another key challenge in the field which benefits from prospective data is the question of comorbid psychopathology. For example, psychopathology and psychiatric problems seem to increase the risk of early substance use initiation[144, 145]. Thus, in addition to disentangling the neural causes and consequences of substance use, it will also be crucial to understand whether there are neurobiological features which are closely linked to emerging psychopathology, and begin to disentangle whether it is precisely these neurobiological indicators or other downstream factors related to the psychopathology which increase SUI risk. Importantly, early SUI and comorbid psychopathology is thought to be linked to markedly worse outcomes later in life, considering the higher risk of developing an SUD[146]. This underscores the importance of delineating the diverging and shared etiology. A recent comprehensive review on the topic generally concluded

that comorbid externalizing disorders were linked to variations in frontal and basal ganglia structure whereas comorbid internalizing disorders were less clear[147]. Interestingly, the neural correlates of SUD seem to be more robust when compared to those involved in psychopathology[147].

Substance use assessment

Some of the inconsistent findings of adolescent substance use and long-term brain morphology could be attributed to the exposure assessment. In smaller, focused cohorts, it is clear that extensive assessment is necessary and is also often very feasible. However, in large prospective epidemiological studies, it is often not possible to extensively asses substance use in detail, and thus shorter screening tools are frequently used. In the reviewed studies, substance use in adolescence was assessed in multiple ways with a variety of instruments. When examining substance use in adolescence, a good starting point is to focus on age of initiation, quantity and frequency of use, and variability of use. If resources allow, it is then of course desirable to focus on additional substance use disorder related criteria, including impaired control, physical dependence, social problems and risky use.

Generally, self-reported information is thought to provide valid and reliable information, however, bias (e.g., recall, social desirability) always is possible[148]. For example, in a group of 200 adolescents aged 16 years (with or without a family history of substance use disorder or psychiatric disorder), imperfect concordance between self-reported marijuana use during the prior 48 hours in an interview format and urinalysis was observed[149]. Thus, biological information (e.g., blood/urine/hair samples) information and self-reported information can clearly complement each other. A promising technology to assess substance use could be hair toxicology, especially to determine substance use covering a longer period (± 3 months). In a large urban cohort study of young adults aged 20 years (N=1002)[150], hair tests were more sensitive than self-reports. However, these biological assays can be expensive and also have their limitations, for example hair toxicology results have been shown to be sensitive to hair characteristics (e.g., color, type, and external hair exposures)[151-153] .

Polysubstance use

In addition, it is crucial to not only focus on the substance of interest for the study, but to also collect information about polysubstance use as the findings generally described in this review showed larger effect sizes. Polysubstance use patterns are relatively common in adolescents[8, 154]. Understanding the specific neurobiological correlates of a given substance is complicated by this relatively high prevalence of polysubstance use; how to best characterize these neural correlates when participants very frequently present with polysubstance use? In this review, several of the studies used a mutual adjustment approach to correct for co-use. However, interpreting each effect estimate from such models as being independent is likely inaccurate and has been described as the Table 2 fallacy[155]. Strict study inclusion/exclusion criteria selecting in individuals with single-use profiles is also likely suboptimal; individuals who use a single substance are likely to be fundamentally distinct from polysubstance users, and thus such selection criteria likely lead to bias. Another point of attention is that when multiple substances are used there may be drug-to-drug interactions. For example, when alcohol is used along with other substances that act as inhibitors, such as cannabis, it can enhance its effect[156].

At the same time, brain morphology variations related to substance use might not be substance-specific; instead, they could be generalized across different substances. A recent meta-analysis combining 45 studies on neural correlates of adult SUD reported that 91% of structural neuroimaging findings mapped to a common brain network, involving the ACC, dorsolateral PFC, insula and thalamus[157]. Although the current review focuses on substance use in adolescent/young adult samples, this common brain network is well reflected across alcohol, cannabis and tobacco studies (see Figure 1 and Figure 2). Importantly, whereas Stubbs et al.[157] reported a pattern of smaller brain regions, our review displays substance-specific differences in directionality: cannabis use was associated with both smaller and larger brain regions, while alcohol and tobacco use were primarily associated with smaller brain regions. This could indicate substance-specific brain features, or could also reflect neurodevelopmental timing differences, for example substance use effects could become more stable over time.

Future Opportunities

Several areas of focus within adolescent substance use research are ripe with opportunities in the coming years. First, various advances in neuroimaging techniques and image analysis are observed regularly. For example, acquisition times have been shortened

dramatically[158], allowing for more high quality data to be acquired within reasonable scan times. This, for example, makes novel diffusion imaging acquisition and more elegant image analysis modeling, which could be increasingly sensitive to alterations in white matter microstructure, more feasible[21]. Ultra-high field imaging also improves signal-to-noise ratio, and will allow for more fine-grained mapping of the anatomical and functional organization of the brain, but also particularly how metabolites (e.g., even some neurotransmitters) are related to substance use[159].

Another area likely to see substantial new development is related to the deployment of multivariate techniques to detect complex patterns in high dimensional neuroimaging data[160]. As it is relatively common to conduct 'mass univariate' analyses with imaging data, where each region/voxel of the brain is considered independent from the others, it has been suggested larger effect sizes may be attainable when many small effect sizes are 'pooled' using multivariate techniques[161]. Given the availability of large, high quality datasets[162, 163], as well as important consortium efforts to pool data[164], it becomes ever more feasible to generate models which are less prone to overfitting and are more generalizable. However, care must be taken to ensure the models are utilized properly to prevent overfitting[165] and that true, out of sample generalizability is tested[166]. Most crucially in the context of overfitting, care must be taken to ensure models are particularly not overfit in ways which increases disadvantage or disparity in minority groups. Lastly, as these methods are generally well-suited and primarily used for prediction work (i.e., not for etiological/causal inferences), it is important that the specific aim and goal of the research is specified clearly to avoid confusion[20]. Indeed, such methods are being more frequently used for several kinds of research, including causal inference[167], and with a focus on explainability and interpretability[168].

Another opportunity lies in the improvement of inferring causality from observational data. For example, Bayesian causal network modeling[169] has been applied to investigate the direction of effects between brain morphology and alcohol/cannabis use in the IMAGEN sample[170, 171]. Target Trial Emulation (TTE)[172, 173], which simulates a randomized controlled trial within an observational study setting, is another promising option for leveraging observational data to make causal inference. With careful planning of data collection and study design, it could be implemented in neuroimaging studies of substance use. Lastly, with the availability of genetic data, methods like Mendelian randomization[174] and latent causal variable analysis[175] can help explore causal relationships between substance use and brain morphology by identifying genetic

instruments[176, 177]. Triangulation [178] will be particularly crucial when making causal inferences from observational substance use neuroimaging data.

Finally, addressing brain-substance use relationships poses a challenge to distinguish direct effects of a substance's active compound (e.g., tetrahydrocannabinol (THC) in cannabis, and nicotine in tobacco) from by-products (e.g., resulting from the combustion process). The overlap in findings for cortical thinning for tobacco and cannabis use might even support the idea that the combustion by-products of tobacco and cannabis cigarettes explain an important part of the association. Preclinical studies have linked direct THC exposure to altered prefrontal cortical maturation[179]. However, in human observational work, disentangling the impact of a substance's active compound from that of such byproducts remains challenging. Utilizing route of administration information could provide valuable insight into underlying factors contributing to the reported brain findings, and future studies should both consider this during data collection/inclusion, as well as data analysis.

Rich, large-scale data collections such as the ABCD study open up new and exciting opportunities, with prospective data acquisition which is of exceptionally high quality. These datasets allow for understanding temporality, prediction as well as etiological research, methods development, and much more. Further, next to valuable exposure and outcome data, large prospective epidemiological studies often include highly detailed information on potential confounding factors, which allows for adjustment of statistical models to minimize the amount of bias in effect estimates. It thus is crucial for all studies of substance use to consider which confounding factors might bias results and ensure such information is collected during data collection.

Conclusion

This review summarizes the current state of the literature regarding adolescent initiated substance use and later structural brain outcomes. Several well-powered studies, a number of which ascertained substance use prospectively and included repeated-measures neuroimaging, offer important insights into the potential consequences of early substance use initiation on the brain. Overall, the findings summarized point towards involvement of the frontostriatal circuit with exposure to different classes of substances, and the insula and limbic structures appear

robustly across studies as well. However, generally speaking, within a particular class of substances, divergent findings were nearly as common as convergent findings across studies.

Additional information

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Olga Boer: Conceptualization, Methodology, Investigation, Data curation, Writing - Original draft, Visualization. **Hanan El Marroun:** Conceptualization, Data curation, Writing - Original draft, Writing - Review & Editing, Funding acquisition, Supervision. **Ryan Muetzel:** Conceptualization, Data curation, Writing - Original draft, Writing - Review & Editing, Funding acquisition, Supervision.

Data availability

Not applicable

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Figure 1

Long-term structural cortical brain outcomes associated with substance use initiated in adolescence: overview of the current literature. Findings are mapped onto the Desikan-Killiany atlas within the R package ggseg (https://cran.r-project.org/package=ggseg), which visualizes the brain's surface in an inflated and flattened manner to show all brain areas simultaneously. Blue indicates a smaller brain region, and red indicates a larger brain region (either in gray matter volume, cortical thickness or surface area). Darker blue/red indicates a larger number of studies reporting substance use-related differences in a specific brain region. Abbreviations (left-right, clockwise): TT = transverse temporal gyrus, lOFC = lateral orbitofrontal cortex, pars or = pars orbitalis, pars tr = pars triangularis, pars op = pars opercularis, r/cMFG = rostral/caudal middle frontal gyrus, PRG = precentral gyrus, POG = postcentral gyrus, STG = superior temporal gyrus, banksSTS = banks of the superior temporal sulcus, MTG = middle temporal gyrus, ITG = inferior temporal gyrus, LOG = lateral occipital gyrus, IPG = inferior parietal gyrus, SPG = superior parietal gyrus, SMG = supramarginal gyrus, PCG = paracentral gyrus, SFG = superior frontal gyrus, c/rACC = caudal/rostral anterior cingulate cortex, mOFC = medial orbitofrontal cortex, entorh = entorhinal cortex, PHG = parahippocampal gyrus, FFG = fusiform gyrus, PCC = posterior cingulate cortex, PRCU = precuneus, CUN = cuneus.

Figure 2

Long-term structural subcortical brain outcomes associated with substance use initiated in adolescence: overview of the current literature. Findings are mapped onto the automatic subcortical segmentation (ASEG) atlas within the R package ggseg (https://cran.r-project.org/package=ggseg). Blue indicates a smaller brain region, and red indicates a larger brain region (either in gray matter volume, cortical thickness or surface area). Darker blue/red indicates a larger number of studies reporting substance use-related differences in a specific brain region. Abbreviations: ventral DC = ventral diencephalon.