Brain morphology predictors of alcohol, tobacco, and cannabis use in adolescence: A systematic review

Olga D. Boer a, b, *, Hanan El Marroun a, b, Ingmar H.A. Franken a

a Department of Psychology, Education and Child Studies, Erasmus School of Social and Behavioral Science, Erasmus University Rotterdam, 3000 DR Rotterdam, the Netherlands
b Department of Child and Adolescent Psychiatry, University Medical Center Rotterdam, Erasmus MC, Sophia Children’s Hospital, 3000 CB Rotterdam, the Netherlands

ARTICLE INFO

Keywords:
Neuroimaging
Alcohol
Cannabis
Tobacco
Adolescence
Risk factors

ABSTRACT

In the last decade, extensive research has emerged on the predictive value of brain morphology for substance use initiation and related problems during adolescence. This systematic review provides an overview of longitudinal studies on pre-existing brain variations and later initiation of alcohol, tobacco, and cannabis use (N = 18). Adolescent structural neuroimaging studies that started before substance use initiation suggest that a smaller anterior cingulate cortex (ACC) volume, thicker or smaller superior frontal gyrus, and larger nucleus accumbens (NAcc) volume are associated with future alcohol use. Also, both smaller and larger orbitofrontal cortex (OFC) volumes were associated with future cannabis and combined alcohol/cannabis use. Smaller amygdala volumes were related to future daily tobacco smoking. These findings could point to specific vulnerabilities for adolescent substance use, as these brain areas are involved in cognitive control (ACC), reward (NAcc), motivation (OFC), and emotional memory (amygdala). However, the reported findings were inconsistent in directionality and laterality, and the largest study on alcohol use predictors reported null findings. Therefore, large population-based longitudinal studies should investigate the robustness and mechanisms of these associations. We suggested future research directions regarding sample selection, timing of baseline and follow-up measurements, and a harmonization approach of study methods.

1. Introduction

Adolescence is a period of transition between childhood and adulthood which is accompanied by an accelerated brain development. Brain development during adolescence is characterized by the maturation of subcortical brain areas while maturation of cortical development is not yet complete. This process has been associated with a variety of behaviors in adolescents, such as impulsivity and risk-taking, as the frontal-subcortical circuitry and connectivity within this circuitry are still developing while the limbic system is relatively overactive (Casey and Jones, 2010; Crews et al., 2007). Although risk-taking behaviors can serve a beneficial role for survival and social development (Salas-Rodriguez et al., 2021), it is also thought to make adolescents more prone to initiate substance use and to experiment with substances such as alcohol, tobacco, and cannabis. Indeed, substance use is prevalent among adolescents: in the US, the average 15-year-old consumes about 6 L of alcohol a year (Baranger et al., 2020), 45 % of adolescents have tried cannabis before the age of 17–18 years (Wade et al., 2019), and 90 % of smokers reported to have initiated smoking before the age of 18 years (Chaarani et al., 2019). This poses a significant public health concern, as adolescents are not only more prone to use substances, but might also be more vulnerable to the harmful effects of substance use (Bava and Tapert, 2010). Adolescent substance use has been associated with brain abnormalities in prefrontal, hippocampal and cerebellar regions, and white matter integrity, as well as increased risk for deficits in attention, memory, and executive functioning, although there are contrasting reports on executive functioning deficits (Bava and Tapert, 2010; Boelema et al., 2015). Furthermore, substance use during adolescence, especially when initiated at an early age – often defined as initiation before the age of 15 - is a strong predictor of future substance use and an increased risk for the development of substance use disorders (SUD; Hamidullah et al., 2020; Trujillo et al., 2019). For example, adolescents who initiate alcohol use before the age of 15 have a two- to threefold increased risk of developing alcohol abuse and dependence,
compared to adolescents who stay alcohol-naïve until age 19 (DeWit et al., 2000).

Once a SUD has been developed, this often has long lasting detrimental effects. For example, in Europe alcohol use disorders are the third biggest contributor to the overall burden of mental disease (Wittchen et al., 2011). On an individual level, this burden could even be bigger since SUDs show high comorbidity with mood and anxiety disorders (Lai et al., 2015). Therefore, early prevention of substance use disorders through population-wide prevention programs is of paramount importance. This necessitates thorough identification and understanding of the major risk factors involved in the initiation and continuation of substance use.

The current literature has indicated several groups that are thought to have increased risk to initiate substance use early or are vulnerable to development of SUD. These groups consist of individuals that are prenatally exposed to maternal substance use (Baer et al., 2003; O’Brien and Hill, 2014), that have a family history of SUD (Cservenka et al., 2015; Hanson et al., 2010; Hill et al., 2013), or show specific traits that may facilitate adolescent substance use risk, for example persons with childhood internalizing and externalizing problems (Brown et al., 2008; Zucker et al., 2008), impulsivity (Ernst et al., 2006; McGue et al., 2001) and aggressive traits (Ernst et al., 2006). It is thought that the neurodevelopment of regions involved in reward, motivation, and cognitive control underlies the above-mentioned behavioral constructs (Brunback et al., 2016). Therefore, recent studies have focused on understanding the role of brain development in substance use risk.

Brain morphology includes structural magnetic resonance imaging (MRI) measures of the brain such as volume, cortical thickness, surface area and white matter integrity, and has been reported as a predictor of various mental disorders as well as cognitive functions years later (Mateos-Perez et al., 2018; Sabuncu et al., 2015; Ullman et al., 2014). Although using structural and functional MRI (sMRI and fMRI) as complementary methods can be useful when investigating neural markers for substance use initiation (Madan, 2017), studies often focus on either brain morphology (using sMRI) or brain activity (using fMRI). The current systematic review focuses on brain morphology studies only (i.e., sMRI T1-weighted structural images and/or diffusion tensor imaging), as brain structure and its associated traits related to substance use behavior seem to be more stable over time as compared to task-dependent brain activity (Sato et al., 2021; Vetter et al., 2017). This continuity is particularly useful in the interpretation of longitudinal findings. One of the key issues is to disentangle brain alterations that predict future substance use before substance use initiation from brain alterations that are a result of substance use (Squeglia et al., 2009). In that way, specific pre-existing vulnerability markers can be detected, which in turn could inform future neuroimaging studies in the formulation of a priori hypotheses regarding the interplay of brain morphology and substance use. This necessitates a prospective longitudinal research design in which subjects are substance-naïve at the time of their first neuroimaging measurement. Several previous studies and reviews have focused on adolescents with a family history of substance use and prenatal substance exposure. To reduce potential family confounding, the current review aims to systematically evaluate the existing literature on brain morphology predictors of substance use during adolescence in the general population. This review specifically focuses on alcohol, cannabis and tobacco use as these are commonly used substances among adolescents (Johnston et al., 2020).

1.1. Aim of the study

The purpose of this study is to 1) systematically review the available literature on brain morphology predictors of alcohol, cannabis, and tobacco use during adolescence, 2) compare results from study cohorts and evaluate the generalizability of the results, and 3) provide recommendations for future research and hint towards potential clinical implications.

2. Methods

We conducted a comprehensive literature search strategy using Embase, Medline ALL, Web of Science Core Collection, PsycINFO, Cochrane Central Register of Controlled Trials and Google Scholar and searched for longitudinal structural neuroimaging studies and adolescent substance use. The complete search (see Supplement A) was performed on January 21st, 2021 with the help of professional librarians. The search terms aimed to combine study characteristics (e.g., longitudinal, prospective, cohort analysis) subject characteristics (e.g., adolescence, child development), assessment method (e.g., magnetic resonance imaging (MRI), neuroimaging) and outcome measures (e.g., substance use, drinking behavior, cannabis use, cigarette smoking). As the consulted databases use different thesauri for indexing, our search strategy was specified based on the index terms of the respective database. The terms we searched for in title and abstract were the same for every database, except for Google Scholar, which uses a maximum number of terms in a search. The inclusion process, depicted in Fig. 1, was conducted by author OB, and when in doubt about the selection of specific studies, this was discussed in detail with authors HM and IF until consensus was reached. Studies were included if:

- The study had a prospective longitudinal design, in which the first time point included a MRI measurement consisting of T1-weighted structural images and/or diffusion tensor imaging (DTI) and the last time point included an assessment of substance use.
- Brain morphology, including gray matter volume, cortical thickness, surface area and/or white matter integrity was examined in the MRI measurement.
- Participants were substance-naïve at first neuroimaging measurement, and at follow-up, part of the participants had initiated substance use.
- Participants were not specifically recruited as a member of a high-risk group e.g., those who were prenatally exposed to substances or had a family history of SUD.

Meta-analyses, narrative and systematic reviews were excluded, but the reference lists were screened, although this did not result in additional inclusions. The 18 studies that were selected for the current review showed considerable heterogeneity in terms of brain regions reported, substance use outcomes measured, age at first measurement and follow-up duration and characteristics. Considering that performing robust meta-analyses requires a sufficient number of studies (~17–20) to be comparable on these aspects (Eickhoff et al., 2016), we were not able to conduct a meta-analysis. Before any full-text reviewing, a protocol for data extraction was created to be consulted during the data extraction process. Although preregistration was not possible due to timing limitations, the authors ensured to not deviate from the protocol.

2.1. Data quality assessment

As we aimed to include all relevant studies for our research question, studies were not excluded based on quality assessment. However, a structured quality assessment was conducted to gain insight into the quality of the study and its generalizability to the general population. Furthermore, this quality assessment also informed us to provide recommendations for future research. As no standardized criteria have been established for assessing the quality of structural neuroimaging studies (Soiza et al., 2008), it was decided to combine relevant quality checks from the revised tool for Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2; Whiting, 2011) and the Newcastle-Ottawa Scale (NOS; Wells et al., 2013). Each paper was evaluated and scored on the following items by OB, and when in doubt about specific quality aspects, this was discussed in detail with HM until consensus was reached.
Based on these questions, a maximum composite score of 12 could be obtained (see Fig. 2 and Supplement B). It should be noted, however, that this score is dependent on the available study information, and assessment of study limitations may differ depending on culture, region and
field of expertise of the evaluator. Furthermore, many studies did not report results that could be interpreted independently as we included multiple studies of the same cohort. The Orygen Adolescent Development Study (OADS) cohort (4 studies) consists of 245 participants recruited in Melbourne, Australia at the age of 12. The National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) (2 studies) employed a high-risk enhanced community sample of 831 participants in five research sites across the United States. The IMAGEN project cohort (3 studies) consist of 2,000 participants, recruited at the age of 14 at eight research sites across Germany, Great Britain, France and Ireland. The University of California-San Diego cohort first described by Tapert et al. (2003; 5 studies), later referred to as the San Diego cohort, consists of 296 participants recruited at local public schools in San Diego.

3. Main body

3.1. Predictors of future alcohol use

As alcohol is the most commonly used substance among adolescents (Hamidullah et al., 2020), the majority (N = 10) of the available research focuses on brain morphology predictors of future alcohol use (see Table 1 and Fig. 3). Two studies reported a smaller volume of parts of the anterior cingulate cortex (ACC), an area involved in cognitive control mechanisms, in future alcohol users as compared to future non-users. Cheetham et al. (2014) reported an association between smaller left dorsal and rostral paralimbic ACC volumes at age 12 and alcohol-related problems at age 16 (OR = 0.95, 95% CI [0.92-0.98]). In this study, alcohol-related problems were defined as negative consequences of alcohol use, including getting sick or injured, showing impulsive sexual or violent behavior, and experiencing dependence symptoms. Cheetham et al. (2014) examined pre-existing brain differences in future heavy drinkers, where the heavy drinking classification was based on a combination of the number of drinks consumed per occasion, and the number of drinking occasions per month (described in Cheetham et al., 2012). In this study, smaller right rostral (η² = 0.16) and caudal (η² = 0.13) ACC volumes at baseline (age 12–17 years) predicted heavy drinking at follow-up (age 15–20 years). Furthermore, a smaller baseline volume of the left isthmus cingulate, part of the posterior cingulate cortex, was associated with heavy drinking at follow-up (η² = 0.11). Although both studies indicated an association between smaller ACC volumes and future alcohol use, laterization and exact location of these differences within the ACC seemed inconsistent. Furthermore, participants in the study by Cheetham et al. (2014) were older at both baseline and follow-up measurement, and the outcome measurement was more focused on alcohol use itself rather than its negative consequences. Orbitofrontal cortex (OFC) variations have been investigated as a predictor for future alcohol use as well, considering the role of this region in motivation and reward processing (Schoenbaum et al., 2006). In a study by Luby et al. (2018), thinner orbitofrontal cortex at age 7–12 predicted higher alcohol use frequency as well as steeper increases in alcohol use frequency-six years later. When exploring the link between baseline differences in cortical measures of the nucleus accumbens (NAcc), an area involved in reward processing, and future alcohol use, Morales et al. (2019) reported that greater NAcc volume at age 14 was related to alcohol use 2 years later (β = 0.15). For men, but not women, this could be explained by an indirect effect through sensation seeking (β = 0.04).

Besides variations of the ACC and OFC, various studies reported other frontal structural predictors of later alcohol use. Jacobus et al. (2016) reported a thicker left superior frontal gyrus at age 12–14 in adolescents who initiated alcohol use by the age of 18 as compared to non-initiators. When examining frontal gyrus volume, Baranger et al. (2020) reported that smaller right middle and superior frontal gyri volumes at baseline (age 11–15 at baseline) were associated with earlier initiation of alcohol use. Other frontal brain metrics that predicted heavy drinking at follow-up were a smaller surface area of the right dorsolateral prefrontal cortex at age 12–14 (IRR = 0.77; Brumback et al., 2016) and smaller volume of the right pars triangularis, a brain area located in the inferior frontal lobe, at age 12–17 (η² = 0.13; Squeglia et al., 2014). Although most baseline structural differences were found in the frontal lobe, some parietal and temporal lobe differences were reported. Greater volume of the left postcentral gyrus, as well as a smaller volume of the right parahippocampal gyrus at age 14, were associated with binge drinking at 2-year follow-up (Whelan et al., 2014). Some studies investigated whether variations in white matter integrity
could predict future alcohol use. Less white matter in the right cerebellum at baseline (age 12–17 years) predicted heavy drinking around 2 years later ($r^2 = 0.09$; Squeglia et al., 2014). Furthermore, lower baseline (age 14–15 years) fractional anisotropy (FA) in white matter proximal to the ventral pallidum, an area that receives input from the NAcc (Ikei, 2010), was associated with earlier onset of binge drinking (Morales et al., 2020) (right effect $b = 0.43$, left effect $b = 0.40$).

Lastly, Squeglia et al. (2017) reported reduced cortical thickness as a global predictor for future alcohol use: Using a robust machine learning technique, the authors demonstrated that thinner cortices of 13 areas across the cortex (see Table 1) at age 12–14 were associated with moderate to heavy alcohol use at age 18 (Cohen’s $d$ ranging from 0.36 to 0.87). However, in their large study ($N = 1492$), Seo et al. (2019) did not report any gray matter volume differences at age 14 years to be predictive of drinking behavior at 19 years.

Summarized, the above-mentioned studies collectively suggest an association between pre-existing structural differences in areas involved in reward processing, motivation and decision making (ACC, NAcc, OFC and other prefrontal areas), and future alcohol use. In Fig. 3, brain areas that are smaller in future alcohol users are depicted in blue (e.g., ACC, OFC, and frontal gyri), and brain areas that are bigger are depicted in red (e.g., NAcc). Importantly, it must be kept in mind that the largest study reported null findings, which is not displayed in the figure.

### 3.2. Predictors of future cannabis use

Another frequently used substance which use is often initiated during adolescence is cannabis (marijuana, weed or hashish). While variations in a multitude of brain areas were suggested as possible predictors for future alcohol use, future cannabis use has consistently been associated with pre-existing brain alterations in one brain region, i.e. the OFC, which was found relevant in all four selected studies (see Table 2 and Fig. 4). Cheatham et al. (2012) reported that smaller OFC volume at age 12 years predicted cannabis use initiation by age 16 years. When controlling for other substance use, only smaller right lateral OFC volume predicted future cannabis use initiation (OR = 0.98, 95 % CI [0.96–1.00]). In line with this finding, Spechler et al. (2019) found smaller right OFC volumes at age 14 in adolescents who initiated

---

**Table 1**

| Author            | Cohort       | ROIs | Substance use assessment | N     | Age at baseline in years | Follow-up duration in years | Main predictor | Main outcome |
|-------------------|--------------|------|---------------------------|-------|--------------------------|-----------------------------|----------------|-------------|
| Baranger et al.   | TAOS         | 15 cortical regions using the primary sulcal structures. | SUQ   | 223 | 11–15 | Up to 6 | ↓ GMV of right middle + superior frontal gyr | Earlier alcohol use initiation |
| Brumback et al.   | San Diego    | Surface area and cortical thickness of: dIPFC, IFG, OFC, ACC, Insular cortex, parietal cortex | CDDR  | 265 | 12–14 | 13 | ↓ SA of right dorsolateral prefrontal cortex | ↑ Binge drinking |
| Cheatham et al.   | OADS         | Amygdala, hippocampus, ACC, OFC | Youth risk behavior survey | 98   | 12       | 4 | ↓ GMV of left dorsothal + rostral paralimbic ACC | ↑ Alcohol-related problems |
| Jacobus et al.    | San Diego    | Cortical thickness | CDDR | 69  | 12–14 | 6–8 | ↑ CT of left superior frontal gyrus | Alcohol use initiation |
| Luby et al.       | St Louis     | OFC and striatum | Diagnostic interview and CIDI | 135  | 7–12 | 6 | ↑ CT of OFC | Alcohol use frequency and change in alcohol use frequency. |
| Morales et al.    | NCANDA       | NAcc | CDDR | 516 | 14 | 2 | ↓: ↑ GMV of NAcc, indirect through sensation seeking. | ↑: ↑ GMV of NAcc | ↑: ↑ Alcohol use |
| Morales et al.    | NCANDA       | FA in white-matter pathways connecting the NAcc to the rest of the brain | 90-day TLFB | 40  | 14–15 | 6 | ↑ FA in WM proximal to ventral pallidum | Earlier onset of binge drinking |
| Seo et al.        | IMAGEN       | ACC, amygdala, CN, mPFC, OFC, putamen, thalamus, insula | ESPAD | 1472 | 14 | 5 | No associations reported | No associations reported |
| Squeglia et al.   | San Diego    | All brain regions | CDDR | 40  | 12–17 | 3 | ↓ GMV of right rostral + caudal ACC, right pars triangularis, left isthmus cingulate, ↓ WM in right cerebellum | ↑ Heavy drinking |
| Squeglia et al.   | San Diego    | Cortical thickness | CDDR | 137 | 12–14 | 4–6 | Global cortical thickness effect, consists of ↓ CT of left + right superior parietal, ↓ CT of left banks of superior temporal sulcus, lateral occipital, lingual, rostral anterior cingulate, supramarginal, transverse temporal, ↓ CT of right middle temporal, pars orbitalis, precuneus, rostral middle frontal, superior frontal, temporal pole | Moderate to heavy drinking before the age of 18 |
| Whelan et al.     | IMAGEN       | Regional gray matter volume, total parenchymal volume, and whitegray matter ratio | ESPAD | 271 | 14 | 2 | ↓ GMV of right parahippocampal gyrus, ↑ GMV of left postcentral gyrus | Binge drinking |

---

**Table footnote:** CDDR = Customary drinking and drug use record, CIDI = composite international diagnostic interview, CT = cortical thickness, ESPAD = European School Survey Project on Alcohol and Drugs, FA = fractional anisotropy, GMV = gray matter volume, ROIs = Regions of Interest, SA = surface area, SUQ = Substance use questionnaire, TLFB = Timeline followback, WM = white matter.
cannabis use by the age of 16, but only in women ($r = -0.09$). Furthermore, thinner orbitofrontal cortices at age 7–12 have been associated with future cannabis use initiation as well as an increase in cannabis use frequency (Luby et al., 2018). Interestingly, not only smaller but also larger OFC volumes have been suggested as a predictor for future cannabis use, as in the study of Luby et al. (2018) an increase in OFC volume over time was associated with cannabis use initiation at follow-up. Likewise, a greater left lateral OFC volume at baseline (age 12–15)

Fig. 3. Brain morphology predictors of future alcohol use. Blue = smaller/thinner in future alcohol users. Red = bigger/thicker in future alcohol users. x$^n$ = reported across n cohorts. SFG = superior frontal gyrus, MFG = middle frontal gyrus, PCG = postcentral gyrus, dIPFC = dorsolateral prefrontal cortex, PHG = parahippocampal gyrus, l/mOFC = lateral/medial orbitofrontal cortex, ACC = anterior cingulate cortex, NAcc = nucleus accumbens. * smaller white matter volume of the cerebellum is depicted here. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

| Author          | Cohort     | ROIs                                | Substance use assessment | N   | Age at baseline in years | Follow-up duration in years | Main predictor                                                                 | Main outcome                              |
|-----------------|------------|-------------------------------------|--------------------------|-----|-------------------------|----------------------------|--------------------------------------------------------------------------------|-------------------------------------------|
| Cheetham et al. (2012) | OADS       | OFC, amygdala, ACC, hippocampus     | Youth risk behavior survey | 121 | 12                      | 4                          | ↓ GMV of orbitofrontal cortex (OFC), right lateral OFC when controlling for other substance use | Cannabis use initiation                    |
| Luby et al. (2018) | St Louis   | OFC and striatum                    | Diagnostic interview and CIDI | 135 | 7–12                    | 6                          | ↓ CT of OFC and ↑ GMV (over time) of OFC – ↓ CT of OFC                       | Cannabis use initiation – Increase in cannabis use frequency |
| Spechler et al. (2019) | IMAGEN     | Total GMV and 278 GMV ROIs across the brain | ESPAD                    | 1216 | 14                      | 2                          | $\varphi$: ↑ GMV of right medial PFC and $\varphi$: ↑ GMV of left midcingulate cortex. | $\varphi$, $\delta$: Cannabis use initiation |
| Wade et al. (2019) | San Diego  | OFC medial lateral, surface area volume and CT | CDDR                    | 118  | 12–15                   | 13                         | ↑ GMV of right pre-SMA and ↓ GMV of right OFC – ↑ GMV of left lateral OFC | Regular cannabis use                      |

Table footnote: CDDR = Customary drinking and drug use record, CIDI = composite international diagnostic interview, CT = cortical thickness, ESPAD = European School Survey Project on Alcohol and Drugs, GMV = gray matter volume, ROIs: Regions of Interest.
predicted regular cannabis use at follow-up (age 16–26 years; Wade et al., 2019) (OR = 1.81, 95% CI [1.08, 3.04]).

In addition, in a study that employed the IMAGEN sample (N = 1216), several other brain morphology predictors of future cannabis use were reported (Spechler et al., 2019). For boys, a greater volume of the right medial PFC and a smaller volume of the left midcingulate cortex at 14 years were associated with cannabis use initiation by a 2-year follow-up. For girls, in addition to the before-mentioned findings for right OFC volumes, greater volumes of the right pre-supplementary motor area (pre-SMA) predicted cannabis use initiation at follow-up.

Summarized, the above-mentioned studies collectively suggest an association between pre-existing differences in OFC volume and cortical thickness and future cannabis use, depicted in Fig. 4. The direction of these reported differences might be hemisphere-specific; smaller right (in blue) and larger left (in red) OFC volumes were found as predictors for future cannabis use. Furthermore, the largest study on future cannabis use suggested sex-specific predictors. Differentiating specific predictors of future cannabis use from predictors of combined cannabis and tobacco use is difficult, however, considering that cannabis and tobacco are often mixed when smoking (Tucker et al., 2019).

3.3. Predictors of future tobacco use

Despite the common use of tobacco and other nicotine-containing products among adolescents, little research has focused on brain morphology predictors of future tobacco use. Our systematic search only revealed one study on this topic: Cheetham et al. (2018) found an association between smaller right amygdala volumes at 12 and daily smoking by age 18 (effect = -0.08, SE = 0.03; see Table 3). In this study, smaller amygdala volume also partially mediated the relationship between externalizing symptoms and smoking behavior (direct effect = 0.03, SE = 0.01). Although no other studies explored specific predictors of tobacco use, studies on future cannabis use might reflect shared predictors of combined cannabis and tobacco use, as these are often mixed when smoking (Tucker et al., 2019).

**Table 3**

| Author            | Cohort    | ROIs                          | Substance use                        | N  | Age at baseline in years | Follow-up duration in years | Main predictor | Main outcome          |
|-------------------|-----------|-------------------------------|--------------------------------------|----|-------------------------|---------------------------|----------------|-----------------------|
| Cheetham et al.   | ORYGEN    | OFC and amygdala              | Youth risk behavior survey           | 109| 12                      | 6                         | ▼ GMV of right amygdala | Daily smoking |

*Table footnote: GMV = gray matter volume, ROIs: Regions of Interest.*
3.4. Predictors of combined substance use

While most studies have focused on predictors for specific substances, it is well-known that substance use is often not restricted to only one substance. Therefore, the studies described below explored structural predictors of combined use, as well as clinically assessed substance use disorder (SUD). Similar to the findings regarding predictors for later cannabis use, in general, the studies reported an association between OFC alterations at baseline and alcohol and cannabis co-use at follow-up (see Table 4). Again, the alterations found were inconsistent and sometimes even contradictory. Wade et al. (2019) found greater left lateral OFC volume at baseline (age 12–15 years) in adolescents who classified as alcohol-cannabis co-users at follow-up (age 16–27 years, OR = 2.59, 95 % CI [1.29, 5.21]), while in a study by Luby et al. (2018), smaller total OFC volume at age 7–12 years was related to an increase in accumulated alcohol and cannabis use frequency at 6-year follow-up. Moreover, a greater decline in cortical thickness of the OFC over time was related to earlier initiation and higher frequency of accumulated alcohol and cannabis use (Luby et al., 2018). It must be noted that participants of the study by Luby et al. (2018) were younger than in the study by Wade et al. (2019), at baseline and follow-up. A study by Cheetham et al. (2017) also reported smaller volume of the OFC to be predictive of later combined use; smaller medial OFC volume at age 12 years was associated with a lifetime history of SUD by the age of 18 years. The SUD group included adolescents with alcohol use disorder only, cannabis use disorder only and combined use disorder, but the sample size did not allow for separate analyses. Another study that assessed symptoms of substance use disorder at follow-up reported that smaller left NAcc volumes at age 15–18 were related to the initiation of clinical-level alcohol, tobacco, cannabis or other drug use 2.25 years later (OR = 0.99, 95 % CI [0.97–1.00]; Urosević et al., 2015). Clinical-level use was defined as consuming 2 units of alcohol on four occasions per week, in combination with ever using other substances once or more. Thus, the studies by Cheetham et al. (2017) and Urosević et al. (2015) differed with regard to amounts of substance use.

Jacobus et al. (2016) explored pre-existing cortical thickness differences in adolescents who initiated alcohol and cannabis use at follow-up. No differences were found between future alcohol and cannabis co-users and adolescents that remained substance naïve. However, there were differences observed between future alcohol and cannabis co-users and adolescents who initiated alcohol use only. Compared to alcohol-only initiators, combined initiators had thinner cortices in six frontal regions, one parietal region and the insula, and a thicker left parahippocampal cortex (see Table 4) at baseline. Furthermore, Jacobus et al. (2013) reported that white matter integrity in future alcohol and cannabis initiators was greater than or equal to white matter integrity in future alcohol-only initiators. Contrary to Jacobus et al. (2016) however, white matter integrity findings were not compared with a group that remained substance-naïve at follow-up. Thus, although this study provides insight into a differentiation between alcohol use initiators and alcohol and cannabis co-use initiators, results cannot be directly compared with other findings that included a substance-naïve group at follow-up.

Summarized, the above-mentioned studies collectively suggest an association between pre-existing OFC and NAcc differences and future combined use of alcohol and cannabis. Similar to cannabis use-only studies, smaller right, as well as larger left OFC volumes, were found as predictors for future combined substance use. Furthermore, thinner cortices at baseline seemed to differentiate future combined alcohol/cannabis users from alcohol-only users, suggesting specific vulnerability markers for future cannabis use.

3.5. Cohort comparison

It is important to note that several studies in this systematic review report results from the same cohort. Even when only a selection of the original sample is analyzed, studies are still likely to overlap in participants, which means results cannot be independently interpreted. Therefore, in this section, we compare the findings within and between the selected cohorts.

For alcohol use, two brain morphology predictors were consistently reported across cohorts. Firstly, smaller ACC volumes were related to future alcohol use in the San Diego cohort (Squeglia et al., 2014) as well as the OADS cohort (Cheetham et al., 2014). Pre-existing alterations of the superior frontal gyrus were also reported in two cohorts, namely the San Diego cohort (Jacobus et al., 2016) and the TAOS cohort (Baranger et al., 2020). The directionality of these findings was not consistent: future alcohol use was associated with a thicker superior frontal gyrus in the San Diego cohort (Jacobus et al., 2016), but with a smaller superior frontal gyrus volume in the TAOS cohort (Baranger et al., 2020). Other brain predictors were reported within cohorts only: predictive metrics of the NAcc for later alcohol use (as well as of the ventral pallidum, who

Table 4
Studies on predictors of future combined substance use (N = 4).

| Author          | Cohort          | ROIs                          | Substance use assessment | N  | Age at baseline in years | Follow-up duration in years | Main predictor                                    | Main outcome                                    |
|-----------------|-----------------|-------------------------------|--------------------------|----|--------------------------|-----------------------------|---------------------------------------------------|-------------------------------------------------|
| Jacobus et al.  | Own cohort      | WM integrity                  | CDDR                     | 16 | 16–18                    | 3                           | ↑ = WM integrity                                | Combined alcohol/cannabis use, as compared to alcohol use only |
| Jacobus et al.  | San Diego       | Cortical thickness            | CDDR                     | 69 | 12–15                    | 6–8                         | ↓ CT of right inferior parietal gyrus, precentral gyrus, paracentral gyrus, rostral middle frontal gyrus, pars triangularis, superior frontal gyrus, insula and left precentral gyrus. ↑ CT of parahippocampal gyrus | Combined alcohol/cannabis use initiation, as compared to alcohol use initiation only |
| Luby et al.     | St Louis         | OFC and striatum              | Diagnostic interview and CIDI | 135 | 7–12                     | 6                           | ↓ GMV of OFC – ↓ Greater decline of CT of OFC     | Increase in alcohol/cannabis use frequency – Earlier onset and higher frequency of alcohol/cannabis use |
| Wade et al.     | San Diego       | OFC medial lateral, surface area volume and CT | CDDR                      | 118 | 12–15                    | 13                          | ↑ GMV of left lateral OFC                        | Alcohol/cannabis co-use |

Table footnote: CDDR = Customary drinking and drug use record, CIDI = composite international diagnostic interview, CT = cortical thickness, GMV = gray matter volume, ROIs = Regions of Interest, WM = white matter.
Before interpreting these findings, we have to take study quality assessment, and thus the limitations of the studies into account (see Fig. 2 and Supplement B). Most cohorts acknowledge the limitations in the specific studies, which largely relate to interpretation or generalizability of results: several studies employed a sample below 50 or one that to some extent was not representative of the general population, and the majority of studies did not apply multiple testing corrections. Other limitations included a short follow-up time for outcomes to occur, and limited statistical control for potential relevant confounding factors. Finally, although this was not scored within the quality assessment, many of the included studies only selected ROIs based on the theoretical background of substance use behavior, as opposed to using a whole-brain approach. This might have thwarted the detection of other pre-existing brain variations in future substance users. As most studies showed at least one limitation regarding the interpretation of findings, only highlighting the studies with a lower number of limitations would not be a comprehensive representation of the current findings. One of the IMAGEN studies had a very large sample size (N = 1472) that was adequately representative of the general population and corrected for multiple testing. Importantly, the authors of that study failed to find significant brain morphology predictors for future alcohol use (See et al., 2018). Furthermore, a recently published paper investigating partly the same cohort (N = 799) reported no link between cortical thickness at baseline (age 13–16 years) and cannabis use initiation at 5-year follow-up (Albaugh et al., 2021). Finally, most effect sizes in the reviewed literature were small to medium. Current findings should therefore be interpreted with caution, as more high-powered studies are needed to investigate robustness of the reported associations (Button et al., 2013; Ioannidis, 2005).

It should be emphasized that research on developmental neuroscience and substance use is novel and has only emerged a decade ago. As pioneers in this unexplored field of research, the authors of the above-mentioned studies have laid an important foundation for other longitudinal large cohort studies examining adolescent development (e.g. the Adolescent Brain Cognitive Development (ABCD) study (N ≈ 11,000, Casey et al., 2018) and the Generation R study (N ≈ 10,000, Kooijman et al., 2016), early childhood development with long follow-up (e.g., FinnBrain; Karlsson et al., 2018; GUSTO; Soh et al., 2014), or life-course development.

4.1. Current findings

The present systematic review is a first attempt to provide future studies with an overview of the current state of the art, which could stimulate hypothesis-driven studies. However, there are several issues that need further attention. In the current literature review, we noted similarities between the reported brain morphology predictors of future substance use and brain areas implicated in dominant theories of addiction (Lees et al., 2021). Specifically, the reward processing pathway to SUD suggests that either hypo- or hyperactivation of the ventral striatum (including the NAcc) can be a risk factor for substance abuse (Björk et al., 2012; Blum et al., 2000), and the cognitive control pathway to SUD suggests that aberrations of dorsolateral PFC, ACC and OFC circuits are associated with substance use related problems (Feil et al., 2010; Koob and Volkow, 2010). However, there seems to be an inconsistency between the directionality of structural differences in these regions (e.g. smaller volume) and its behavioral outcomes (e.g. earlier initiation of substance use). A possible explanation for these findings might involve an individual’s phase of cortical maturation. Typically, both cortical thickness and gray matter volume show an increase until the age of 9–11 and then decrease non-linearly in a parietal to frontal direction until the age of 22 (Vills et al., 2016). Delay or acceleration of this process have been associated with various childhood mental disorders (Shaw et al., 2010). In the current literature, smaller and thinner frontal areas are reported most often as predictors for later substance use, suggesting early cortical maturation of these regions in

receives input from the NAcc) were uniquely reported within the NCANDA cohort (Morales et al., 2019; Morales et al., 2020). As the NCANDA cohort was the only cohort that was oversampled for individuals with at least one risk factor for alcohol use, this might have influenced their findings. Moreover, the NCANDA cohort did not include ROIs other than the NAcc, which limits the comparison of NCANDA studies with studies that used a whole-brain approach. Associations were found between smaller NAcc and clinical-level substance use in the Minnesota cohort (i.e. consuming 2 units of alcohol on four occasions per week, in combination with ever using other substances once or more), but this substance use involved combined use, instead of alcohol use specifically (Urosevic et al., 2015). While the San Diego cohort reported frontal structural predictors in almost all studies, the IMAGEN cohort only reported predictors in the parietal and temporal lobe (Whelan et al., 2014). The IMAGEN cohort, although being the largest in sample size, was also the only cohort reporting null findings, which implies no association was found between structural brain measures and future alcohol use (See et al., 2019). When attempting to explain these differences between cohorts, it should be noted that IMAGEN was the only cohort based in Europe, conducted across four countries, while a majority of the other cohorts was based in the US. The differences in drinking culture and governmental policies between Europe and the US might have affected findings from these cohorts (Noel, 2019; Sudhinaraset et al., 2016). Furthermore, although the average age of alcohol use initiation is lower in Europe as compared to the US (Inchley et al., 2020; Johnston et al., 2022), the baseline age of the IMAGEN study was slightly older than in most cohorts based in the US. Finally, baseline differences in OFC metrics in future alcohol users were only found in the St. Louis cohort (Luby et al., 2018), which may be somewhat unexpected considering the various indications for OFC metrics as a predictor for future cannabis use and combined use. However, as the St. Louis cohort was oversampled for symptoms of depression, which is thought to be associated with cortical thickness of the OFC (Sacher et al., 2012), these findings should be interpreted with caution.

For cannabis use, OFC alterations were consistently associated with later use in all four cohorts that examined adolescent cannabis use: San Diego, OADS, IMAGEN and St. Louis. For combined use and clinical-level use, this association was reported in three of these cohorts: San Diego, OADS and St. Louis. However, some notable differences between cohorts were observed: the San Diego cohort reported bigger left lateral OFC volume for future cannabis use as well as combined use (Wade et al., 2019), while the OADS cohort reported smaller right lateral OFC volume for future cannabis users (Cheetham et al., 2012) and smaller medial OFC volume for future combined users (Cheetham et al., 2017). Besides differing in research site location (San Diego in the US, OADS in Australia), the OADS sample was selected to represent a broad spectrum of temperamental risk for later onset of psychopathology. This difference in participant characteristics might have influenced the differences in reported findings between cohorts.

Finally, although sex-specific brain morphology predictors for future substance use were suggested in two cohorts (IMAGEN and NCANDA), the other five cohorts did not conduct sex-specific analyses to examine vulnerability to later substance use initiation or continuation.

4. Discussion

In the recent decade, various prospective longitudinal studies have reported an association between pre-existing brain morphology and future substance use. This systematic review shows that the findings are (partly) substance-specific. Overall, the studies showed that several pre-existing brain characteristics across the frontal lobe have been associated with future alcohol use, while pre-existing differences in the OFC only were more often associated with future cannabis use and combined use. Also, baseline differences in amygdala volume were related to future tobacco use, although our systematic search only retrieved one study regarding this relationship.

Before interpreting these findings, we have to take study quality assessment, and thus the limitations of the studies into account (see Fig. 2 and Supplement B). Most cohorts acknowledge the limitations in the specific studies, which largely relate to interpretation or generalizability of results: several studies employed a sample below 50 or one that to some extent was not representative of the general population, and the majority of studies did not apply multiple testing corrections. Other limitations included a short follow-up time for outcomes to occur, and limited statistical control for potential relevant confounding factors. Finally, although this was not scored within the quality assessment, many of the included studies only selected ROIs based on the theoretical background of substance use behavior, as opposed to using a whole-brain approach. This might have thwarted the detection of other pre-existing brain variations in future substance users. As most studies showed at least one limitation regarding the interpretation of findings, only highlighting the studies with a lower number of limitations would not be a comprehensive representation of the current findings. One of the IMAGEN studies had a very large sample size (N = 1472) that was adequately representative of the general population and corrected for multiple testing. Importantly, the authors of that study failed to find significant brain morphology predictors for future alcohol use (See et al., 2018). Furthermore, a recently published paper investigating partly the same cohort (N = 799) reported no link between cortical thickness at baseline (age 13–16 years) and cannabis use initiation at 5-year follow-up (Albaugh et al., 2021). Finally, most effect sizes in the reviewed literature were small to medium. Current findings should therefore be interpreted with caution, as more high-powered studies are needed to investigate robustness of the reported associations (Button et al., 2013; Ioannidis, 2005).

It should be emphasized that research on developmental neuroscience and substance use is novel and has only emerged a decade ago. As pioneers in this unexplored field of research, the authors of the above-mentioned studies have laid an important foundation for other longitudinal large cohort studies examining adolescent development (e.g. the Adolescent Brain Cognitive Development (ABCD) study (N ≈ 11,000, Casey et al., 2018) and the Generation R study (N ≈ 10,000, Kooijman et al., 2016), early childhood development with long follow-up (e.g., FinnBrain; Karlsson et al., 2018; GUSTO; Soh et al., 2014), or life-course development.

4.1. Current findings

The present systematic review is a first attempt to provide future studies with an overview of the current state of the art, which could stimulate hypothesis-driven studies. However, there are several issues that need further attention. In the current literature review, we noted similarities between the reported brain morphology predictors of future substance use and brain areas implicated in dominant theories of addiction (Lees et al., 2021). Specifically, the reward processing pathway to SUD suggests that either hypo- or hyperactivation of the ventral striatum (including the NAcc) can be a risk factor for substance abuse (Björk et al., 2012; Blum et al., 2000), and the cognitive control pathway to SUD suggests that aberrations of dorsolateral PFC, ACC and OFC circuits are associated with substance use related problems (Feil et al., 2010; Koob and Volkow, 2010). However, there seems to be an inconsistency between the directionality of structural differences in these regions (e.g. smaller volume) and its behavioral outcomes (e.g. earlier initiation of substance use). A possible explanation for these findings might involve an individual’s phase of cortical maturation. Typically, both cortical thickness and gray matter volume show an increase until the age of 9–11 and then decrease non-linearly in a parietal to frontal direction until the age of 22 (Vills et al., 2016). Delay or acceleration of this process have been associated with various childhood mental disorders (Shaw et al., 2010). In the current literature, smaller and thinner frontal areas are reported most often as predictors for later substance use, suggesting early cortical maturation of these regions in
individuals at risk for later use. This seems in line with studies by Harper et al. (2017) and Berns et al. (2009) reporting links between respectively early cortical thickness reduction in (pre)frontal brain regions and excessive alcohol use, and white matter maturation and risk behavior during adolescence. However, larger and thicker frontal areas, that could indicate delayed cortical maturation, have also been reported as substance use predictors, especially for future cannabis use (Spechler et al., 2019). This suggests that various types of deviation from typical cortical development might be involved in substance use vulnerability.

Another possible explanation for the contrasting direction of brain morphology predictors might involve the volumetric hemispheric ratio (VHR), defined as the volumetric ratio between a brain area in the left hemisphere and its corresponding area in the right hemisphere. Several studies suggest an association between substance use in adolescence and hemispheric asymmetry, as substance use seems to affect hemispheres differentially (Gordon, 2016). Specifically, less rightward VHR of the NAcc has been associated with substance use dependence (Cao et al., 2021). These findings possibly in part reflect pre-existing VHR differences. In the current literature, both greater left lateral OFC volume (Wade et al., 2019), smaller right lateral OFC volume (in women; Spechler et al., 2019), smaller right lateral OFC volume (Cheetham et al., 2012), smaller medial OFC volume (Cheetham et al., 2017) and thinner OFC (Luby et al., 2018) have been associated with future cannabis use and alcohol/cannabis co-use. Interestingly, bilateral OFC volume has not often been reported as a predictor for later substance use, suggesting that the VHR of the OFC might be a better predictor than bilateral volume. As specifically smaller right OFC volume has been associated with vulnerability to alcoholism (Dom et al., 2005; Hill et al., 2013), a less rightward VHR of the OFC might be related to substance use vulnerability. Several studies also report pre-existing variations in the medial or lateral OFC only, which have been associated with, respectively, reward encoding processes such as evaluating hedonic value, and cognitive control processes such as evaluation of negative reinforcers (Fettes et al., 2017; Krügelbach and Rolls, 2004). Although further research is needed to elucidate this distinction, the findings in this review might indicate that reward encoding processes are more related to addiction vulnerability, while cognitive control processes are more related to vulnerability to initial use and continuation of use.

Nonetheless, it should be noted that brain morphology variations can correspond to many interindividual factors, such as genetic aspects, age and personality traits, which may underlie the study results (Madan, 2017). Furthermore, a recent study by Picci et al. (2021) reported an interaction between gene variants, brain morphology and subsequent substance use. Examining these interactions would increase understanding of substance use vulnerability and identification of youth at risk for substance use related problems.

4.2. Future directions

Further longitudinal research is needed before scientific findings from developmental neuroscience can inform treatment, prevention and policy on substance use problems in adolescence. This section includes recommendations for such future studies.

To allow for better generalizability of findings to the general population, studies on brain morphology predictors of future substance use should aim for a large representative sample (Button et al., 2013) in which potential relevant confounders are controlled for (e.g., comorbid psychopathology, socioeconomic factors, health-related factors and other substance use), and appropriate multiple testing corrections are applied, while taking correlation between neuroimaging outcomes into account (Hagler et al., 2006). A large sample may also allow for sex-specific analyses within the study. Considering the sex differences in the development and continuation of SUD (NIDA, 2021b), as well as differences in cortical maturation timing (Brouwer et al., 2021; Giedd et al., 2006; Lenroot et al., 2007), sex-specific analyses may provide valuable information on vulnerability to future substance use. This is further supported by the sex-specific findings in this review and recent studies (Mankiw et al., 2021). Sex-specific analyses were not conducted in a majority of the cohorts included in this review, limiting the possibility to compare sex-specific findings across cohorts. Therefore, they form a critical recommendation for future studies.

To improve the validity of future studies, we suggest that participants should be recruited at a younger age and followed for a longer time. Recent reports show that alcohol, cannabis and tobacco use can already be prevalent at age 12 (Johnston et al., 2020; van Laar et al., 2021). Therefore, to avoid the exclusion of early initiators, studies using substance-naïve participants at baseline should aim to recruit before age 12 and assess substance use at baseline. Consequently, follow-up duration should be longer for outcomes to occur, taking type and prevalence of the substance use of interest into account.

Considering that the reported pre-existing brain morphology variations in this review were not limited to hypothesis-driven ROIs, we recommend more data-driven approaches in future studies. In recent years, data-driven machine learning techniques have been increasingly used to test the predictive value of brain imaging data on substance use related outcomes (as reviewed in Rashid and Calhoun, 2020; or Rawls et al., 2021; Shane and Denomme, 2021; Squeglia et al., 2017). Machine learning tools that account for a large number of neuroimaging predictors (e.g. the random forests technique) can be used to determine key regions in substance use vulnerability.

Another way of obtaining more insight into neural predictors of later substance use is multimodal research. In the current literature, structural (sMRI) and functional (MRI, EEG/MEG) brain data are often not collected simultaneously, which can hinder the integration and interpretation of structural and functional findings. With the exception of the OFC and NAcc (Morales et al., 2019; Morales et al., 2020; Spechler et al., 2019), most structural and functional predictors did not show overlap (Norman et al., 2011; Wetherill et al., 2013). Furthermore, a study by Squeglia et al. (2013) showed that cortical thinning between the ages 12 and 14 was not related to brain activity, suggesting differences between structural and functional developmental processes. This raises the question of whether variations in the structure and function of specific brain areas and their connectivity could contribute separately to substance use vulnerability. Multimodal neuroimaging methods could provide a direct comparison between these variations, minimizing statistical heterogeneity. Finally, as the current literature hints towards the existence of substance-specific vulnerabilities, we suggest presenting findings separately for each type of substance use or co-use. It is important to specify co-use as it is prevalent among adolescents (McCabe et al., 2012; NIDA, 2021a), but varies considerably across countries due to differences in cultural factors and governmental policies (Akl et al., 2011; Gobel et al., 2016; Popova et al., 2007). Types of co-use could be defined based on common patterns of substance use, as described in Halladay et al. (2020). As comorbidities are common in individuals with SUD, another approach could be to contrast brain predictors of psychopathology to compare whether associations are specific for substance use (Castellanos-Ryan et al., 2014; Goodkind et al., 2015).

Finally, the reliability of studies within the research field might improve with a harmonization approach of study methods. The current literature shows heterogeneity regarding the definition of substance naïvety, substance use initiation and co-use, which hinders the conduction and interpretation of meta-analyses or mega-analyses.

4.3. Clinical implications

In terms of clinical relevance, brain morphology measurements should at the moment not be used to predict risk for SUD on an individual level. Nevertheless, differentiating pre-existing vulnerabilities in the brain from neural consequences of substance use is needed to highlight brain areas that are specifically vulnerable to the effects of substance use. Moreover, prevention programs can aim to specifically
target cognitive aspects associated with pre-existing vulnerabilities, like inhibitory control and problem solving in the Promoting Alternative Thinking Strategies program (PATHS; Riggs et al., 2006), and decision-making and impulse inhibition in Life Skills Training (LST; Beets et al., 2009). Furthermore, brain morphology studies can direct to specific timing of prevention (i.e. in which phase of brain development do adolescents benefit the most from the program) and evaluation of prevention effects (Riggs, 2015).

4.4. Summary

In conclusion, the literature discussed in this systematic review cautiously suggests that pre-existing volumetric variations in brain areas involved in cognitive control, motivation and reward processing may predict future initiation of alcohol, cannabis and tobacco use in adolescence. Reported findings were inconsistent in directionality and laterality, and the largest study on alcohol use predictors reported null findings. Therefore future longitudinal large population-based cohort studies should investigate the robustness and mechanisms of these associations. Such studies could further elucidate the missing link between brain morphology and substance use in adolescence, and provide valuable insights into AUD vulnerability and opportunities for prevention programs.

CRediT authorship contribution statement

Olga D. Boer: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft. Hanan El Marroun: Conceptualization, Supervision, Validation, Writing – review & editing. Ingmar H.A. Franken: Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of Competing 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.

Acknowledgements

The authors wish to thank Sabrina Meertens-Gunput, Elise Krabbenb, Maarten Engel, Wichor Bramer, and Christa Niehot from the Foundation, Writing round: able insights into SUD vulnerability and opportunities for prevention effects (Riggs, 2015).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.brainres.2022.148020.

References

Aki, E. A., Gunukula, S. K., Alem, S., Obeid, R., Josaudie, P. A.,HONEINE, R., & IRANI, J. (2011). The prevalence of waterpipe tobacco smoking among the general and specific populations: a systematic review. BMC Public Health, 11, 244. 1471-2458:11-244 (pp. 10.1186/1471-2458-11-244).

Albaugh, M.D., Ottino-Gonzalez, J., Sidwell, A., Lepage, C., Juliano, A., Owens, M.M., Chaaari, B., Spechler, P., Fontaine, N., Bioux, P., Lewis, I., Jean, S., Evans, A., D’Souza, D., Radhakrishnan, R., Banaschewski, T., Bokde, A.L.W., Quinlan, E., Conrod, P., Desrivières, S., Flor, H., Grigs, A., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.L., Paillère Martinot, M.L., Nees, F., Papadopoulos Orfanos, D., Paas, T., Poutsa, L., Millen, S., Fröhner, J.H., Smolka, M.N., Walter, H., Whelan, R., Schumann, G., Potter, A., Garavan, H., 2021. Association of cannabis use during adolescence with neurodevelopmental. JAMA Psychiatry 78 (9), 1021.

Baranger, B.A.A., Demers, C.H., Elsayed, N.M., Knodt, A.R., Radke, S.R., Desmarais, A., Few, L.R., Agravall, A., Heath, A.C., Barch, D.M., Squeglia, L.M., Williamson, D.E., Hariri, A.R., Bogdan, R., 2020. Convergent evidence for predispositional effects of genetic vulnerability in substance use or alcohol consumption. Biol. Psychiatry 88 (8), 631-639.

Bava, S., Tapert, S.F., 2010. Adolescent brain development and the risk for alcohol and other drug problems. Neuropsychol. Rev. 20 (4), 398-413. https://doi.org/10.1007/s11065-010-9146-6.

Beets, M.W., Flay, B.R., Vuchinich, S., Snyder, F.J., Acocak, A., Li, K.K., Burns, K., Washburn, J.L., Durlak, J., 2009. Use of a social and character development program to prevent substance use, violent behaviors, and sexual activity among elementary-school students in Hawaii. Am. J. Public Health 99 (8), 1438-1445.

Berry, G.S., Moore, S., Capra, C.M., García, A.V., 2019. Adolescent engagement in dangerous behaviors is associated with increased white matter maturity of frontal cortex. PLoS ONE 4 (8), e6773.

Bjork, J.M., Smith, A.R., Chen, G., Hommer, D.W., 2015. Mesolimbic recruitment by nondrug rewards in detoxified alcoholics: effort anticipation, reward anticipation, and reward delivery. Hum. Brain Mapp. 33 (9), 2174-2188.

Blum, K., Braverman, E.R., Holder, J.M., Labar, J.F., Mon, V.A., Miller, D., Comings, D.E., 2000. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J. Psychoact. Drugs 32 Suppl, i–iv, 1-122. https://doi.org/10.1080/02791072.2000.10736099.

Boelma, S.R., Harakeh, Z., van Zandvoort, M.J.E., Reijnsveld, S.A., Vurutel, F.C., Ormel, J., Velolbergh, W.A.M., Wallander, J.L., 2015. Adolescent heavy smoking does not affect maturation of basic executive functioning: longitudinal findings from the TRAILS study. PLoS ONE 10 (10), e0131986.

Brouwer, R.R., Schutte, J., Janssen, R., Boomsma, D.J., Huls Hof, F. E., & Schneck, G. (2021). The speed of development of adolescent brain age depends on sex and is genetically determined. Cereb Cortex, 31(2), 1296-1306. 5929823 (pp. 10.1093/ cercor/bbaa296).

Brown, S.A., McNea, M., Maggs, J., Schulerberg, J., Hington, R., Swartvelder, S., Martin, C., Chung, T., Tapert, S.F., Sher, K., Winters, K.C., Lowman, C., Murphy, S., 2008. A developmental perspective on alcohol and youths 16 to 20 years of age. Pediatrics 121 (Supplement 1), S290-S310.

Brumback, T.B., Worley, M., Nguyen-Loui, T.T., Squeglia, L.M., Jacobus, J., Tapert, S.F., 2016. Neural predictors of alcohol use and psychopathology symptoms in adolescents. Dev. Psychopathol. 28 (4), 1209-1216.

Button, K.S., Ioannidis, P.A.D., Mokryz, C., Nosek, B.A., Flint, J., Robinson, E.S.J., Munafò, M.R., 2013. Power failure: why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. 14 (5), 365-376.

Cao, Z., Ottino-Gonzalez, J., Cupertino, R.B., Schwab, N., Hoke, C., Catherine, O., Cousijn, J., Dagher, A., Fox, J., Joudiaia, A.E., Rester, H., Hutchison, K., Li, G.-S., Hondund, D.E., Lorenzo-Santos, R., Luijten, E., Fontaine, N., Rioux, P., Lewis, L., Jeon, S., Evans, A., Bjork, J.M., Smith, A.R., Chen, G., Hommer, D.W., 2012. Mesolimbic recruitment by nondrug rewards in detoxified alcoholics: effort anticipation, reward anticipation, and reward delivery. Hum. Brain Mapp. 33 (9), 2174-2188.
