Neuroanatomical Predictors of Alcohol Consumption in Adolescents via in vivo Structural Imaging: A Systematic Review of Longitudinal Studies

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Abstract

Aims

This study aimed to systematically review the literature on neuroanatomical predictors of future problematic drinking in adolescents.

Methods

Using PRISMA guidelines, a systematic review was conducted to evaluate neuroanatomical predictors of problematic drinking in adolescents. Embase, MEDLINE, and PsycINFO databases were searched from inception to January 6th, 2023. Studies were included if they were original, had a prospective design, had a sample size of at least 12, had a follow-up period of at least one year, had at least one structural neuroimaging scan before 18 with no prior alcohol use, and had alcohol use as the primary outcome. Studies were excluded if: had animals only; and were not in English. Risk of bias was conducted using the CASP tool.

Results

Out of 1,412 studies identified, 19 studies met the criteria, consisting of eleven gray matter (n = 4,040), five white matter (n = 319), and three assessing both (n = 3,608). Neuroanatomical predictors of future problematic drinking in adolescents were reported to be distributed across various brain regions such as the orbitofrontal cortex and paralimbic regions. However, the findings were largely heterogeneous.

Conclusions

This is the first systematic review to map out the existing literature on neuroanatomical predictors of problematic drinking in adolescents. Future research should focus on the aforementioned regions to determine their role in predicting future problematic drinking with more certainty.

Introduction

Alcohol consumption is the most frequently observed substance use in adolescence (Squeglia, Jacobus, & Tapert, 2014). According to the National Institute of Alcohol Abuse and Alcoholism, in 2019 alone, more than seven million adolescents consumed alcohol substantially (NIAAA, 2020). Since adolescence is a crucial transition from the juvenile period to adulthood, deleterious substance-related cognitive and physiological changes have long-lasting effects on the lifestyle and later prospects of the individual (Cservenka & Brumback, 2017). Various lines of evidence consistently suggest that early-onset adolescent alcohol usage is the primary risk factor for substance use and alcohol dependence later in

adulthood (Hemovich & Crano, 2009; Kranzler & Soyka, 2018; McCambridge, McAlaney, & Rowe, 2011; Spear, 2018).

Over the last two decades, data obtained from structural brain imaging research has elucidated the important role that the cortico-striatal brain regions play in regulating habits such as problematic drinking (Kühn et al., 2019). It has been suggested that such phenotypic presentation is linked to the delayed development of brain regions associated with behavioral control in comparison to those concerning reward and emotion pathways (Brumback et al., 2016; Casey, Jones, & Somerville, 2011). A better understanding of the pre-existing neuroanatomical differences between alcohol users and non-users would prove extremely valuable for clinicians and researchers alike. For example, it has been understood that physiological processes governing impulsivity and executive function differ between adolescent problematic drinkers from non-users (O'Halloran, Nymberg, Jollans, Garavan, & Whelan, 2016). Therefore, identifying specific neuroanatomical predictors could help with determining who is at risk of developing problematic drinking, thereby allowing earlier interventions to be implemented (Squeglia & Gray, 2016).

While extensive neuroimaging studies on animal models of alcohol consumption have been conducted before, the literature on human neuroimaging studies has been relatively limited. Longitudinal studies would serve as the best source of evidence to better understand adolescent neuroanatomical predictors of alcohol use disorders (AUD) due to their ability to investigate the temporal relationships associated with AUDs across development with greater precision. Longitudinal studies are also ideally suited to track the same individuals before and after the onset of alcohol initiation; hence, data obtained from these studies may distinguish predisposing factors through relevant analysis of morphological brain changes.

To our knowledge, no systematic reviews have been published that directly explore the literature surrounding neuroanatomical predictors (including both gray and white matter regions) of problematic drinking. The closest systematic review study was the one by Baker et al. – a white matter study published in 2013 – which aimed to determine what reliable conclusions can be drawn from diffusion weighted MRI studies that demonstrated white matter microstructural abnormalities in adolescent substance users (alcohol and other drugs of abuse) (Baker, Yücel, Fornito, Allen, & Lubman, 2013). This systematic review concluded that a directionality cannot yet be established as to whether white matter abnormalities are a consequence of adolescent exposure to alcohol and other drugs or signify pre-existing differences that increase the risk of substance use disorders. The study attributed this to the fact that most of the available data is cross-sectional.

Given that neuroanatomical predictors of alcohol consumption have potential clinical implications, in this study we aimed to systematically review the literature on neuroanatomical underpinnings of future problematic drinking in adolescents.

Methods

The systematic review was conducted in accordance to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group,

2009). Before conducting the review, the authors wrote the systematic review protocol, including the extraction and selection methods. The protocol was published on the International Prospective Register of Systematic Reviews in April 2020 and is accessible on their website (ID = CRD42020149125).

Literature Search

A systematic literature was conducted by a coauthor, who was a librarian at the University of Toronto, using Medline (Inception-January 6, 2023), EMBASE (Inception-January 6, 2023) and PsycINFO (Inception-January 6, 2023) electronic databases. Search terms were carefully selected to demarcate the age of participants as 'x' where 'x' was defined as $12 \leq x < 18$ years. A full description of all search terms for the three databases is available as supplemental information. Furthermore, the co-first authors manually reviewed the reference lists of the selected articles as well as all the other relevant older systematic review articles to identify additional studies that may have been missed during the electronic search.

Inclusion & Exclusion Criteria

For inclusion, studies must have been original research; used a longitudinal/prospective cohort design; had a sample size of 12 or greater; had a duration of at least 1-year follow-up; had a minimum of one structural neuroimaging scan, before the age of 18, with no previous alcohol use; and measured problematic drinking (defined below) outcomes of alcohol use including frequency, amount or negative consequences. Studies were excluded if they were not original papers (i.e. case reports and conference abstracts), included animals only, and the language of publication was not in English.

Problematic drinking: We included studies that contain information about problematic drinking in adolescents as defined by any of the following conditions: 1) Alcohol use disorders (AUD; a chronic relapsing brain disorder signified by the inability to stop or limit alcohol use despite negative social or health consequences (DSM-5) (American Psychiatric Association, 2013)), 2) Alcohol dependence, 3) Harmful pattern of alcohol use, including hurting oneself or someone else due to one's alcohol habits, 4) Alcohol intoxication, 5) Alcohol withdrawal, 6) Binge-drinking and 7) Alcohol-induced physical and mental disorders.

Formal Screening and Data Collection

A total of 1,412 abstracts from the three databases and other sources were collected by one coauthor and screened for inclusion by two other coauthors independently. After duplicates were removed, each abstract was screened according to eligibility criteria based on the title and abstract. Next, 166 full-text articles were thoroughly reviewed. Any disagreements regarding inclusion/exclusion were resolved by consensus with the senior author. At the end of full-text screening, 19 papers were included from the literature search and are discussed in this review. Figure 1 illustrates the selection process in detail.

Risk of Bias in Individual Studies

The Critical Appraisal Skills Program (CASP) was used to assign a composite quality rating for each study by two coauthors independently. Among these parameters, we looked at validity, cohort representation, the accuracy of outcome, identification of confounding factors, duration and completion of follow-ups, and precision and representation of the result.

Results

Of the 19 papers finalized in our qualitative synthesis, eleven gray matter (n = 4,040), five white matter (n = 319) and three examined both gray and white matter (n = 3,608), where surface area, thickness, and/or volume differences were studied. Assessment of risk of bias for every study using the CASP tool is summarized in **Table 1**.

Gray Matter:

Of the 14 studies (eleven only gray matter and three gray and white matter) six studies were ROI-based and eight examined the whole brain (Baranger et al., 2020; Brumback et al., 2016; Cheetham et al., 2014; Hatoum et al., 2021; Infante, Courtney, Castro, Squeglia, & Jacobus, 2018; Jacobus et al., 2016; O'Brien & Hill, 2017; Rane et al., 2022; Robert et al., 2020; Seo et al., 2019; Squeglia et al., 2017; Urošević et al., 2015; Wade et al., 2019; Whelan et al., 2014) **(Tables 2.1, 2.2, and 4)**. A total of 8,546 participants were included in the review. Almost all studies used T1W imaging, with the exception of Whelan et al. (imaging technique unknown) and Robert et al. (voxel-based and tensor-based morphometry) (Robert et al., 2020; Whelan et al., 2014). Sex ratio was roughly divided in half, with the biggest difference present in the Brumback et al. study (154 males: 111 females; 58%:42%) (Brumback et al., 2016). The shortest follow-up duration was up to two years (Urošević et al., 2015; Whelan et al., 2014), and the longest was up to 13 years (Brumback et al., 2016; Wade et al., 2019). Mean baseline age ranged between 12.7 to 16.5 (Cheetham et al., 2014; Urošević et al., 2015). The following brain regions were mostly implicated in predicting future problematic alcohol use: occipital lobe, frontal lobe, cerebellum, and temporal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, superior frontal gyrus, precentral gyrus, superior parietal lobe, and supramarginal gyrus. In addition, changes in left nucleus accumbens, prefrontal and subcortical regions, and right dorsolateral prefrontal cortex and insula were implicated in alcohol initiation in adolescents.

Whelan et al. utilized machine learning and created models of adolescent binge drinking via extracted data from the IMAGEN project (Whelan et al., 2014). They found that right middle and precentral gyri (Brodmann area 6) and bilateral superior frontal gyrus (Brodmann area 9) are the regions with the strongest prediction of future episodes of problematic drinking (Whelan et al., 2014). It is notable to mention that structural factors that predicted future problematic alcohol use were gray matter volume, total parenchymal volume, as well as gray: white matter ratio.

Rane et al. identified an association between several gray matter areas, particularly in the occipital lobe, and future problematic drinking (Rane et al., 2022). Features from the frontal lobe, cerebellum, and temporal cortex were also of utility in predicting problematic drinking. In the occipital lobe, participants

with problematic drinking predictions had lower grey matter thickness in the right-cuneus, lateral occipital, and pericalcarine cortices, and higher curvature index in left-cuneus and left-pericalcarine cortex. In the frontal lobe, the left-frontal pole and right-precentral gyrus were relevant clusters for future prediction analyses (including from age 14 to 22). In the temporal lobe, the left inferior temporal gyrus and increased left temporal pole volume were relevant. Finally, increased right cerebellum cortex volume was relevant in prediction analyses. Other relevant features included increased right inferior parietal cortex volume, increased right parahippocampal gyrus area, lower left rostral middle frontal gyrus standard deviation of thickness, and lower integrated rectified mean curvature of the right bank of the superior temporal sulcus (Rane et al., 2022). A full list of structures is available in **Table 4**.

Cheetham et al. discovered that smaller left paralimbic anterior cingulate cortex volumes predicted problematic drinking (Cheetham et al., 2014). Interestingly, they did not discover such predictive properties in the amygdala, hippocampus, and the orbitofrontal cortex. Urosevic et al. showed that participants with smaller left nucleus accumbens at baseline had a higher likelihood of initiating alcohol and drug use during follow-up (Urošević et al., 2015). Moreover, similar to the Cheetham et al. study, this study did not identify the amygdala and orbitofrontal cortex as predictors of problematic drinking either. However, the more recent O'Brien and Hill's study found that orbitofrontal cortex to amygdala volume ratio is a significant predictor of alcohol and drug use disorders (O'Brien & Hill, 2017). This study also showed that prefrontal and subcortical morphology correlates with adolescents' age of onset of substance use with and without a family history of substance use disorders.

Brumback et al. showed that dorsolateral prefrontal cortex surface area predicts binge drinking frequency, and that smaller brain surface area is inversely associated with more binge drinking (Brumback et al., 2016).

Jacobus et al. demonstrated that group by time interaction effects predicted cortical thickness in 18 regions in both left and right hemispheres (Jacobus et al., 2016). At baseline, in the left hemisphere, the group that later engaged in problematic drinking over time showed significantly thicker cortices in frontal and parietal areas, such as the left superior frontal gyrus, precentral gyrus, superior parietal lobe, and supramarginal gyrus. The more recent Infante et al. study from the same team showed that significant group differences exist in frontal, parietal and temporal lobes before and after alcohol initiation (Infante et al., 2018). Bilateral medial orbitofrontal cortex and right insula showed surface area reduction in all groups (control, alcohol, and alcohol + cannabis groups). Moreover, the group that initiated problematic drinking had more surface area decreases in the same regions compared to the other groups.

Squeglia et al. identified a total of 34 predictors of alcohol consumption (Squeglia et al., 2017). Of these, 15 predictors were pertinent to structural brain regions. In a decreasing order of importance, decreased cortical thickness in each of the following areas significantly predicted which participants, from 12 to 14 years of age, would initiate moderate to heavy alcohol use by 18: left supramarginal, left transverse temporal, right pars orbitalis, right superior parietal, right precuneus, right temporal pole, right frontal pole, and left superior parietal cortex. Moreover, the study identified several areas with decreased cortical

thickness that, although not individually a significant predictor, would each contribute significantly to the predictive model when allowed to interact with other neuroanatomical variables. These regions were, in a decreasing order of importance, the following: right rostral middle frontal, left lingual, left lateral occipital, left rostral anterior cingulate, right middle temporal, left banks superior temporal sulcus, and right superior frontal.

A study conducted by Wade et al., which primarily studied alcohol and cannabis co-consumption, demonstrated significance in the left lateral orbitofrontal cortex (Wade et al., 2019). However, when examining the alcohol-only cohort, the researchers discovered no significance in the lateral orbitofrontal cortex volume as a predictor of future adolescent problematic drinking (Wade et al., 2019). This was also the case when analyzing results at both the surface area and cortical thickness levels.

Robert et al. showed that accelerated gray matter atrophy rates in the temporal cortices (left and right posterior) and left prefrontal cortex were associated with increased alcohol intoxication (i.e. drunkenness) frequency (Robert et al., 2020). The study suggested a directionality as determined by gray matter atrophy in late binge drinkers compared with non-drinking controls. Seo et al.'s study on the other hand, was the only study that showed no significant differences in gray matter volume between 19-year-old heavy and light drinkers in 24 different brain regions assessed at 14 years of age (Seo et al., 2019).

Results by Baranger et al.'s study highlighted that smaller right dorsolateral prefrontal cortex and insula gray matter volumes predict adolescent alcohol initiation and its future usage during adulthood (Baranger et al., 2020). Moreover, volume reduction in dorsolateral prefrontal cortex served as a predictor of problematic drinking initiation in adolescents who were alcohol naïve at baseline (Baranger et al., 2020).

Finally, Hatoum and colleagues used mixed effects models to determine whether there is an association between polygenic risk scores for both problematic alcohol (PAU-PRS) and drinks per week (DPW-PRS), and changes in cortical gray matter in substance naïve adolescents of European ancestry and those of African ancestry (Hatoum et al., 2021). They found a correlation with PAU-PRS scores and decreased left frontal pole gray matter volume and greater right supramarginal gyrus cortical thickness in the European Ancestry, but no significant association was observed in any of the brain regions for individuals of African ancestry (Hatoum et al., 2021).

White Matter:

Of the eight studies (five only white matter and three white and gray matter) four studies were ROI-based and four examined the whole brain (Chung & Clark, 2014; Hatoum et al., 2021; Jacobus et al., 2013; Jones & Nagel, 2019; Morales, Jones, Harman, Patching-Bunch, & Nagel, 2020; Rane et al., 2022; Squeglia, Rinker, et al., 2014; Wade et al., 2019) **(Tables 3.1, 3.2, and 4)**. A total of 818 participants were included in the review. A total of three structural imaging techniques were used in the studies combined: DTI, T1W, and DWI. Three studies had <40% female participants (Chung & Clark, 2014; Jacobus et al., 2013; Squeglia, Rinker, et al., 2014). The shortest follow-up duration was up to one year (Chung & Clark, 2014),

and the longest was up to 13 years (Wade et al., 2019). Mean baseline age ranged from 13.5 to 17.5 (Jacobus et al., 2013; Jones & Nagel, 2019; Wade et al., 2019). The following brain areas and measures were implicated in predicting future problematic alcohol use: corpus callosum, left insula, midbrain, internal capsule, posterior, fornix, and superior corona radiata, left ventral diencephalon, left inferior and middle temporal gyrus, left caudate, brainstem, frontal cortices, fronto-striatal fractional anisotropy values, medial orbital gyrus, prefrontal cortex, and ventral pallidum.

Rane et al. found several white matter tracts to be of predictive value in future problematic drinking. These include parts of the corpus callosum (e.g., anterior corpus callosum and splenium), internal capsule, and posterior corona radiata, with all these tracts, as well as the brain stem, being found to have lower-than-average intensities (Rane et al., 2022).

In Jacobus et al.'s study, poorer white matter integrity was identified as a potential predictor of problematic alcohol and cannabis use among adolescents (Jacobus et al., 2013). More specifically, the limbic and projection-fiber pathways in the fornix and superior corona radiata predicted risky behaviors.

Chung and Clark's study found that left insula white matter volume was positively correlated with binge drinking frequency (Chung & Clark, 2014). In addition, right insula white matter volume was correlated with alcohol craving/obsession; left insula white matter volume was not. Interestingly, left insula white matter volume was positively correlated with current alcohol abuse/symptom frequency at 1 year, whereas right insula white matter volume was not correlated. Overall, the study showed that left insula white matter volume indirectly predicted binge drinking frequency.

Squeglia et al.'s findings indicated pre-existing volume differences in frontal brain regions in future drinkers and brain volume reduction in subcortical and temporal regions after the initiation of drinking (Squeglia, Rinker, et al., 2014). The specific regions where adolescent problematic drinkers showed greater volume reductions than demographically matched controls over the 3-year follow-up period were the left ventral diencephalon, left inferior and middle temporal gyrus, left caudate, and brainstem. A negative correlation was present between these volumetric changes and the lifetime alcohol use as well as peak number of drinks on one occasion in the past year. This indicates a dose-dependent effect of alcohol and cannabis on cortical thinning. Baseline group differences were present in several frontal cortical volumes. Specifically, adolescents who initiated heavy drinking at 3-year follow-up exhibited smaller cortical volume in three frontal regions, as well as less cerebellar white matter volume, when compared to control adolescents who also participated in the follow-up study. Overall, these findings demonstrate heavy drinking adolescents have subtle brain abnormalities that are present prior to the onset of drinking.

More recently, Jones and Nagel's study showed that less white matter volume was detected prior to alcohol use in adolescents that develop binge-drinking (Jones & Nagel, 2019). Additionally, the fractional anisotropy values were greater in future binge-drinking adolescents when compared to controls in white matter regions in the midbrain and internal capsule, which may represent a predisposition to engage in future drinking. On the other hand, the lower fractional anisotropy values detected previously in binge-

drinking adolescents compared to controls may have been due to the neurotoxic effects of alcohol. In the early stages of adolescence, prior to the initiation of drinking, future binge drinking was associated with changes in the fronto-striatal fractional anisotropy values that surround subcortical regions, and mean diffusivity in fronto-cortical regions. However, many of these changes were shown to be transient and attenuate by late stages of adolescence.

Morales et al. showed that adolescent binge drinkers have abnormalities in white matter microstructure by providing evidence of premorbid differences in fractional anisotropy (lower medial orbital gyrus), which are also associated with the amount of time taken until the onset of binge drinking (Morales et al., 2020). Additionally, a delayed maturation of prefrontal white matter was also present, which was associated with less top-down control over striatal sensitivity to reward. Moreover, individual differences in white matter proximal to ventral pallidum were also present.

Hatoum et al. examined 36 white matter tracts and 26 subcortices of alcohol naïve adolescents of European and African ancestries and did not find any significant association between them and polygenic risk scores for both problematic alcohol (PAU-PRS) and drinks per week (DPW-PRS) (Hatoum et al., 2021).

Moderating Factors

Other factors that may moderate the relationship between neuroanatomical variables and future problematic alcohol use among adolescents include familial history, sex differences, cannabis use, and personality. Familial history is a factor that was identified in several of the examined studies as a predictor of problematic drinking. For example, O'Brien and Hill's study indicated that familial risk status is a significant predictor of alcohol and drug use disorder (O'Brien & Hill, 2017). In addition, Jones and Nagel's study showed that family history of alcoholism was associated with changes in the fronto-striatal fractional anisotropy values that surround cortical regions, and mean diffusivity in fronto-cortical regions (Jones & Nagel, 2019). However, the study noted that the attenuation of the changes by the late stages of adolescence indicated that familial history of alcoholism is only partially associated with the fractional anisotropy and mean diffusivity changes.

In Robert et al.'s study, accelerated gray matter atrophy rates in the temporal cortices (left and right posterior) and left prefrontal cortex were associated with an increased frequency of drunkenness in males more than females (Robert et al., 2020). In Seo et al.'s study, at age 19, female heavy drinkers had gray matter atrophy associations in cue reactivity relevant brain regions (Seo et al., 2019). Negative life events at 19, but not 14, were shown to be positively correlated with heavy drinking in both sexes.

Cannabis use is another factor that could have partially influenced the results. For example, Jacobus et al.'s study showed that at baseline, in the right hemisphere, those who only engaged in problematic drinking had thicker cortices in frontal and parietal regions such as the precentral gyrus, paracentral gyrus, rostral middle frontal gyrus, superior frontal gyrus, para triangularis, and insula cortex when

compared to those who engaged in both problematic alcohol and cannabis consumption (Jacobus et al., 2016).

With regards to personality differences, Seo et al.'s study showed that agreeableness (both sexes) and conscientiousness (males only) were negatively correlated with the heavy drinking group, and hopelessness (females only) was positively correlated with the heavy drinking group (Seo et al., 2019). In addition, Cheetham et al. showed that problematic drinking was associated with higher levels of negative temperamental affectivity (Cheetham et al., 2014). However, no relationship was established between this finding and their other finding that determined the predictive role of anterior cingulate cortex in problematic drinking.

Discussion

The relationship between adolescent brain structures and the onset of alcohol consumption as well as frequency of drinking has predictive power and is important in determining future alcoholic consumption later in adulthood. This work, to our knowledge, presents the first systematic review that maps out existing gray and white matter literature evaluating neuroanatomical predictors of problematic drinking among adolescents. All studies scored ≥ 20 points using the CASP tool, signifying high quality in terms of risk of bias assessment. We found the findings from these studies to be heterogeneous and identifying a unifying pattern continues to be elusive. However, while a specific structural brain region cannot be conclusively determined to be a predictor of problematic drinking, certain brain regions are nonetheless strong candidates for future investigation. Our systematic review highlighted the relevance of the prefrontal cortex as an important player in the alcohol neurocircuitry: a finding that was observed in several studies in this systematic review (Baranger et al., 2020; Brumback et al., 2016; Robert et al., 2020). This is a consistent finding within the literature among adolescents (Medina et al., 2008), adults (Kähkönen, Wilenius, Nikulin, Ollikainen, & Ilmoniemi, 2003) and rodent studies (Weitlauf & Woodward, 2008; Willcocks & McNally, 2013). One explanation could be that reduced white matter microstructural integrity or impairments in the medial prefrontal cortex (which is a top-down mechanism and regulates the bottom-up striatal and limbic systems) results in increased reward seeking and ultimately poor decisions being made. It is also possible that protective factors such as adaptive neurodevelopment may happen in many of these same regions in adolescents. Another example from the included studies that is consistent with the literature is the volume reduction observed in the caudate and brainstem (Kühn et al., 2019).

A gray matter region that has been of particular interest in predicting problematic drinking is the orbitofrontal cortex. This prefrontal region is responsible for emotion and reward in decision-making.[31] Several studies have examined this region and the evidence has been conflicting thus far; Five studies have shown no significance in orbitofrontal cortex predicting problematic drinking (Brumback et al., 2016; Cheetham et al., 2014; Seo et al., 2019; Urošević et al., 2015; Wade et al., 2019). On the other hand, O'Brien and Hill showed the orbitofrontal cortex ratio to amygdala volume was a significant predictor of substance use disorders (O'Brien & Hill, 2017). It is plausible that because alcohol was grouped with other

substances in O'Brien & Hill's study, as opposed to an alcohol-only subcategory, the orbitofrontal cortex was characterized as a significant predictor. Additionally, Infante et al., who solely examined surface area instead of volume, found bilateral medial orbitofrontal cortex showing significant surface area reductions in the group that initiated problematic drinking in the future (Infante et al., 2018). Overall, as previous literature has indicated (Moorman, 2018), the role of this region in predicting problematic drinking is difficult to address, but future longitudinal research focusing on this ROI as well as its sublevels can certainly shed more light on this issue.

Two studies, Infante et al. and Wade et al. had groups that explicitly separated alcohol only and alcohol + cannabis groups (Infante et al., 2018; Wade et al., 2019). The distinction made between these two groups is important, since in Wade et al.'s study, the lateral orbitofrontal cortex volume was a predictor of future alcohol + cannabis co-user status, but not of the alcohol only status. Similarly, Infante et al. also noticed differences between alcohol only and alcohol + cannabis groups, where a more substantial decrease in surface area of the bilateral medial orbitofrontal cortex (most clearly identified in the right medial orbitofrontal cortex) existed in alcohol only group compared to the alcohol + cannabis group. What interestingly separates these two studies is that, as opposed to Infante et al., Wade et al. identified no significant surface area differences at all. The results of these studies clearly show divergent findings, therefore warranting future research.

When comparing primary articles published prior to the latest published review study (O'Halloran et al., 2016) with primary articles published after, Cheetham et al. discovered the left dorsal and rostral gray matter paralimbic regions of anterior cingulate cortex as predictors of future problematic drinking (Cheetham et al., 2014); whereas Seo et al. did not identify such differences in the left anterior cingulate cortex (Seo et al., 2019). We believe the reason behind this discrepancy is due to the fact that Seo et al. targeted anterior cingulate cortex as a whole, instead of analyzing its subregions. In other words, had they also studied the subregions, they may have identified the same areas as Cheetham et al. to be significant predictors. This signifies the importance of analyzing subregions in future studies in order to not miss any potentially significant results.

The right dorsolateral prefrontal cortex is a gray matter region that was identified as a predictor of problematic drinking by two studies: Brumback et al. and Baranger et al. (Baranger et al., 2020; Brumback et al., 2016) Interestingly, both studies had many similarities, including the age range, population size, T1W imaging, smaller ROI size at baseline, etc. One notable difference between these studies was their method of targeted brain scan, where Brumback et al. analyzed the whole brain[9], whereas Baranger et al. aimed at specific ROIs after having examined the results of two other cohorts (Baranger et al., 2020). More importantly, Brumback et al. focused on gray matter surface area whereas the latter used gray matter volume measurements. What is not clear is whether gray matter thickness is also a predictor of problematic drinking or if the decreased volume identified in the Baranger et al. is solely a result of the decreased surface area identified in Brumback et al.'s study.

There were studies that demonstrated significant predictors of problematic drinking, whose findings were neither confirmed nor denied by other studies: 1) Urosevic et al. identified a positive correlation between the smaller left nucleus accumbens and substance use during follow-up (Urošević et al., 2015); 2) Jacobus et al. showed thicker left superior frontal gyrus at baseline compared to controls (Jacobus et al., 2016); 3) Robert et al. discovered accelerated gray matter atrophies being present in the left and right posterior temporal cortices and left prefrontal cortex (Robert et al., 2020); 4) Chung and Clark showed frequency of binge-drinking after one year may be predicted by the left insula white matter volume (Chung & Clark, 2014); and 5) Squeglia et al., a whole brain imaging morphometric study, showed that at baseline, 13 brain regions of future problematic drinkers had volume reductions when compared to healthy controls (Squeglia, Rinker, et al., 2014). Future research is needed to verify the findings of these studies.

Squeglia et al.'s findings were illuminating due to the ranking of structural neuroimaging data alongside demographic and neuropsychological outcomes in order of importance. While certain brain regions in this list were not statistically significant by themselves, they nonetheless had a significant role in the overall performance of the predictive model (Squeglia et al., 2017). For example, both left transverse temporal cortical thickness and the right rostral middle frontal cortical thickness were among the top 34 predictive model variables (Squeglia et al., 2017). However, it is the former variable that is statistically significant by itself, whereas the latter is only significant when interacting with the other variables in the model. This demonstrates the importance of conducting interaction analysis in order to determine the hidden roles of regions that otherwise seem to not be significant.

After taking a closer look at the examined gray matter studies, the importance of having measured all three factors of cortical surface area, thickness, and volume becomes apparent. As Wade et al. notes (Wade et al., 2019), not taking a volumetric measurement could lead to missing on potential cellular and genetic measurements that may not be captured when measuring surface area or thickness alone.

Altered white matter microstructure, as measured by fractional anisotropy, as an index of its myelination and axonal diameter, has proven valuable as a predictor of risk-taking behavior and may signify premorbid risk factors for earlier initiation of heavy drinking in adolescents (Jacobus et al., 2013; Morales et al., 2020). A lower baseline FA in the fornix and superior corona radiata appeared as a significant predictor of substance use 18 months later (Jacobus et al., 2013). An increased risky selection with lower fractional anisotropy existed in left and right ventral pallidum which was associated with earlier onset of adolescent binge drinking (Morales et al., 2020). These findings make sense as the ventral pallidum has been understood as a nexus of brain circuitry involved in reward-seeking, motivation, and reward learning (Prasad & McNally, 2019).

Over time, as adolescents initiate and potentially increase their alcohol intake, lower fractional anisotropy occurs later in life (Jones & Nagel, 2019). Furthermore, in adolescents who binge-drink later in life, changes in maturation trajectory of white matter fibers in regions that connect limbic, striatal, and prefrontal regions appear to have existed prior to alcohol use.

Limitations

While our systematic review comprehensively collated and analyzed the literature on predictors of adolescent problematic drinking, some limitations should be discussed. First, we focused on peer-reviewed papers in English only. It is possible that we may have missed published works exploring the same topic in other languages. Second, the gray literature was not analyzed.

Additionally, some limitations to the literature should be noted. First, when comparing the findings of these studies, two papers included data for alcohol drinking alongside cannabis (Infante et al., 2018; Wade et al., 2019). Since other studies have shown different predictive outcomes for alcohol only versus alcohol + cannabis groups (Brière, Fallu, Descheneaux, & Janosz, 2011; Linden-Carmichael, Stamates, & Lau-Barraco, 2019), it is possible that combined substance use may point to different brain regions compared to alcohol use only. This may cast doubt on whether the identified brain regions truly predict problematic drinking only, since other drugs such as cannabis may have been partial associations of a significant/non-significant result. Second, nine of the 19 studies examined specific ROIs from the inception of their study instead of conducting whole brain analysis and later determining significant regions. This leads to a reduced ability in finding patterns given that only a handful of papers took the more comprehensive approach of examining all brain regions. Third, the different duration of the follow-up for neuroimaging scans in the cohorts may limit the generalizability of the findings. Fourth, certain studies likely used data from the same cohort of participants with potential overlaps. For example, seven studies analyzed data from San Diego middle schools (Brumback et al., 2016; Infante et al., 2018; Jacobus et al., 2016, 2013; Squeglia et al., 2017; Squeglia, Rinker, et al., 2014; Wade et al., 2019). Additionally, four studies used the IMAGEN database to select their subjects (Rane et al., 2022; Robert et al., 2020; Seo et al., 2019; Whelan et al., 2014). Lastly, two studies used databases from schools in Oregon (Jones & Nagel, 2019; Morales et al., 2020). It is not clear to what degree overlapping participants exist between studies within each respective cohort, and it is clear the rest of the studies had completely different cohorts. Nevertheless, it is important to be mindful of potential lack of diversity in subjects.

Future Directions

Existing ROIs are largely scattered across the brain and none has been deemed statistically significant by more than two separate studies. This warrants the following recommendations for any future study aiming to examine structural predictors of problematic drinking: First, to fill the gap in the literature, each ROI should be systematically studied and at the most detailed sublevels. Second, analysis of structural neuroimaging should be conducted in all three measurements of surface area, thickness, and volume to ensure all potential sensitivities are captured. Third, studies should conduct whole brain analysis when possible, to determine the individual roles of specific ROIs, so that no significant region is missed. Fourth, the interactions between different brain regions should be calculated as some individual variables may be non-significant but could significantly contribute to the overall assessment of the predictive model.

Declarations

Conflict of Interest

Author Kamyar Keramatian MD MSc has served on the scientific advisory board of AbbVie.

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Tables

Tables 1 to 4 are available in the Supplementary Files section

Figures

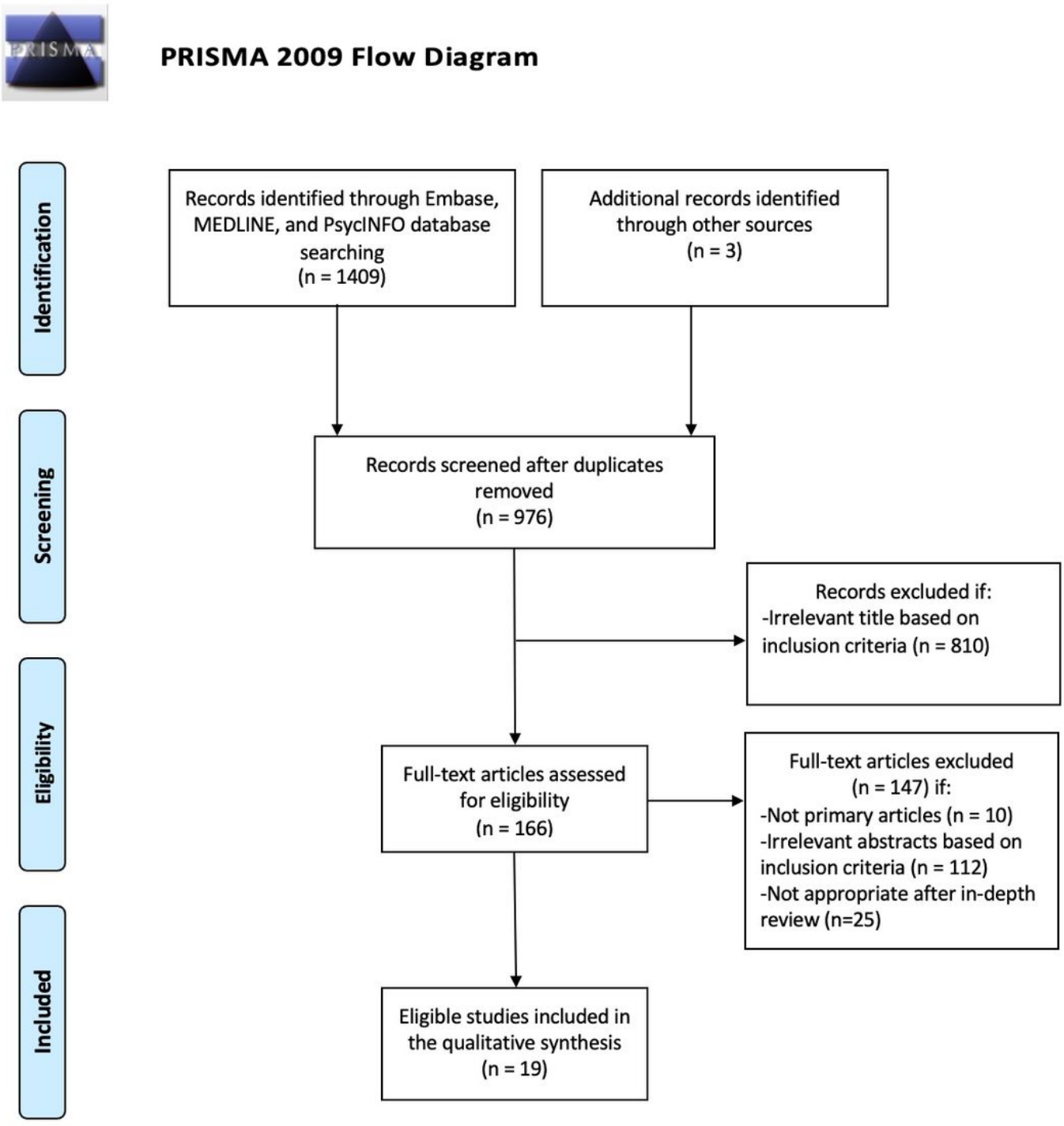

Figure 1

PRISMA flowchart. Out of a total of 1,412 studies, 19 papers were selected based on the inclusion and exclusion criteria.

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