The Influence of Substance Use on Adolescent Brain Development

L. M. Squeglia, B.A.[1,2,3], **J. Jacobus, B.A.**[1,2,3], and **S. F. Tapert, Ph.D.**[2,3,*]
[1]SDSU/UCSD Joint Doctoral Program in Clinical Psychology

[2]VA San Diego Healthcare System

[3]University of California San Diego, Department of Psychiatry

Abstract

Adolescence is a unique period in neurodevelopment. Alcohol and marijuana use are common. Recent research has indicated that adolescent substance users show abnormalities on measures of brain functioning, which is linked to changes in neurocognition over time. Abnormalities have been seen in brain structure volume, white matter quality, and activation to cognitive tasks, even in youth with as little as 1–2 years of heavy drinking and consumption levels of 20 drinks per month, especially if >4–5 drinks are consumed on a single occasion. Heavy marijuana users show some subtle anomalies too, but generally not the same degree of divergence from demographically similar non-using adolescents. This article reviews the extant literature on neurocognition, brain structure, and brain function in adolescent substance users with an emphasis on the most commonly used substances, and in the context of ongoing neuromaturational processes. Methodological and treatment implications are provided.

Keywords

BACKGROUND ON ADOLESCENT SUBSTANCE USE

Substance use during adolescence has been associated with alterations in brain structure, function, and neurocognition. This review will present the current research regarding typical adolescent brain development and the subtle but significant abnormalities in indices of brain functioning associated with alcohol and drug use during this critical developmental period. Studies using neuropsychological assessment and structural and functional imaging will be discussed to help elucidate the relationship between neurocognition with alcohol and marijuana use. Additionally, methodological issues in neuroimaging and neuropsychological assessment research will be reviewed.

While several decades of research with adults have shown that chronic heavy drinking is associated with adverse consequences on the adult brain [1], this relationship has only recently been explored in the adolescent brain. Understanding the effects of alcohol and drug use on adolescent neurocognition is crucial, being that rates of use increase dramatically between ages 12 and 18. Epidemiological studies have shown that past month alcohol use increases from

*Corresponding author: S. F. Tapert, Ph.D., 3350 La Jolla Village Drive (116B), San Diego, CA 92161, US; telephone: 858 552 8585, stapert@ucsd.edu.

17% to 45% between 8th and 12th grade, and illicit drug use prevalence expands from 8% to 22%. Lifetime rates indicate that 73% of youth have used alcohol and 48% have used illicit drugs by their senior year of high school [2]. In the past year, 23% of youth meet diagnostic criteria for a substance use disorder (alcohol or drug abuse or dependence) by age 20 [3].

While the developing brain may be more resilient to neurotoxic effects, exposure to alcohol and drugs during a period of critical neurological development may interrupt the natural course of brain maturation and key processes of brain development. In fact, adolescence may be a period of heightened vulnerability for alcohol's effect on the brain [4–7]. Cognitive deficits resulting from these alcohol and drug related neural insults have potentially harmful implications for subsequent academic, occupational, and social functioning extending into adulthood. Therefore, neurocognitive sequelae from heavy drinking and drug use are important to elucidate.

TYPICAL ADOLESCENT BRAIN DEVELOPMENT

Adolescence marks a period of rapid development between childhood and adulthood involving complex social, biological, and psychological changes. The interactions of these multidimensional factors have considerable implications for adolescent development. Included in these alterations are substantial changes in the efficiency and specialization of the adolescent brain, which is accomplished through synaptic refinement and myelination [8]. Synaptic refinement involves reductions in gray matter by eliminating unnecessary neural connections [9]. During adolescence, this synaptic pruning occurs primarily in the prefrontal and temporal cortex [10] and in subcortical structures such as the striatum, thalamus, and nucleus accumbens [11, 12]. The adolescent brain also undergoes increased myelination, which allows for improved integrity of white matter fiber tracts and efficiency of neural conductivity [13–16]. Higher-order association areas appear to develop only after lower-order sensorimotor regions fully mature [17], with frontal lobes being the final areas of the brain to complete development. Along with these neuromaturational changes, it is suggested that increased myelination allows for smoother, more efficient communication between frontal-subcortical brain regions, allowing for better top-down cognitive control in adolescence [18].

In conjunction with these numerous brain transformations, shifting social influences and peer group affiliation heavily impact adolescent behaviors [19, 20]. This may place youth at a particularly heightened risk for initiating and continuing alcohol and drug use. Specifically, transformations in the prefrontal regions and limbic systems are thought to contribute to increased risk taking and novelty/sensation seeking behaviors [21, 22]. The neuromaturation and neurochemical changes that are present during this period correspond to a range of cognitive, emotional, and behavioral changes, and are hypothesized to contribute to adolescents' increased propensity for alcohol and drug use [23].

ADOLESCENT SUBSTANCE USE AND NEUROCOGNITION

The current literature suggests that heavy drinking during adolescence does have a subtle, but significant, deleterious effects on adolescent neurocognitive functioning. Studies have found that adolescent heavy drinkers exhibit decrements in memory [24], attention and speeded information processing [25, 26], and executive functioning [27–29]. In a study comparing alcohol dependent and healthy control adolescents, Brown et al. [24] found that drinkers recalled 10% less verbal and nonverbal information than controls, even after three weeks of monitored abstinence. A similar degree of reduction was found on attentional and speeded information processing tasks in abstinent adolescent drinkers [25]. These findings are consistent with literature examining neurocognitive deficits in young heavy drinkers, which found similar decreases on attention and information processing, along with deficits in language competence and academic achievement [26]. Deficits in executive functioning, specifically in future planning,

abstract reasoning strategies, and generation of new solutions to problems, have also been found [27].

While it has often been assumed that marijuana use is not linked to long-term cognitive deficits, recent data suggest that even after four weeks of monitored abstinence, adolescents who regularly smoke marijuana performed poorer on performance tests of learning, cognitive flexibility, visual scanning, error commission, and working memory [30]. Further, the number of lifetime marijuana use episodes was significantly related to overall poorer cognitive functioning, even after controlling for lifetime alcohol use.

We [7] prospectively examined neuropsychological functioning in 26 youths with no histories of alcohol or drug problems, and compared them to 47 youths with histories of heavy adolescent alcohol, marijuana, and stimulant use. Follow-up neuropsychological tests were given to the subjects seven different times across 8 years, on average between the ages of 16 to 24. While there were no significant differences between users and non-users on neurocognitive test scores at the first time point, heavy drinkers performed worse on cognitive tasks at age 24 than light drinkers. In particular, those who had a history of alcohol withdrawal symptoms (e.g., orthostatic hypotension, nausea, insomnia, or irritability) were the most likely to have decreases in performance scores, especially on tests of spatial functioning. Overall, heavy drinking during adolescence was linked to a reduction in keeping up with age expectations [7, 25, 31].

In summary, adolescence is characterized by dramatic increases in rates of substance use concurrent with ongoing neuromaturation. While neuropsychological studies have shown that adolescent substance use is linked to poorer spatial, inhibitory, and learning and memory functioning, neuroimaging techniques may elucidate the neural mechanisms of these performance deficits.

ADOLESCENT SUBSTANCE USE AND BRAIN STRUCTURE

Advances in neuroimaging have made it feasible to closely characterize the brain structure and function of adolescent substance users and to pinpoint the circuitry and regions that may subserve the neuropsychological deficits observed in adolescent substance users.

Hippocampal Volume

Magnetic resonance imaging (MRI) was used to examine structural differences in the hippocampus, an area of the brain crucial to intact memory functioning. Participants were classified as: (1) light to non-drinkers (≤ 1 drink per month, ≤ 1 lifetime marijuana use episode), (2) heavy drinking adolescents (history of consuming 4/5+ drinks in a day), and (3) heavy marijuana users who also engaged in heavy episodic drinking. Manual tracing techniques were employed by reliable raters, and revealed that heavy drinkers had smaller left hippocampal volumes ($p<.01$), while marijuana+alcohol users had similar volumes as controls [32]. Additionally, greater alcohol abuse/dependence severity was associated with smaller left hippocampal volumes, a finding that supported previous animal models [33]. Heavy drinkers showed significantly different patterns of hippocampal asymmetry ($p<.05$; smaller left than right hippocampal volumes) compared to light-drinking youths, with an asymmetry ratio linked to memory performance. For controls, greater right than left hippocampal asymmetry correlated with better verbal learning ($p<.05$), but not in user groups [34] (see Figure 1).

These findings support the hypothesis that heavy alcohol use in adolescence has an adverse influence on the hippocampus, potentially affecting subsequent memory performance. Additionally, marijuana, in combination with alcohol use, could have some neuroprotective effects, but further studies are warranted to examine this hypothesis. An alternative explanation is that alcohol and marijuana use may create opposing mechanisms (e.g., neuroinflammation

and myelination suppression), so that macromorphometric variables may actually appear normal. Microstructural hippocampal changes related to marijuana use may include increased glial proliferation and white matter density as well as reduced gray matter, resulting in relatively normal hippocampal volumes despite functional pathology. Alternatively, heavy adolescent marijuana use may subtly interfere with synaptic pruning processes, resulting in larger gray matter volumes, particularly in the left hippocampus [32, 34].

Prefrontal Cortex Volume

During adolescence, the frontal lobe, an area of the brain associated with planning, inhibition, emotion regulation, and integration of novel stimuli, goes through extensive neuromaturation, increasing in efficiency and specialization. In a study comparing prefrontal cortex volumes of adolescent heavy drinkers to non-drinkers and marijuana and alcohol users, prefrontal volumes were smaller in heavy drinkers relative to controls (p=.09) [35] (see Figure 2). This difference was particularly pronounced in females (p<.003), confirming previous studies that examined youth with comorbid drug and psychiatric disorders [36].

Interestingly, in our preliminary comparison of prefrontal cortex volumes of 16 marijuana-using and 16 control adolescents, few differences were observed. However, among females, marijuana users had a 4% *larger* posterior and prefrontal cortex volume (p=.06) than non-users, on average. This was associated with poorer verbal memory, suggesting potentially interrupted synaptic pruning in female users. Marijuana-using adolescents showed larger global gray matter volumes than controls, with increased marijuana use predicting increased volume *(β=. 61, p<.01)* and poorer verbal and attention performance [35]. These findings also suggest that marijuana use during adolescence may disrupt gray matter pruning processes.

White Matter Volume

White matter maturation during adolescence through young adulthood is important for neuronal transmission between connecting brain regions. A recent study comparing adolescent marijuana users and matched controls indicated no significant differences in white matter volumes 37. However, marijuana use (β = .42, p < .04) and smaller white matter volume (β = −.34, p < .03) each predicted increased depressive symptoms on the Hamilton Depression Rating Scale [38]. Further, marijuana use interacted with white matter volume to predict depression scores on the Beck Depression Inventory (BDI) 39. White matter volume was negatively associated with depressive symptoms on the BDI, such that less white matter volume was associated with more depressive symptoms in adolescent marijuana users only (β = −.59, p < .03). Although between-group differences were not found in overall white matter volume, it seems plausible that marijuana use may cause or be linked to subtle alterations in white matter tracts that are responsible for mood regulation and depressive symptoms.

Quality of White Matter

Chronic alcoholic adults show clear abnormalities in brain white matter volume as well as microstructural alterations in white matter tissue organization 40−42. Typically, less white matter suggests dissipation of myelin-coated axons [43]. Diffusion tensor imaging (DTI) characterizes the integrity of water matter by examining the diffusion of water molecules in white matter tissue. Therefore, DTI provides information on the organization of localized white matter fiber tracts. Two commonly used scalar measurements are fractional anisotropy (FA), which reflects white matter coherence by providing an estimate of the directionally dependent movement of water molecules, and mean diffusivity (MD), an index of the overall displacement of water molecules.

In a preliminary analysis, we looked at the effects of both binge drinking alone and with combined marijuana use on white matter integrity [44]. Forty-two participants (ages 16–19) were

identified as controls (*n*= 14), binge drinkers (≥ 4 drinks on an occasion for females, ≥ 5 drinks on an occasion for males; *n*= 14), or binge drink+marijuana users (*n*= 14). Adolescent participants received DTI with whole brain coverage. Diffusion weighted data were collected on a 3-Tesla GE magnetic resonance scanner (repetition time=12000 ms; echo time=93.4 ms; 36×3.0 mm thick axial slices; voxel resolution $1.875 \times 1.875 \times 3.0$ mm^3 , b-value = 2000 s/mm^2). Diffusion-weighted images were acquired in 15 directions, in addition to a normalization image (b=0) with no diffusion encoding [45]. Four volumes were acquired and averaged for each direction and the b = 0 volume. FA (or MD) maps from each participant were submitted to Tract-Based Spatial Statistics (TBSS [46]), which facilitated voxelwise between-group comparisons.

Significant group differences were found in eight white matter regions, including frontal association fibers such as frontal-occipital and superior longitudinal fasciculi. Bingers and binge+marijuana users displayed lower FA than controls (*p*s ≤ .016). Interestingly, bingers demonstrated significantly lower FA than the binge+marijuana group (*p*s .014 to .043). No significant MD differences were found in the 8 clusters identified by the FA analyses. Our findings suggest poorer white matter integrity in adolescents with histories of binge drinking than non-drinkers. However, teens with concomitant binge drinking and marijuana use showed a lesser degree of reduced fiber tract coherence than those engaging in binge drinking alone.

These findings are largely consistent with our previous structural imaging studies that found small yet significant effects of marijuana use on adolescent brain structure and function [34, 37], and stronger associations between alcohol use and tissue status. In a study that looked specifically at adolescents with alcohol use disorders, we found reduced white matter microstructural integrity compared to demographically matched youths without alcohol use disorders [47]. Significantly lower FA was found in the splenium of the corpus callosum, and trends for lower FA were also found in the rest of the corpus callosum, suggesting possible alcohol-related white matter alterations. The callosal fibers are a massive collection of white matter tissue that connect the left and right hemispheres of the brain, and are important for efficient transfer of information. Microstructural changes in the corpus callosum may underlie neurocognitive changes associated with alcohol use during adolescent brain maturation. Notably, decreased white-matter integrity was significantly related to longer duration of heavy alcohol use, greater number of past alcohol withdrawal symptoms, and recent consumption of large amounts of alcohol.

Overall, our findings of reduced FA suggest possible myelination alterations in brain regions developing during adolescence, and underscore the impact of the effects of alcohol on white matter maturation during adolescence. Our more recent findings indicate that even subtle binge drinking behaviors can have a substantial impact on tissue development, as adolescents with both alcohol use disorders as well as less frequent or new-onset binge drinking habits were found to have altered white matter integrity. Future studies will follow these cohorts over the adolescent years to see if changes in substance use are followed by changes in indices of white matter quality.

Brain Blood Flow

Understanding cerebral blood flow (CBF) is important since inadequate blood flow can damage brain tissue. CBF can also influence the blood oxygen dependent signal interpreted in functional magnetic resonance imaging (fMRI). Moreover, chronic alcoholics have been shown to have reduced blood flow into the brain [48]. In a study examining CBF in alcohol dependent young women (n=8), we found decreases as compared to female light drinkers (n=8) using perfusion-weighted magnetic resonance imaging [49]. In these 18–25 year-olds, decreases were seen in six prefrontal and parietal regions (η^2 = .47 to .83), and there were no regions in which perfusion was greater for alcohol dependent participants compared to controls. These

findings may help clarify the metabolic changes behind differences in functional brain activity seen in adolescents with histories of alcohol misuse.

ADOLESCENT SUBSTANCE USE AND BRAIN FUNCTIONING

In addition to alterations in brain structure, recent findings have suggested decrements in brain functioning associated with adolescent substance use. Functional magnetic resonance imaging (fMRI) investigates neural activity of the brain by measuring changes in blood oxygen level dependent (BOLD) signal [50], which indicates areas of increased activation in response to a mental task or stimulus [51]. This technique is noninvasive and does not require injections or radioactive materials, making it a safe and appropriate technique for examining adolescent brain functioning.

Spatial Working Memory

Numerous studies involving adult alcoholics suggest neural disruption while executing cognitive tasks; however, it is unclear to what extent drinking must progress, and at what age, before abnormalities manifest. Our group [52] found that adolescents who drank heavily for one to two years showed abnormalities in brain response on cognitive tasks measuring spatial working memory (SWM) as compared to light drinkers. While both the heavy and light drinkers performed similarly on the task, heavy drinkers exhibited increased activation in the parietal lobe, with decreased activation in the occipital and cerebellar regions, compared to light drinkers [52]. Additionally, youth with more hangover experiences and greater alcohol consumption showed greater abnormalities. These results suggest that after as little as one to two years of heavy drinking, adolescents may exhibit subtle neural reorganization that includes compensation, highlighting the potential early influence of drinking on neurocognitive functioning during the escalation of alcohol use disorders.

In another study by our lab [53], young adults who had engaged in four to five years of heavy drinking showed poorer performance on the same SWM task during fMRI, in addition to decreased activation in parietal and frontal regions. Together, these results suggest that the adolescent brain may be able to compensate for subtle neural abnormalities associated with drinking; however, repeated heavy drinking episodes may interfere with the brain's ability to make up for alcohol-related deficiencies in neural functioning.

Additional studies from our laboratory (e.g., [54] compared young adult marijuana users (ages 16–18) after one month of abstinence to matched controls on the same SWM task described in the previous studies. Although there were no differences in task performance between the marijuana users and controls, the marijuana users exhibited increased activation in parietal, temporal, and frontal (including insula) brain regions. The marijuana users also showed less activation in cerebellum and occipital cortices than controls. Findings remained significant after controlling for alcohol and other drug use, and also suggest compensatory and possibly inefficient SWM-related neural response associated with marijuana use.

Verbal Encoding

Decrements in verbal encoding abilities have also been observed in binge drinking adolescents during fMRI tasks involving recall of learned word pairs [55]. Compared to nondrinkers, bingers showed less response in right superior frontal and bilateral posterior parietal cortices, with more response in occipital cortex, during the verbal encoding task. This suggests less utilization of working memory systems during encoding for bingers compared to nondrinkers on tasks of encoding. In addition, drinkers encoded marginally fewer words than nondrinkers ($p=.07$), and had no differential activation to novel stimuli. Together, these results suggest slightly poorer

initial verbal learning, disadvantaged verbal processing, and decelerated learning for adolescents who engage in binge drinking compared to abstinent adolescents.

Further studies in our laboratory comparing verbal encoding abilities between adolescents reporting marijuana use and matched controls have found no differences on task performance. Yet, marijuana users evidence more frontal and less temporal activation compared to matched controls. Although both groups performed similarly on the fMRI task, adolescent marijuana users have shown poorer performance on sensitive measures administered as part of an extensive neuropsychological test battery (e.g., California Verbal Learning Test-II, Wechsler Memory Scale-III Story Memory), particularly on initial learning trials [30]. Taken together, changes in brain activation in adolescent marijuana users on a verbal encoding task may be indicative of less allocation of attentional resources toward encoding the novel material.

Inhibition

In addition to decrements in spatial working memory and verbal encoding, modestly decreased ability to inhibit behaviors has been found in binge drinking adolescents. A pilot study from our group [56] found greater BOLD response relative to controls in the frontal areas and less activation in the cerebellar areas during a go/no-go task of response inhibition administered during fMRI [57–59], despite similar task performance. On response selection ("go") trials, drinkers exhibited less BOLD response than controls in the mid-cingulate, subcortical, and temporal areas. Better task accuracy was linked to more frontal response during these trials among controls, but not among drinkers ($p<.025$). These findings suggest that even infrequent exposure to large doses of alcohol may influence inhibitory processing. As with all cross-sectional studies described, follow-up evaluations will help elucidate the temporal relationship between inhibition and alcohol use.

We [59] also looked at response inhibition in marijuana users after 28 days of monitored abstinence, as compared to matched controls. Participants were excluded for any neurological problems or Axis I diagnoses other than cannabis abuse or dependence. The study used the same go/no-go task described above, and although marijuana users performed similarly as controls, they exhibited increased activation on inhibition ("no-go") trials in right dorsolateral prefrontal cortex, bilateral medial frontal cortex, bilateral inferior and superior parietal lobules, and right occipital gyri. On "go" trials, marijuana users had increased activation in right prefrontal, insular, and parietal cortices ($p<.05$, clusters >943 µl). More response during "no-go" trials related to worse neuropsychological performance (e.g., impulsivity, complex attention, cognitive flexibility, planning). Neuropsychological indicators of impulsivity were in turn linked to more medial temporal and less anterior cingulate response in marijuana users ($p<.05$). Differences remained even after controlling for lifetime and recent alcohol use. This suggests that marijuana users have increased brain processing effort during an inhibition task despite showing intact task performance, even after 28 days of abstinence. Such increased neural processing effort to achieve inhibition may predate the onset of regular use, or result from it.

Cue Reactivity

Adolescent response to alcohol advertising is of concern, as they are exposed to alcohol-related ads on a daily basis in many countries [60]. We [61] have observed that heavy drinking youth show greater brain activation while viewing alcohol advertisements than they do to non-alcohol beverage ads. This substantially greater brain activation to alcoholic beverage pictures was observed throughout the brain, particularly in the prefrontal area, nucleus accumbens, hypothalamus, posterior cingulate, and temporal lobe, and was prominent in the left hemisphere, limbic, and visual cortices. This suggests that reward, visual attention limbic, appetitive, and episodic memory systems were preferentially invoked in response to alcohol

ads relative to non-alcohol ads in heavy drinking teens. Only the inferior frontal gyrus showed more activation in light drinkers during the task, potentially indicating a negative valence to these alcohol stimuli in non-drinking teens. Overall, light drinkers showed more response to non-alcoholic beverage pictures. These findings extend previous studies in adults, and link alcohol advertisement exposure in youth to activation in reward, desire, positive emotion, and episodic recall brain areas [62].

Predicting Relapse

Relapse is a common clinical problem in individuals with substance dependence. Previous studies have implicated a multifactorial process underlying relapse; however, the contribution of specific neural substrates had yet to be examined. We [63] looked at whether results from functional imaging shortly after drug cessation could predict relapse in stimulant dependent individuals. The goals were to evaluate the neurobiology of decision-making dysfunction in stimulant dependent subjects, and to determine if functional imaging could be used as a tool to predict relapse.

Participants included treatment seeking methamphetamine dependent adult males (*N*=46). All individuals underwent fMRI three to four weeks after cessation of substance use. Of the 40 subjects who were followed a median of 370 days, 18 relapsed and 22 did not. The main outcome measure was BOLD activation during a simple two-choice prediction task. During the prediction task, a house was presented, flanked by a person on its left and right. The participant decided on which side of the house a car would appear. Each trial was self-paced to maximize self-determined action, thus the subject determined the number of trials by the latency to select a response. Immediately following the subject's response, the car was presented for 300 ms on the far left or right side. The screen provided the feedback whether the prediction was correct. Unbeknownst to the participant, the computer determined the response based on the participant's selection. Three error rate block types included a high chance level (20% of responses were "correct"), a 50% chance-level, and a low (80% of responses were "correct") chance level. The task captures the key elements of decision-making: the probability of an outcome associated with an option, the positive or negative consequence, and the magnitude of the consequence [64].

The fMRI activation patterns in right insular, posterior cingulate, and temporal cortex correctly predicted 20 out of 22 subjects who did not relapse, and 17 out of 18 subjects who did. A Cox regression analysis revealed that the combination of right middle frontal gyrus, middle temporal gyrus, and posterior cingulate activation best predicted the time to relapse. In total, this is the first investigation to show that fMRI can be used to predict relapse in substance dependent individuals. It is likely that relapse corresponds with less activation in structures that are critical for decision-making, and thus poor decision-making sets the stage for relapse. The insular cortex may act through the interoceptive system to influence ability to differentiate between good versus poor choices, while the inferior parietal lobule may play a role in poor assessment of decision-making situations and subsequent reliance on habitual behavior. Overall, substance dependent adults show brain patterns that can be used to predict whether and when relapse may occur. Future studies are needed to determine if this is true for adolescents, and whether brain activation patterns can be used to evaluate an individuals' readiness for treatment completion or treatment response.

Summary

Overall, changes in brain functioning in adolescents differ by substance use pattern. Research has shown that heavy drinking during adolescence can lead to decreased performance on cognitive tasks of memory, attention, spatial skills, and executive functioning. These behavioral ramifications of heavy alcohol use may emerge as a consequence of the reduced

volume of important brain structures (e.g., hippocampus), compromised quality of white matter, and abnormalities in activation during cognitive tasks. Studies have also shown that marijuana use during adolescence can result in decreases in cognitive functioning, particularly learning and sequencing scores. In integrating and interpreting the results of adolescent marijuana studies from our laboratory, it is important to note that the groups are generally equivalent on task performance, and therefore the underlying brain responses in controls and users can be largely assumed to represent activity to the same mental action. Corresponding marijuana-related changes in cognition may be related to increases in gray matter tissue volume, decreases in white matter microstructural integrity, and increases in neuronal activation during cognitive tasks.

In sum, we can reasonably rule out recent use as accounting for the observed differences between substance groups, given that participants in some studies have been abstinent one month or greater. Substance using adolescents have been found to differ from non-users on neuropsychological performance, brain tissue volume, white matter integrity, and functional brain response. Longitudinal studies are essential to fully understand how alcohol and marijuana use affect adolescent neurodevelopment.

METHODOLOGICAL CONSIDERATIONS

The cross-sectional nature of the majority of studies examining adolescent neurocognitive functioning makes it difficult to determine the influence of alcohol and drug use on adolescent neurocognition. Therefore, ongoing longitudinal neuroimaging studies are essential to ascertain the degree to which substance intake is linked temporally to adverse changes on indices of brain integrity, or whether neural abnormalities reflect pre-existing patterns. In cross-sectional or longitudinal work, several methodological features are critical to evaluate the potential influence of adolescent substance use on neurocognition. These issues pertain to ensuring participant compliance, accurately assessing potential confounds, and maximizing participant follow-up.

Adolescent compliance as a research participant can be maximized by attending to rapport, building trust, and ensuring privacy of self-report data to the extent that is ethical and feasible to the setting. For behavioral tasks within or outside of imaging, it is critical to ensure participants comprehend task instructions, are fully trained on fMRI tasks, and then are given reminders just prior to task administration. Motion during scan acquisition is detrimental to the quality of imaging data, and is often worse in younger adolescents than older teens or adults. Adolescent head motion can be minimized by the following steps: discuss the importance and rationale for keeping the head still multiple times before and at the scan appointment; model and practice how to say "yes" and "no" when communicating with the research subject from the scanner; model and practice techniques for relaxing and ensuring subjects are in a position suitable for long-term comfort (e.g., legs are not crossed) before scanning begins; maximize participant comfort by using soft cushions around the head and under the knees; and many studies, especially those with younger participants, find practicing scanning in a less expensive mock scanner results in improved participant comfort and more reliable data during data acquisition.

Accurately measuring and accounting for confounds frequently present in adolescent substance-using populations is essential for elucidating the true effect of substance use on adolescent neurocognitive functioning. Common confounds in this population include head injury, depression, ADHD, conduct disorder, prenatal exposure to neurotoxins, family history-related effects, and polysubstance involvement. Conversely, excluding subjects for the aforementioned confounds may impede the generalizability of results. The tradeoff between

minimizing confounds and having meaningful, ecologically valid results is an important study design decision, especially given the high cost of fMRI sessions.

Accurately measuring abstinence is another important consideration in substance-related research protocols. If abstinence is required for participation (and compensation) in a study, the dynamics of self-report could change. While biological data may help confirm self-report, these measures are imperfect and do not pinpoint the quantity of specific timing of substance intake [65, 66]. Regarding abstinence from cannabis, obtaining serial quantitative THC metabolite levels, normalized to creatinine, is the best approach for guarding against new use episodes [67].

Tracking participants over time is a critical part of many clinical issues when interested in the degree to which a variable (e.g., alcohol or marijuana use) might result in neural changes. Although some statistical approaches can help manage attrition, effective tracking procedures are more desirable to ensure study integrity. To maximize participant follow-up, frequent contact with participants must be maintained [68]. Having a well-trained, friendly staff experienced with the population also helps retain participants and parents, and ensures that all participants fully understand the tasks and expectations during the study. Collecting comprehensive contact information can help track adolescents over time in case they should relocate. Additionally, follow-up measures and procedures should be as similar as possible to baseline, except to mitigate learning and practice effects [69]. For imaging studies, field map unwarping of EPIs (e.g., fMRI and DTI) should also be considered, as this technique appears to produce more consistent localization of activations [70]. Finally, as technical problems are common, back up plans for each piece of equipment used in the neuroimaging session should be in place.

CONCLUSIONS

Current research suggests that substance use in adolescence leads to abnormalities in brain functioning, including poorer neurocognitive performance, white matter quality, changes in brain volume, and abnormal neuronal activation patterns. fMRI studies have illuminated enhanced cue response in adolescent drinkers, and have shown the potential to predict treatment outcomes in stimulant dependent adults.

A few questions still remain, such as whether heavy substance use during adolescence causes cognitive impairments and changes in neurodevelopment, if and when are critical periods of heightened vulnerability to such effects, and if observed abnormalities remit with reduced use. We have the capability to design studies in which we restrict or control for nicotine and most other drug use, but few adolescent drug users do not also use alcohol. It is also important to understand if results generalize to youth with psychiatric problems, other substance use histories, and low socioeconomic status, and to further explore implications for changes in brain activation for learning and behavioral control, along with mood and psychiatric illness. Harder parametric tasks that include conditions on which behavior does differ between groups would help us better understand the cognitive domains we have observed differences on. Lastly, we need to better understand the biochemical changes that may mediate macrostructural, microstructural, and functional neuronal changes in response to substance use, such as cannabinoid receptor activity changes. Multimodal approaches to neuroimaging may help us disentangle such questions (e.g., PET, spectroscopy).

Our group is currently conducting longitudinal studies of adolescent substance users as well as youth at risk for substance problems due to family history or early conduct disorder (minimal use at the time of the first imaging session). Follow-up scan data, already underway, will elucidate if substance use during the follow-up interval predicts changes in brain functioning.

These investigations will ascertain if: (1) substance (alcohol and marijuana, predominantly, given sample characteristics) use during adolescence seems to cause detrimental changes in neurodevelopment, or if (2) substance use does not account for the differences, the previously observed differences would likely represent pre-existing markers of risk for heavy substance use during adolescence.

Acknowledgments

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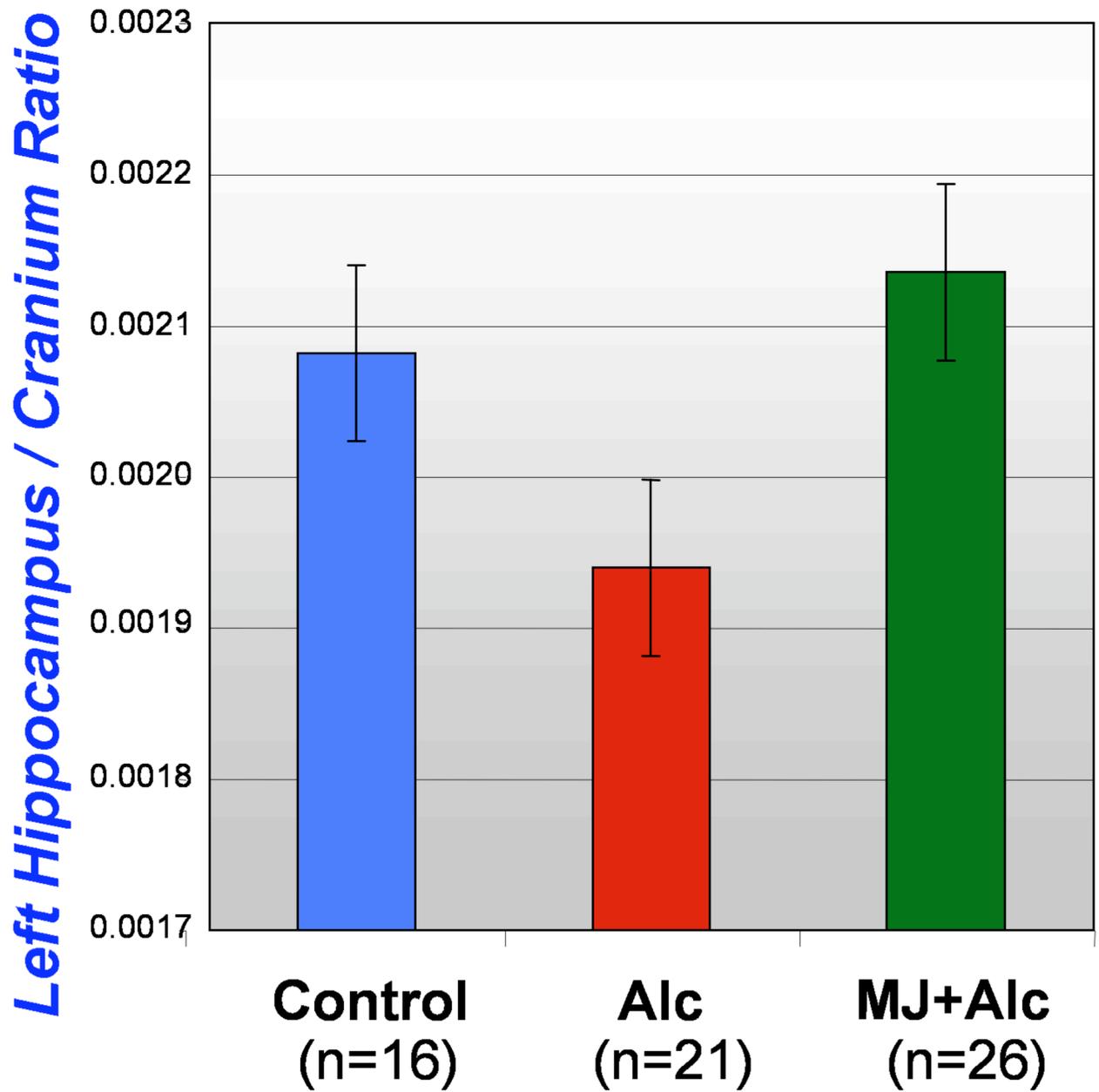
Figure 1.
Hippocampal volume for adolescents with different substance use patterns. Adolescent users of alcohol, but not alcohol plus marijuana, showed significantly smaller left hippocampal volumes than demographically similar non-users (Medina et al., 2007).
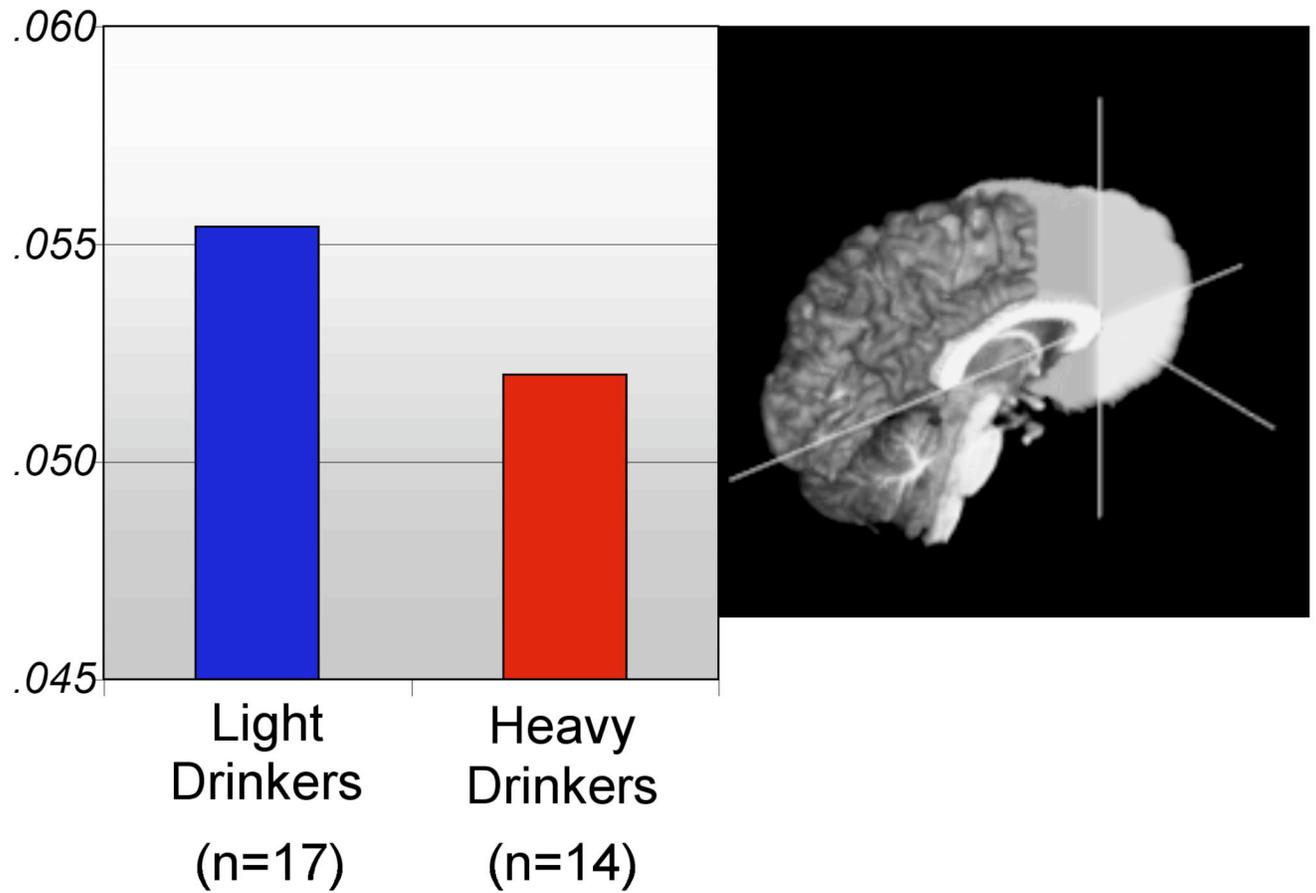
Figure 2.
Ventral prefrontal volume in adolescents with minimal and heavy drinking histories; ventral prefrontal region is highlight in white in the figure to the right.