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The Effects of Alcohol and Cannabis Co-Use on Neurocognitive Function, Brain Structure, and Brain Function

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Abstract

Purpose of review: Given increases in the rates of alcohol and cannabis co-use among adolescents and young adults, this review aims to summarize literature on the effects of alcohol and cannabis co-use on neurocognitive functioning, brain structure, and brain function.

Recent findings: The limited existing studies examining concurrent, recent, and lifetime alcohol and cannabis co-use suggest effects on the brain are likely multifaceted. The majority of studies report that co-use is associated with negative outcomes such as impaired cognitive function and significant alterations in key structural and functional regions of the brain, while others report null effects of co-use compared to non-substance using control and single-substance use groups.

Summary: Current studies lack a general consensus on methodology, definitions of concurrent and simultaneous use, and neuroimaging approaches, which makes it challenging to draw strong conclusions about the effects of co-use. More studies are needed to explore the effects of co-use in the context of simultaneous alcohol and cannabis use.

Keywords

Co-use; Concurrent; Alcohol; Cannabis; Neuroimaging; Cognition

Introduction

Alcohol and cannabis are two of the most commonly used substances in the United States among adolescents and young adults [1]. Large-scale national survey data shows that 54% of young adults report past month alcohol use and 23% report past month cannabis use [1]. Moreover, the co-use of alcohol and cannabis is highly prevalent, with 58% of alcohol users also reporting cannabis use and over 75% of cannabis users also reporting alcohol use [2]. Among users of both alcohol and cannabis, most use concurrently (use of each substance on at least one occasion) or simultaneously (use of both substances at the same time during

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an occasion, such that their effects overlap) [3–6]. Concurrent use is associated with an increased risk for negative outcomes, such as increased frequency and quantity of alcohol and cannabis use, decreased academic performance, and greater likelihood of developing a substance use disorder [6–9]. However, studies show that the additive and synergistic effects of simultaneous use on cognitive, perceptual, and motor functions place individuals at greater risk for more severe negative outcomes (i.e., driving under the influence, poorer mental-health and cognition, co-morbid substance use disorder) relative to concurrent and single-substance use [7, 10, 11]. Although the mechanisms underlying the link between the co-use of alcohol and cannabis and risk for negative outcomes remains unclear, one potential pathway is the extent to which the co-use relates to changes in neurocognitive functioning, brain structure and function [12–16•].

The negative effects of alcohol or cannabis alone on cognitive processes have been established in prior literature. Alcohol use is linked to poorer cognitive function, including deficits in impulse control related to decreased cortical thickness, altered white matter (WM) integrity, and substantial decreases in gray matter (GM) integrity [17–20]. Research also shows that the acute and long-term effects of cannabis on cognition are similar to alcohol [20], while effects on brain structure and function are mixed. Some studies show no effect of cannabis use on WM integrity or GM volume [20, 21], while others suggest cannabis use is associated with decreased cortical thickness, altered WM integrity, and decreased GM volume [22•–25]. However, generally studies do not characterize participants by their co-use patterns, so it is unclear how much of this inconsistency in findings is attributable to the potential differences in co-use of other substances, such as alcohol. While prior research demonstrates the effects of alcohol and cannabis alone on neurocognitive, structural and functional aspects of the brain, research on the effects of the co-use of alcohol and cannabis is limited and has led to inconsistent findings. The purpose of this review is to provide an overview of the limited findings, the inconsistencies in the co-use literature, and how methodological limitations in the existing research may be contributing to a lack of clarity on co-use effects. Our purpose is to also summarize key considerations in the implementation of future neurobehavioral research on the effects of co-use.

Methods

PubMed and Scopus databases were searched for articles examining the effects of alcohol and cannabis co-use on neurocognitive functioning and neuroanatomical outcomes using the following search terms: *neuroimaging, structural, functional, cognition, cognitive function, fMRI, and MRI* in combination with *cannabis, alcohol, co-use, polysubstance use, concurrent alcohol and cannabis use, simultaneous alcohol and cannabis use*. In addition to the online literature search, reference lists of the articles found were searched to identify any relevant articles not returned by the literature search. For the purpose of this review, and due to lack of consistency in the existing literature, we will define co-use of alcohol and cannabis as concurrent (alcohol and cannabis use on at least one occasion), recent co-use (alcohol and cannabis use in the past 2 months), and lifetime co-use (alcohol and cannabis use across the lifetime). Prior studies have examined varying timescales of co-use. Because different operationalizations of co-use may have distinct effects on the brain, evaluating findings using these operationalizations may clarify differences in outcomes

between studies. Findings in each section are presented in order of concurrent, recent, and lifetime co-use. While simultaneous use (use of both substances at the same time during an episode of use, such that their effects overlap) has been examined in other areas, we are not aware of any literature examining the effects of simultaneous use on any of these neurocognitive, functioning, or neuroanatomical domains. Studies examining the effects of alcohol and/or cannabis co-use were considered, excluding those that involve administration of substances. A list of key co-use articles published in the last 5 years is provided in Table 1. Studies in the table are grouped by whether they examined concurrent, recent, or lifetime co-use.

Neurocognitive Function

Neurocognitive studies provide considerable evidence for the effects of alcohol or cannabis use on the brain [26–31]. Although adolescents and young adults frequently report the use of alcohol and cannabis together [2], research is limited on the effects of co-use with neurocognitive processes and the few studies that do exist have provided inconsistent findings.

Concurrent Use

Only one study has examined the effects of concurrent alcohol and cannabis use on neurocognitive function. Among adolescents and adults, more frequent past month binge-alcohol and cannabis co-use days were associated with poorer selective attention accuracy, assessed using a visual search and cancellation task [Ruff 2&7, 32], above and beyond the effects of alcohol or cannabis use alone [33•]. Selective attention plays a key role in academic domains such as language, literacy, and mathematics [34], and impairments in this domain could be a potential mechanism that explains prior findings demonstrating that co-use leads to poorer academic performance [9]. Notably, co-use days were not associated with executive function, verbal fluency, learning and memory, and delayed recall. Although this study examined concurrent use, it is unclear how many of the reported co-use days involved simultaneous alcohol and cannabis use. While it is likely that simultaneous use occasions are embedded in concurrent use days, quantifying co-use in this way does not capture the additive or synergistic effects of simultaneous use. Future research should examine simultaneous use as this would clarify effects on other cognitive domains such as executive function, verbal fluency, learning and memory, and delayed recall.

Recent Co-use

Research examining the effects of recent co-use on neurocognitive function and impulsivity has shown mixed findings. In a large sample (N=730) of young adults, there were no differences in assessments of verbal intelligence, working memory, probability discounting, short-term verbal memory, or behavioral inhibition between the binge-drinking and daily cannabis use, binge-drinking and weekly/monthly cannabis use, and binge-drinking only groups [35•]. However, individuals who engaged in binge-drinking and daily cannabis use showed greater discounting of future rewards (i.e., delay discounting) when compared to the binge-drinking and weekly/monthly cannabis use group or binge-drinking only group [35•]. Notably, no differences were observed for delay discounting between the binge-drinking

only and binge-drinking and weekly/monthly cannabis use groups [35•]. These findings suggest the effects of co-use among individuals who binge-drink may depend on the frequency with which cannabis is used with alcohol. However, a cannabis-only comparison group was not included, and so it is unclear if the observed effects in this study are attributable to co-use or to increasing frequency of cannabis use. Simultaneous use likely occurs more often in those who binge drink and use cannabis daily, and this simultaneous use could be a determining factor in whether negative effects emerge when comparing to other alcohol or cannabis using groups. A study comparing performance on the Stop Signal task among freshmen and sophomore college students also found no differences between groups when comparing binge-drinking only, binge-drinking and cannabis use, and minimal substance using controls [36•]. In contrast to the two studies that largely showed no performance-based differences, studies examining the personality trait of impulsivity have mixed findings. In a study that included a cannabis-only group, recent co-users showed significantly elevated levels of impulsive sensation seeking (ImpSS) compared to both cannabis users and controls [12•], whereas no group differences emerged between co-users and alcohol users. Moreover, in a community sample of adolescents there were no differences in ImpSS between recent co-users of alcohol, cannabis, and tobacco, single-substance users (alcohol, cannabis, tobacco) and non-substance using controls [37•]. Given measures of impulsivity (e.g., task-based behavioral, self-report) vary across studies, future research should examine the effects of co-use across multiple domains of impulsivity in order to clarify and integrate the conflicting findings from previous studies.

Lifetime Co-use

Studies also examine the effects of co-use on neurocognitive function using methodological approaches that capture alcohol and cannabis use across the lifetime. These studies show that lifetime co-users demonstrate impairments across cognitive domains that are similar to concurrent and recent co-use. A cross-sectional study classified adolescents into four groups: cannabis users, heavy-episodic drinkers, lifetime co-users, and controls, and found that lifetime co-users (>100 cannabis episodes and >100 heavy episodic drinking episodes) had worse executive function and poorer attention, verbal recall, and working memory compared to controls (<10 drinking episodes, <5 cannabis episodes) [38]. Notably, co-users showed similar impairment in cognitive flexibility and verbal recall as alcohol users relative to controls and further, co-users and cannabis users showed similar impairments on task accuracy relative to controls. Given co-users demonstrated significant impairments in neurocognitive function compared to controls, this finding suggests that the effects of recent co-use on neurocognitive processes may be similar to the use of alcohol and cannabis alone. Further, longitudinal research has also examined the effects of lifetime co-use on neurocognitive function relative to alcohol users and non-substance users. Jacobus and colleagues [16•] followed alcohol and cannabis-using adolescents over a 3-year period and found that lifetime co-users performed significantly worse on complex attention, memory, processing speed, and visuospatial functioning at baseline and both the 1.5 year and 3-year follow-ups compared to the minimal-substance using control group (≤9 lifetime cannabis use episodes, minimal alcohol use). These findings are in line with previous research by the same group which also found lifetime co-users (>200 lifetime cannabis episodes) exhibit greater impairments in complex attention, memory, processing speed,

and visuospatial functioning relative to controls [39]. Subsequent work by this group found more specific cognitive effects over time in a separate sample, such that alcohol users and minimal-substance using controls (<3 lifetime alcohol use episodes, no cannabis use episodes) demonstrated better complex attention at baseline and the 6-year follow-up compared to lifetime co-users [14•]. Across these studies, lifetime co-users demonstrated worse neurocognitive performance compared to the alcohol-only and minimal substance using control groups, suggesting lifetime adolescent co-users are at greater risk for poorer cognitive functioning over time. However, neither study included a comprehensive set of both single-substance use groups (e.g., alcohol and/or cannabis) which limits the ability to generalize findings across subgroups of individuals.

Based on previous research it appears that the co-use of alcohol and cannabis adversely affects neurocognitive performance across attention, executive function, learning and memory, and visuospatial functioning. The limited research on the effects of co-use on impulsivity has led to inconsistent findings. Given prior research demonstrating that simultaneous use is associated with more severe negative outcomes relative to concurrent use (e.g., lower academic achievement) [7], the relationship between cognitive function and concurrent use may be driven by the synergistic effects of alcohol and cannabis use. Notably, no prior research has examined the association between simultaneous alcohol and cannabis use on domains of memory, attention, or impulsivity. It is not clear from the current studies whether effects of co-use are in fact synergistic or whether they simply reflect the impacts of alcohol and cannabis combined. More research is needed to determine the impact of concurrent and simultaneous use on neurocognitive function in order to clarify and integrate findings from previous studies.

Structural Neuroimaging

Structural neuroimaging studies provide strong evidence of the adverse effects of either alcohol or cannabis use on brain structure among adolescents and young adults [19, 24, 37•]. Important indicators of these effects are measurements of WM integrity, GM integrity, and cortical thickness. Previous research has shown that alcohol users demonstrate reductions in fractional anisotropy (FA), a marker of WM integrity, in a variety of widespread brain regions [19], while the effects of cannabis use are less clear [21, 30]. Moreover, the effect of alcohol and cannabis on GM integrity remains a controversial topic with previous research suggesting cannabis may protect against the detrimental effects of alcohol use [40•]. Although studies suggest alcohol and cannabis differentially affect brain structure, research examining the effects of co-use is limited and studies have mixed findings.

Concurrent Use

WM integrity typically follows a linear maturation pattern well into late adolescence and normal development is important for efficient cognitive functioning [41, 42]. A recent study examining structural integrity in a community sample of adolescents found that more frequent past month concurrent binge-drinking and cannabis use days were associated with lower WM integrity across frontolimbic tracts, such as the cingulum cingulate gyrus, relative to cannabis or binge-drinking alone [15•]. Notably, past month concurrent use episodes have

been shown to be associated with poorer attention [33•], and given the cingulum plays a key role in higher order cognitive functioning [43], these findings highlight the importance of brain-behavior connections as a result of concurrent use. While the results of this study cannot determine the synergistic effects of simultaneous alcohol and cannabis use on brain structure, it is one of the first to measure concurrent use as a predictor of WM integrity.

Recent Co-use

In a cross sectional study of WM integrity in early-phase psychosis patients with a history of alcohol and cannabis consumption, lifetime alcohol use was negatively correlated with FA values, whereas lifetime cannabis use was positively correlated [22•]. Previous research suggests cannabis use among binge-drinking adolescents moderates regional alterations in WM integrity [44]; however, no effects were observed for the interaction of alcohol and cannabis on FA values in this cross-sectional study [22•]. While this study suggests changes in WM integrity are not associated with lifetime co-use, prior research has shown decreases in WM integrity as a result of concurrent use [15•]. Taken together, these studies support the need for additional studies examining effects of recent co-use on structural differences.

Lifetime Co-use

Studies comparing WM changes between lifetime co-users, single-substance users, and controls result in mixed findings. One study found that lifetime co-users (180–1800 cannabis lifetime use episodes, 50–700 alcohol lifetime use episodes) demonstrated lower FA values in 10 regions of the brain primarily responsible for attention, working memory, and processing speed compared to minimal-substance using controls [45]. Similar research, in a separate sample of adolescents and young adults, found that lifetime co-users (histories of at least 1 episode of ≥ 4(female)/5(male) drinks on one occasion, 180–1800 lifetime cannabis episodes) had lower FA values in 3 clusters, 2 clusters in the corona radiata clusters and 1 cluster in the superior longitudinal fasciculus, compared to controls [44]. Co-users showed higher FA values in 4 of 8 regions (corona radiata, inferior fronto-occipital fasciculus, middle cerebellar peduncle, superior longitudinal fasciculus) compared to the binge-drinking only group [44]. Notably, co-users in this sample reported more lifetime drinking occasions (M=152.9) compared to the binge-drinking only group (M=54.6). The authors suggest that this finding reflects cannabis' potential to mitigate alcohol-related changes in WM integrity. Given the lack of comparison groups within these studies, it is unclear if alterations in WM integrity are unique to co-use among individuals who binge-drink or rather, the use of alcohol or cannabis alone.

Several longitudinal studies examining the effects of lifetime co-use on adolescent brain development suggest co-users show differential WM integrity compared to alcohol-only and non-using substance use groups [46, 47]. In a small sample (N=16) of minimally substance using adolescents at baseline, subgroups of co-users (significant increase in both alcohol and cannabis use from baseline to 3 year follow-up) had significantly decreased WM integrity at 3 year follow-up compared to alcohol-only users (≤10 cannabis episodes at each follow up, significant increase in alcohol use from baseline to 3 year follow-up) [46]. Given adolescents in this sample were minimal-substance users at baseline, findings suggest a potentially harmful effect of co-use on structural integrity. Another longitudinal study

examining adolescents who binge-drink, lifetime binge-drinking cannabis users (co-users), and controls found no differences in WM integrity between co-users and the binge-drinking group, despite co-users reporting significantly higher levels of alcohol use compared to the binge-drinking group [47]. Although changes in WM integrity appear to be nuanced, future studies should include exclusive cannabis users, or cannabis users with minimal alcohol use, in order to distinguish between the effects of using a single-substance and concurrent use.

Another important indicator of the effects of alcohol and cannabis use on brain structure is the measurement of cortical thickness. The cortex typically undergoes significant cortical pruning during adolescence and previous studies demonstrate that changes in cortical thickness (i.e., thinning) are associated with better neurocognitive performance [48]. One study found increased cortical thickness in the left entorhinal cortex and medial temporal lobe in lifetime co-users compared to non-substance using controls [39]. Given the typical cortical pruning that occurs during adolescence, these findings suggest co-users may be at risk for less cortical pruning that may be associated with worse neurocognitive function. Similarly, longitudinal studies suggest lifetime co-use is associated with greater cortical thickness compared to alcohol-only and minimal-substance using control groups [13•, 14•]. A sample of adolescents (N=68), followed over a 3-year period, was divided into 2 groups: 30 lifetime co-users (≥120 lifetime cannabis episodes, ≥22 lifetime alcohol episodes) and 38 minimal-substance using controls (≤9 lifetime cannabis use episodes and minimal alcohol use [13•]. Co-users demonstrated thicker cortical estimates across 18 of 23 brain regions, primarily in the parietal and frontal lobes, compared to the minimal-substance using control group. Notably, cumulative cannabis use days were associated with increased thickness estimates by the 3-year follow-up. While previous findings demonstrate a negative association between cannabis use and cortical thickness [39], the contrasting results of this study suggest the mechanism by which cannabis alters brain structure may vary depending on whether alcohol consumption is proximally present. Jacobus and colleagues [14•] expanded upon previous work examining cortical thickness by including an alcohol-only comparison group. Alcohol users demonstrated thicker cortices prior to alcohol initiation, similar to minimal-substance using controls (<3 lifetime alcohol use episodes, no cannabis use episodes), but underwent a more substantial decrease in cortical thickness into young adulthood when compared to lifetime co-users. Prior research has shown that alcohol use disrupts age-appropriate cortical thinning and findings from this study suggest thinning may occur faster than normal among alcohol users [49]. Further, previous research suggests that cannabis use during this developmental stage may attenuate normative age-dependent cortical thinning [50] and findings from these studies suggest synapses that would typically be eliminated as part of refinement are preserved in the presence of cannabis. Although these studies included lifetime co-users and controlled for alcohol use, the specific effects of cannabis remain unclear as there were no cannabis-only comparison groups in either study. Future research should include cannabis-only groups in order to determine whether the effects of co-use on cortical thickness are unique to co-use or cannabis use alone.

Neuroimaging studies examining the effects of lifetime co-use on GM integrity are a point of contention as studies suggest cannabis may protect against the detrimental effects of alcohol use. Prior research has shown that GM volume typically increases in early childhood followed by post-adolescent decreases [51, 52]; however, longitudinal work found that

adolescent alcohol users show substantial, problematic decreases in GM surface area in the orbital frontal cortex compared to lifetime co-users [40•]. Damage to this region in the frontal lobes is associated with greater impulsivity and risk-taking behavior [53] and decreases in GM surface area among alcohol users may place them at greater risk for associated outcomes. However, findings from this study suggest the adverse effects of alcohol on the developing brain, and the magnitude of these effects, may depend on co-use with cannabis. Cannabis may have the potential to ameliorate the negative effects of alcohol on the brain or alternatively, alcohol and cannabis use may result in activation of opposing mechanisms in which neuroanatomical changes may appear normal. Notably, there were no significant differences in alcohol use days from baseline to follow-up when comparing lifetime co-users to alcohol users. This suggests brain differences may exist for co-users without differences in the occurrence of a single substance used. Despite prior research suggesting a neuroprotective effect of cannabis, this study did not include a cannabis-only group and it is difficult to determine if the effects of co-use on GM volume are more or less harmful compared to cannabis use alone. Co-use may activate neural pathways that contribute to altered brain morphology separate from single substance use and more research is needed to determine the extent to which cannabis use attenuates deficits in GM volume.

Functional Neuroimaging

Functional neuroimaging studies show that alcohol vs. cannabis use alone differentially impact neural responses in specific regions of the brain implicated in executive function, response control, and reward processing [54–58]. Patterns of dysfunction within these studies are identified using functional magnetic resonance imaging (fMRI) tasks and the measurement of blood oxygen level-dependent (BOLD) responses. Prior research shows that there is a natural “imbalance” in functional development across brain regions, with earlier development occurring in posterior and subcortical regions and anterior, cortical regions progressing later, which leads to underdeveloped connections between reward and inhibitory regions [59]. Although studies suggest alcohol and cannabis differentially affect brain function, research examining the effects of co-use is limited.

Concurrent Use

To our knowledge, no prior research has examined the effects of concurrent alcohol and cannabis use on brain function. It is important that future research examine the potential effects of concurrent use on brain function as these changes may reflect differences in neural activation that do not correspond with the effects observed for alcohol or cannabis use alone.

Recent Co-use

Research on co-use has examined multiple cognitive functions including response inhibition and reward anticipation. In a study using the go/no-go task to measure response inhibition, total number of substance use days in the past month (sum of alcohol use and sum of cannabis use days) was associated with less neural activation in the left inferior frontal gyrus (IFG) and right insula [60•]. The IFG plays an important role in attention and response inhibition [61], and these findings suggest co-users may be particularly susceptible to changes in neural circuits leading to decreased attention. Although it is likely adolescents

in this sample were engaging in co-use, given 97.9% reported both alcohol and cannabis use during the past month, it is unclear how many of the substance use days involved concurrent and/or simultaneous use and if the effects observed are driven by concurrent or single-substance use.

Studies using a monetary incentive delay (MID) task to measure reward anticipation among co-users and single-substance users demonstrate inconsistent findings. When adolescents are matched on age, gender, and frequency of use of any common substance within six distinct groups: cannabis-only, tobacco-only, alcohol-only, cannabis/tobacco-only, cannabis/alcohol/tobacco, and non-substance using controls, all groups show comparable behavioral performance on a MID task [37•]. Brain activation in the nucleus accumbens during the MID task differed between the tobacco-only compared to all other groups, while the cannabis/alcohol/tobacco group showed similar brain activation responses to non-substance using controls [37•], suggesting that alcohol and cannabis may have counter intuitive effects. While this study speculated that findings may suggest a neuroprotective effect of cannabis, the effect of different combinations of co-use are unclear. More recent research has examined brain activity in response to reward and inhibitory tasks among binge-drinking college students [36•]. Among the five groups in this study (non-binging controls, standard binge, excessive binge, cannabis/standard binge, cannabis/excessive binge), no group differences were observed in behavioral performance or neural correlates of the stop signal and MID task. This suggests that co-use among individuals who binge-drink is not associated with differences in impulse control or reward learning relative to binge-drinking alone or minimal substance using controls. Although this study aimed to examine the effects of concurrent and/or simultaneous alcohol and cannabis use, there was no measurement of the quantity of alcohol and cannabis used and it is not clear how much of the reported substance use constituted as a simultaneous use occasion. Future studies should consider more specific inquiry regarding the details of co-use use occasions to help clarify the extent to which simultaneous use affects brain function on reward processing and inhibitory control.

Other research has examined the effects of recent co-use on a related domain of impulsivity, risky decision making, to determine whether neural responses to the Balloon Analogue Response Task (BART) differ among adolescents who primarily use alcohol or cannabis, primary users of both alcohol and cannabis (recent co-users), and non/infrequent alcohol and cannabis using controls [12•]. When brain activation was measured during risky decisions versus non-risky decisions, all groups showed greater response to risky decisions in the dorsal anterior cingulate cortex (dACC), anterior insula, ventral striatum, and lateral prefrontal cortex. Co-users showed decreased activation in the insula, striatum, and thalamus during risky decision making compared to controls [12•], which was proposed to reflect enhanced valuation of reward in the control group. In addition, co-users had a stronger correlation between risk probability and activity in the dACC than controls, suggesting differential sensitivity to risk assessment.

The effects of recent co-use were also examined on functional brain responses to a test of associative and episodic memory. When brain responses are characterized during a verbal paired associates task, adolescents who reported binge-drinking only showed significantly

less activation in the bilateral cuneus and lingual gyrus than binge-drinking cannabis users [62]. Given these regions of the brain play a vital role in visual processing related to the identification and recognition of words [63], findings suggest cannabis may mitigate some of the deleterious effects of alcohol in these regions.

Only one study has examined the effects of single or combined alcohol, cannabis, and tobacco use on dynamic functional network connectivity (dFNC) [64•]. dFNC determines the presence of brain states that are characterized by whole brain connectivity patterns, and the relative amount of time that individuals spend in a given brain state (i.e., occupancy rate). This study found that the alcohol and cannabis co-use group had lower occupancy rates compared to controls in a state whose centroid was defined by increased connectivity between visual and sensorimotor networks. In addition, within this state, the co-use group had greater connectivity values between the postcentral and inferior frontal gyrus and the left putamen/caudate and postcentral, compared to the alcohol-only group; no differences in connectivity were found between the alcohol and cannabis co-use and cannabis-only groups. Given previous work has shown alcohol use decreases, while cannabis use increases overall brain connectivity [65, 66], findings from this study suggest alcohol and cannabis may interact in ways that counterbalance changes in connectivity related to the use of alcohol alone. Although findings from these studies provide valuable insight regarding the impact of co-use on brain function and connectivity, there was no measurement of concurrent or simultaneous use patterns. The synergistic effects of concurrent and/or simultaneous use occasions may result in neural activation and functional connectivity that differ from alcohol and cannabis co-use and single-substance use.

Lifetime Co-use

We failed to identify any studies examining the effects of lifetime co-use on brain function. Lifetime co-users may experience unique neuroadaptations, reflecting earlier and/or more frequent additive responses to alcohol and cannabis use, placing them at greater risk for atypical brain responses. Alternatively, lifetime co-use may not be sensitive enough as an operationalization to systematically impact functional brain responses, and thus null findings may have not been published.

Summary of Findings

Longitudinal studies examining the effects lifetime co-use on neurocognitive function show that co-use is associated with impairments in cognitive function that are similar to the use of alcohol alone. However, only one study compared the effects of co-use to cannabis alone, while all others failed to include a cannabis-only comparison group. When more recent co-use or more specifically, concurrent use is examined, individuals who report more frequent past month co-use days show detrimental performance in the domain of selective attention accuracy. In sum, it is not clear from the current studies examining neurocognitive processes whether there is evidence of a synergistic effect of co-using alcohol and cannabis, or whether the observed effects are attributable to the separate impacts of alcohol and cannabis combined. Further, longitudinal studies demonstrate that lifetime co-use differentially affects structural integrity of the brain compared to alcohol alone.

Some studies demonstrate that lifetime co-users show similar decreases in WM integrity as alcohol users, while others suggest lifetime co-users show more substantial decreases in WM integrity, greater cortical thickness, and greater GM surface area compared to alcohol users. To our knowledge, only one study demonstrates that concurrent use is associated with lower WM integrity in areas of the brain associated with higher order cognitive functioning. However, structural neuroimaging studies largely focus on changes in brain structure as they relate to lifetime co-use and none compare to cannabis alone. It is not clear from the current structural neuroimaging studies if the observed effects are attributable to co-use or rather, the use of alcohol or cannabis alone. Lastly, neuroimaging studies have found that recent co-use impacts neural function in ways that are both similar and different compared to alcohol alone. When recent co-users undergo a risky decision-making task, they show no difference in brain activation compared to alcohol users and cannabis users. However, when brain activation is examined during a verbal learning task, co-users demonstrate greater activation compared to alcohol alone. Notably, recent co-users show higher brain connectivity compared to alcohol users, but these differences are not observed when compared to cannabis users. In sum, it is not clear from the current functional neuroimaging studies if co-use results in brain responses or connectivity that differs from alcohol or cannabis alone.

Limitations and Future Directions

While research has more conclusively established the effects of alcohol or cannabis alone on the neurocognitive, structural and functional aspects of the brain, as this review demonstrates, very little research has examined well-defined concurrent use of cannabis and alcohol effects on the brain and few studies have included both alcohol and cannabis-only comparison groups. Studies suggest concurrent, recent co-use and lifetime co-use differentially affect neurocognitive processes [14•, 16•, 33•, 35•]. Several studies have also found that the co-users exhibit decreased cortical thickness, lower white matter integrity, and decreased neuronal activation across several brain regions [12•, 14•, 15•]. Although the impact of alcohol and cannabis co-use appears to be nuanced, several limitations within the literature need to be addressed. Prior research has predominantly examined co-use in the context of recent co-use and lifetime co-use; however, definitions of co-use across studies are not consistent and may limit the replicability of findings among subgroups of individuals. Although it is likely that co-users engage in simultaneous alcohol and cannabis use, substance use measures within these studies did not assess these patterns of use. Thus, it is possible that simultaneous use may be accounting for some of the effects observed in these studies. More specific inquiry regarding the details of co-use occasions (e.g., ever used alcohol and cannabis at the same time, frequency of these occurrences) may help to clarify the extent to which simultaneous use affects neurocognitive function, brain structure and function. Future studies should use clear definitions of concurrent and simultaneous use and consider better assessments of these behavioral patterns when characterizing their samples.

Most studies included in this review did not include a cannabis-only comparison group and it is not clear whether the effects of co-use are unique to the co-use of alcohol and cannabis or are similar to cannabis use alone. Future studies should include exclusive cannabis users, or cannabis users with minimal alcohol use, in order to further distinguish

between the effects of using a single-substance and simultaneous use. Further, the majority of studies captured the quantity of alcohol used but did not measure or quantify the amount of cannabis used. Given that studies suggest a dose-dependent relationship between cannabis and neurocognitive function [65], it is important to understand how specific patterns of consumption (i.e., quantity) may affect neurobiological outcomes. While cut-offs for the measurement of alcohol use are well-established in the existing literature [67], quantification of cannabis use has been inconsistent and unreliable. This may be due to the variability in patterns of consumption (e.g., mode of use, potency) and absence of a standardized unit for cannabis which may lead to less generalizability of findings across studies. While some studies measured or required specific periods of abstinence before undergoing study procedures, these periods differed widely between studies (e.g., 3 hours, 24 hours, 3 weeks) and others did not report on this at all. Given studies show abstinence may be associated with recovery of neurocognitive function, brain structure and function [68, 69], some of the inconsistencies in the literature on the effects of co-use may be attributed to the lack of measurement and/or consistency in abstinence periods across studies. Lastly, prior research examines alcohol and cannabis co-use as it pertains to adolescent brain development and few studies include samples of young adults. Although adolescence is a period in which cognition and the brain undergo dramatic parallel development [66], longitudinal studies suggest development continues well into emerging adulthood [70, 71] which is the same time that alcohol and cannabis use increases [72]. More research is needed to examine the effects of co-use on neurocognitive function, brain structure and function among young adults.

Finally, the most fundamental limitation of the reviewed research is that none of the studies were designed to specifically test the effects of concurrent or simultaneous use on cognitive, structural, or functional brain mechanisms. While secondary analysis is an important initial step in identifying potential mechanisms, the inconsistencies in the literature may be, at least in part, attributable to the inconsistencies in identifying concurrent and/or simultaneous users in existing samples. For every study, no metrics of simultaneous use were available, and all simultaneous use was embedded in a broader definition of concurrent use. Simultaneous use may have very specific effects due to the potential for synergistic substance use effects on the brain and cognition. Research that is specifically designed to recruit and compare individuals that use alcohol and cannabis simultaneously across multiple cognitive domains is needed to more clearly ascertain risk and/or protective effects from co-use.

Conclusions

Research on the effects of alcohol and cannabis co-use on neurocognitive function, brain structure and function is limited and existing studies provide inconsistent findings. Current studies lack a general consensus on methodology, definitions, and neuroimaging approaches which makes it challenging to draw strong conclusions about whether there is evidence for the effects of co-use on neurocognitive function, brain structure or function. The majority of studies did not include a cannabis-only comparison group which limits our ability to draw inferences about potential differences between concurrent co-users relative to cannabis users. Future work should consider including a more comprehensive set of single-substance

using groups to clarify and integrate findings. There are very few studies that include clear definitions of concurrent and simultaneous use of alcohol and cannabis, and of the existing studies, none have directly examined the effect of simultaneous use on the brain. Given the discrepant findings, future research should use clear and consistent definitions of use patterns and better assessments of behavioral patterns to when characterizing samples.

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Table 1.

Summary of Studies Published in Last 5 Years Reporting on Cannabis and Alcohol Co-use and Neurocognitive Function, Brain Structure and Brain Function.

Author and Year	Age Range (yrs)	Sample Size (N)	Sample Characteristics	Substance Use Groups or Variables for Analysis	Task/Outcome	Main Findings
Concurrent Alcohol and Cannabis Episodes						
[33]Wade N et al., 2020 *	15–26	232	Community sample of adolescents and adults with a range of substance use from none to weekly (<50 lifetime use episodes of any other illicit substances). Alcohol breath analysis and urinalysis verified abstinence from all substances, other than nicotine, at study sessions.	Total number of past month BD episodes [*episodes >4 or more drinks (female), >5 or more drinks (male)*] Total number of past month CA episodes. Total number of past month BD+CA episodes.	CVLT-II, D-KEFS, RCFT, Ruff 2&7, WAIS-III.	More past month BD+CA episodes associated with poorer selective attention accuracy (Ruff 2&7). Co-use not associated with executive function, verbal fluency, learning and memory, and delayed recall.
[15]Wade N et al., 2020 *	16–26	75	Community sample of adolescents and adults with a range of substance use from none to weekly (<50 lifetime use episodes of any other illicit substances). Alcohol breath analysis and urinalysis verified abstinence from all substances, other than nicotine, at study sessions.	Total number of past month BD episodes [*episodes >4 or more drinks (female), >5 or more drinks (male)*] Past month CA use (*total grams*) Total number of past month BD+CA episodes.	WM integrity (AD, FA, MD, RD).	More past month BD+CA episodes associated with lower AD (left inferior longitudinal fasciculus) and lower FA (left inferior longitudinal fasciculus, right anterior thalamic radiation, left cingulum cingulate gyrus). Co-use not associated with MD and RD in any tract.
Recent Alcohol and Cannabis Co-use (e.g., past 2 months)						
[60]Feldstein Ewing S et al., 2015 **	14–18	95	Community sample of high-risk youth (involved in justice day-program) (97.9% had both alcohol and cannabis use in past month). Abstinence prior to study session not reported.	Sum of alcohol use days + sum of cannabis use days in past month.	Go/No-Go fMRI Task	Significant negative correlations between past month alcohol and cannabis use days and response inhibition (left IFG, right insula BOLD activation).
[37]Karoly HC et al., 2015	14–18	132	Community sample of adolescents from larger study focused on HIV/STI risk reduction, included those with no current substance use in addition to more frequent substance users. Abstinent from any substances (including tobacco) at least 3 hours prior to study session.	ALC users (*≥2 ALC days in past month*). CA users (*≥10 CA days in past month*). TOB users (*≥27 TOB days in past month*). CA+TOB users (*≥10 CA days, ≥27 TOB days in past month*). CA+ALC+TOB users (*≥10 CA days, ≥27 TOB days, ≥2 ALC days in past month*). CON (*0 ALC, CA, TOB days in past month*).	ImpSS, Monetary Incentive Delay Task (Reward, Loss, Neutral trials)	No differences in impulsivity/sensation seeking or reaction time and percentage of hits for reward, loss, neutral trials between ALC, CA, TOB, CA+TOB, CA+ALC+TOB, CON. TOB less activation in left NAcc compared to CA+ALC+TOB across all Reward-Neutral contrasts. No differences in NAcc activation between CA+ALC+TOB and CA+TOB or between CA+ALC+TOB and CON on all Reward-Neutral contrast.
[12]Claus E et al., 2018 **	14–18	189	Community sample of high-risk youth (involved in justice day-program). Abstinence verified by self-report 24 hours prior to study session.	ALC users (*>1 ALC use episode in past month*). CA users (*>1 CA use episode in past month*). CA+ALC users (*>1 CA use episode, >1*	Balloon Analogue Risk Task (fMRI), ImpSS.	CA+ALC decreased activation in insula, striatum, and thalamus during risky decision making and stronger correlation between risk probability and activity in dACC compared to

Author and Year	Age Range (yrs)	Sample Size (N)	Sample Characteristics	Substance Use Groups or Variables for Analysis	Task/Outcome	Main Findings
				ALC use episode in past month). CON (*≤1 ALC or CA use episode in past month*).		CON. CA+ALC significantly greater levels of impulsive sensation seeking compared to CA and CON.
[64]Vergara V et al., 2019	18–55	534	Community sample of adults who had varying ranges of substance use confirmed by interview self-report and urinalysis. Abstinence prior to study session not reported.	ALC users (*>8 AUDIT-C*). CA users (*≥15 days 60-day TLFB*). TOB users (*≥7 FTQ*). ALC+TOB users (*>8 AUDIT-C, ≥7 FTQ*). CA+ALC (*≥15 days 60-day TLFB, >8 AUDIT-C*). CA+TOB (*≥15 days 60-day TLFB, ≥7 FTQ*). CA+ALC+TOB (*≥15 days 60-day TLFB, >8 AUDIT-C, ≥7 FTQ*). CON [*no CA or TOB use, did not assess AUDIT-C scores, but did not meet criteria for ALC abuse/dependence (DSM-IV*)].	Dynamic Functional Network Connectivity	CA+ALC lower occupancy rates in state 2 (supplementary motor area-6 and right fusiform/lingual) than CON. CA+ALC higher connectivity in state 1 (between postcentral and inferior frontal gyrus) and 4 (left putamen/caudate and postcentral) than ALC. CA+ALC no differences in connectivity compared to CA.
[36]Tong T et al., 2020	18.7 (SD=0.66)	221	Freshmen and sophomore college students. Participants who had a positive drug screen for other substances, except cannabis, or met criteria for SUD (DSM-IV), other than AUD, were excluded. Abstinence prior to study session not reported.	sBinge users [*2+sBinge episodes (4 (female)/5(male) drinks within 2-hour drinking session) in past month, <3 CA use & no more than 30 occasions of lifetime CA use*]. eBinge users [*2+eBinge episodes (>4 (female)/5(male) drinks within 2-hour drinking session) in past month, <3 CA use & no more than 30 occasions of lifetime CA use*]. CA+sBinge users (*sBinge criteria, 4+ episodes CA use).* CA+eBinge users *(eBinge criteria, 4+episodes CA use).* CON (*no history of CA use or sBinge/eBinge, but ALC use consisting of 1–2 drinks per occasion*).	Monetary Incentive Delay (Reward, Loss trials), Stop-Signal	sBinge, eBinge, CA+sBinge, CA+eBinge CON showed strong brain activation, but no group differences were observed in behavioral performance or neural correlates of monetary incentive delay and stop-signal tasks.
[35]Petker T et al., 2021	19.5–23	730	Community sample of emerging adults reporting high risk drinking, widely varying cannabis use, and minimal tobacco use. Abstinence prior to study session not reported.	HRD [*≥2 instances of high-risk drinking (>4(male)/3(female) standard drinks) in past month*]. HRD + monthly/weekly CA (*one high-risking drinking instance in past month, monthly/weekly CA*). HRD + daily/multiple times daily CA (*one high-risking drinking instance in past month, daily/multiple times daily CA*).	Delay and Probability Discounting, Digit Span Task, Go/No-Go Task, Shipley Verbal Scale.	HRD + daily/multiple times daily group significantly greater impulsive delay discounting than HRD and HRD + weekly/monthly CA. No differences observed between HRD, HRD+weekly/monthly CA, and HRD+daily/multiple times daily CA for any other neurocognitive measures.
Lifetime Alcohol and Cannabis Co-use						
[16]Jacobus J, Squeglia L, Infante A et al., 2015 †	16–19 baseline, 1.5 & 3-year follow up	108	Adolescents/Young adults from local high schools and colleges. Participants with history of lifetime SUD (DSM-IV) other than alcohol or cannabis abuse/dependence were excluded. Substance using	CA+ALC (*≥60 lifetime CA episodes, concomitant ALC use*). CON (*≤9 lifetime CA episodes, minimal ALC use*).	CVLT-II, D-KEFS, PASAT, WAIS-III, WASI, WMS-III.	CA+ALC significantly worse performance, across time points (baseline, 1.5-year, 3 year), in the domains of complex attention, memory, and visuospatial functioning compared to CON.

Author and Year	Age Range (yrs)	Sample Size (N)	Sample Characteristics	Substance Use Groups or Variables for Analysis	Task/Outcome	Main Findings
			participants abstained for at least 3 weeks on average prior to completing the protocol.			No differences were observed between CA+ALC and CON for processing speed or executive function.
[13]Jacobus J, Squeglia L, Meruelo A et al., 2015 †	16–19 baseline, 1.5 & 3-year follow up	68	Adolescents/Young adults from local high schools and colleges. Participants with history of lifetime SUD (DSM-IV) other than alcohol or cannabis abuse/dependence were excluded. Substance using participants abstained for at least 3 weeks on average prior to completing the protocol.	CA+ALC (*≥120 lifetime CA episodes, ≥22 lifetime alcohol episodes*). CON (*≤9 lifetime CA episodes, ≤20 lifetime AC episodes, on average*).	Cortical Thickness.	CA+ALC greater cortical thickness estimates in all four lobes of brain (frontal, parietal, temporal, occipital) than CON across time points. 18 of 23 regions in which differences observed were in frontal and parietal cortex.
[14]Jacobus J et al., 2016 ††	12–14 baseline, 18–21 by 6–8 year follow-up	69	Adolescents from local schools. Participants with history of lifetime SUD (DSM-IV) other than alcohol or cannabis abuse/dependence were excluded. Abstinence prior to study session not reported.	ALC (*<40 cumulative CA episodes, similar lifetime ALC use by follow up*). CA+ALC (*>50 cumulative CA episodes by follow-up*). CON (*<3 lifetime ALC episodes, no cannabis episodes by follow-up*).	CVLT-Children, CVLT-II, D-KEFS, WAIS-III, WASI, WISC-III. Cortical Thickness.	ALC and CON performed better on complex attention than CA+ALC. ALC and CON demonstrate greater cortical thickness at baseline and more substantial decrease by follow-up compared to CA+ALC.
[40]Infante A et al., 2017 ††	12–14 baseline, 17–21 by ~6-year follow up	69	Adolescents from local schools. Participants with history of lifetime SUD (DSM-IV) other than alcohol or cannabis abuse/dependence were excluded. Abstinence prior to study session not reported.	ALC (*>20 cumulative lifetime ALC episodes, <40 cumulative CA episodes by follow-up*). CA+ALC (*>50 cumulative CA days, >20 cumulative lifetime ALC episodes by follow-up*). CON (*<3 lifetime ALC episodes, no cannabis or other substance use episodes by follow up*).	GM Surface Area.	CA+ALC and CON greater surface area at baseline and follow-up than ALC. ALC more substantial decrease in bilateral medial orbitofrontal cortex and right insula than CON and CA+ALC. ALC greater decrease in right medial orbitofrontal cortex surface area than CA+ALC.
[22]Cookey J et al., 2018	19–35	21	Early phase psychosis patients typically <5 years from diagnosis. Participants with lifetime history of SUD (DSM-IV) for any other substances, other than alcohol, cannabis, or tobacco were excluded. Abstinence prior to study session not reported.	Cannabis *alcohol lifetime occasions.	WM integrity (FA).	No significant interaction effect of lifetime alcohol and cannabis use on FA values.

*, **, †, ††Studies with matching superscripts derived participants from the same overall sample. Note: Main findings reported are relevant to the co-use of alcohol and cannabis. ALC-alcohol, AUDIT-C-Alcohol Use Disorder Identification Test-Consumption, AD-axial diffusivity, BD-binge-drinking, BD+CA-binge drinking and cannabis, BOLD-blood oxygen level dependent, CA-cannabis, CA+ALC-cannabis and alcohol, CA+TOB-cannabis and tobacco, CON-control, CVLT-II California Verbal Learning Test-Second Edition, dACC-dorsal anterior cingulate cortex, D-KEFS-Delis-Kaplan Executive Function System, DSM-IV-fourth edition of the diagnostic and statistical manual of mental disorders, eBinge-extreme binge-drinking, fMRI-functional magnetic resonance imaging, FTQ-fagerstrom tolerance questionnaire, FA-fractional anisotropy, GM-gray matter, HRD-high-risk drinking, ImpSS-impulsivity and sensation seeking scale, MD-mean diffusivity, MID-monetary incentive delay task, OFC-orbitofrontal cortex, RCFT-Rey Complex Figure Task, RD-radial diffusivity, sBinge-standard binge-drinking, SUD-substance use disorder, TLFB-timeline followback, TOB-tobacco, WAIS-III-Weschler Adult Intelligence Scale-Third Edition, WM-white matter.