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Examining Neurocognitive Markers in Adolescence as Predictors of Changes in Later Substance Use

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Examining Neurocognitive Markers in Adolescence as Predictors of Changes in Later Substance Use

A dissertation submitted in partial satisfaction of the requirement for the degree Doctor in Philosophy

in

Interdisciplinary Research on Substance Use

by

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2022

The Dissertation of Nafisa Ferdous is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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LIST OF ABBREVIATIONS

YAR	Youth at Risk
ECF	Executive cognitive functions
SUD	Substance use disorder
DERS	Difficulties in Emotion Regulation Scale
EMA	Ecological Momentary Assessment
BOLD	Blood Oxygenation Level Dependent
MID	Monetary Incentive Delay task
PRISMA-ScR	Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
ERPs	Event-related potentials
EEG	Electroencephalograph
MTFS	Minnesota Twin Family Studies
CD	Conduct Disorder
ODD	Oppositional Defiant Disorder
ADHD	Attention deficit/hyperactivity disorder
AUD	Alcohol Use Disorder
WOF	Wheel of Fortune
CDDR	Customary Drinking and Drug Use Record
DPDD	Drinks per Drinking Days
PeakDr	Peak Drinks
CVLT	California Verbal Learning Test
LDFR	Long Delay Free Recall

D-KEFS	Delis-Kaplan Executive Function System
CWI	Color-Word Interference
WASI	Wechsler Abbreviated Scale of Intelligence
WAIS-IV	Wechsler Adult Intelligence Scale- Fourth Edition
NSDUH	National Survey on Drug Use and Health
MTF	Monitoring the Future
ANOVA	Analysis of variance
NIAAA	National Institute on Alcohol Abuse and Alcoholism

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PUBLICATIONS

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ABSTRACT OF THE DISSERTATION

Examining Neurocognitive Markers in Adolescence as Predictors of Changes in Later Substance Use

by

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Doctor of Philosophy in Interdisciplinary Research on Substance Use

University of California San Diego, 2022
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Objective: Much research has investigated the effect of adolescent substance use on neurocognitive abilities but the influence of neurocognition on later use behaviors has been relatively less studied, especially among youth who are already engaged in substance use. Hence, the goal of this dissertation project was to explore predictive associations of neurocognitive markers with substance use behaviors via the following 3 aims (*Chapters*).

Methods: *Chapter 1*- A scoping review was conducted on the existing literature to synthesize current research on minimally reviewed neurocognitive domains and their predictive associations with substance use (hence papers on well-reviewed impulsivity facets were excluded). Secondary analyses were conducted in Chapter 2 and 3 with data from a longitudinal study for adolescents (Youth *At* Risk study) to investigate neurocognitive performance in late adolescence during

maximum substance use, as predictors of changes in later use. *Chapter 2*- Hierarchical linear regression models with 4 neurocognitive abilities (inhibition/cognitive flexibility, visuospatial ability, verbal memory, working memory) predicting change in follow-up alcohol use (drinking days, average drinks per drinking day, peak drinks, binge episodes) were estimated, while covarying for baseline age, follow-up duration, and sex. *Chapter 3*- To investigate relationships between neurocognition and cannabis and nicotine use, in addition to alcohol, hierarchical linear regression models predicting change in follow-up overall substance use frequency index scores and individual substance (alcohol, cannabis, nicotine) use outcomes were estimated. Follow-up analyses exploring this relationship within 3 groups of one-, co- and tri-substance users were also conducted independently.

Results: Our scoping review revealed a common theme where cognitive processing in constructs of working memory, attention, emotion regulation, and elevated reward circuit activity during decision making in childhood and early adolescence predicted earlier onset, greater use escalation, and even development of substance use disorders in some instances. Findings from our 2 analytical aims suggest working memory, verbal memory, visuospatial ability, and inhibition/cognitive flexibility at maximum substance (alcohol, cannabis, and/or nicotine) use in late adolescence are useful as predictors of changes in later use behaviors.

Conclusion: Our results have potential to inform policies and intervention research on cognitive vulnerability markers in youth that predict substance use into adulthood.

INTRODUCTION

The following dissertation investigates the predictive ability of neurocognitive markers on later substance use behaviors in the adolescent and young adult population. This direction of investigation, where neurocognitive abilities may act as potential predictors of prospective drug and alcohol use, is a noteworthy inquiry because it presents an opportunity to identify specific cognitive domains that may serve as risk or protective factors (vulnerability markers) for changes in substance use patterns as adolescents transition into adults. The knowledge of risk/protective factors of prospective substance use in this vulnerable age group can be beneficial to researchers in designing more efficacious prevention and intervention approaches and inform policy recommendations regarding prevention efforts with youth.

Compared to research on the influence of substance use on neurocognition, studies on neurocognitive markers as predictors of substance use initiation and changes in substance use across time is scant. Due to this paucity of investigation, the nature of the directionality of the relationships between neurocognitive abilities and most substances remains largely untested. More importantly, very little research has investigated how neurocognition can predict changes in use behaviors for adolescents who are already engaged in substance use.

Hence, this dissertation examined the predictive effects of neurocognitive abilities vital for executive function (working memory, verbal memory, visuospatial ability, and inhibition/cognitive flexibility) post substance use initiation, during a stage when the brain is most taxed with maximum use of alcohol, cannabis, and nicotine use. Within the small scope of research that has looked in this direction, studies investigating adolescent cognitive functioning at the stage of maximum drug and alcohol use as prospective predictors of substance use behaviors is significantly lacking.

The current project makes the following contributions and additions to the body of knowledge in the direction of neurocognition influencing substance use via three aims:

I) Provides an up-to-date and thorough scoping review covering published research on neurocognitive abilities as vulnerability markers for substance use, with special focus on the minimally researched executive neurocognitive domains as predictors. This review highlights such domains and summarizes the existing literature investigating the predictive associations between neurocognitive domains with prospective substance use. This work can guide future research in locating research gaps in and aid in informing future directions to further the characterization of the longitudinal relationships between neurocognition and substance use.

II) Using the longitudinal Youth at Risk (YAR) dataset, evaluates if performance in the above-mentioned neurocognitive domains during maximum substance use in adolescence can successfully predict changes in use behaviors across a 3–7-year follow-up period.

The two analytical aims that drove the comprehensive investigation are:

1. Determine if neurocognitive task performance during maximum alcohol use in adolescence predicts changes in use of alcohol 3-7 years later.

   Hypothesis: We hypothesized that better performance in the neurocognitive measures of memory, inhibition, and cognitive flexibility at time of maximum alcohol use will predict greater reductions in alcohol use at follow-up.

2. Determine if neurocognitive task performance during maximum substance use (alcohol, cannabis, and/or nicotine) in adolescence predicts changes in overall use 3-7 years later.

Hypothesis: We hypothesized that better performance in the neurocognitive measures of memory, inhibition, and cognitive flexibility at time of maximum substance use will predict greater reductions in overall substance use at follow-up.

CHAPTER 1: Neurocognition as a Predictor of Later Substance Use: A Review

Abstract

Background: A plethora of studies have investigated the influence of substance use during adolescence on later neurocognitive capabilities, but the reverse direction of cognitive processing abilities as vulnerability markers for prospective substance use has been relatively less researched. Within this small scope of research, most studies investigated the multifaceted impulsivity domain as a predictor of later substance use, while other executive domains integral for efficient cognitive control in adulthood have been largely ignored. Hence, the aim of our scoping review was to examine the research done on the executive neurocognitive domains which have not previously been reviewed and summarize the existing literature investigating their predictive associations with prospective substance use.

Methods: We conducted a scoping review to systematically map out existing academic literature on PubMed using key search terms encompassing neurocognition and substance use, including both cross-sectional and longitudinal studies, yet excluding papers on impulsivity facets given the multiple recent reviews on this neurocognitive domain.

Results: We located a total of 32 articles across six higher order neurocognitive domains (working memory, visuospatial ability, planning, attention, reward processing and decision making, and emotional regulation) reporting associations and predictive effects on substance use. Deficient working memory and attention, maladaptive emotion regulation and heightened reward-related neural response during decision making in early adolescence were largely predictive of substance (alcohol, cannabis, tobacco smoking, and other drugs) use onset, as well as greater frequency of use and problematic use through adolescence and into young adulthood.

Conclusion: Most of the neurocognitive markers summarized in our review show potential as useful predictors of prospective substance use in adolescent populations. Widening the scope of longitudinal neurobehavioral research on these constructs would aid in identification of early risk factors and preventive measures for future drug and alcohol use among youth.

Keywords: Scoping Review, Neurocognition, Predictors, Substance Use, Alcohol, Cannabis, Nicotine, Drugs, Adolescence

Introduction

The high prevalence of alcohol and drug use initiation, experimentation, and even escalation during the sensitive neural and social developmental period of adolescence, is well-documented.[1,2] According to data from 2019 National Survey on Drug Use and Health (NSDUH), 50.8% of people 12 years or older reported past month alcohol use.[3] A more recent (pre-COVID) report from the 2020 Monitoring the Future study revealed an estimated 20% of 8th graders report using alcohol within the past year, which more than doubled to 55% among 12th graders.[4] Further 4.5% of 8th graders and 16.8% 12th graders reported past year binge drinking (>5 drinks for males on one occasion and >4 drinks for females on one occasion)[5] which is indicative of problematic alcohol use in adolescence.[4]

Cannabis is another widely used drug among adolescents,[6,7] and as per the 2020 Monitoring the Future survey, 11.4% of 8th graders reported past year use which triples to 35.2% among 12th graders.[4] The use of nicotine is also prevalent among teenagers with nicotine vaping showing dramatic increases between 2017 and 2019.[4] Specifically, among 8th graders, past-year nicotine vaping went from 7.5% to 16.5% during this timeframe. Similar rising trends were observed in the 10th and 12th grades where past-year vaping reports approximately doubled (10th graders: 15.8% to 30.7%; 12th graders: 18.8% to 35.3%).[4] It was also reported that substance misuse (i.e., therapeutic use beyond prescribed dosage or indications)[8] is on an upward trend among 8th graders.[4]

Among young adults in the US (ages 18-25 years), past year cannabis use increased from 29.8% in 2002 to 35.4% in 2019,[3] and past year illicit drug use increased from 37.5% in 2015 to 39.1% in 2019.[3] Early initiation and continued experimentation with substances in the adolescent/young adult age group (13- 25 years) may also increase susceptibility to developing a

substance use disorder (SUD).[9] Data from 2009-2010 National Surveys on Drug Use and Health reported that approximately 8% of adolescents aged 12 to 17 years and 21% young adults aged 18 to 25 years met the diagnostic criteria for SUD.[10]

Given that higher order cognitive constructs involved in memory, goal directed behavior, self-regulation, attention, abstract reasoning, and planning, have extended progressive development during adolescence through young adulthood, the early onset of use and experimentation with drugs and alcohol during this period may impair development of these vital cognitive constructs.[11] Thus, understanding the influence of drugs and alcohol on the brain during this sensitive period of neuromaturation has long been a priority for researchers. Many studies have investigated the influence of alcohol and drug use on neurocognition during adolescence and reported concurrent/future deficits and/or impairment in various cognitive capabilities.[11-16]

Neurocognition is critical for making healthy, adaptive decisions and executing goal-directed behaviors,[17-19] thus it holds importance to look at it as a predictor of later drug and alcohol use as well. Yet, there is a paucity of research on neurocognitive markers as prospective predictors of later substance use. These markers hold great promise in detecting prospective problematic use and can be beneficial to researchers in designing more efficacious prevention and intervention approaches and informing policy recommendations. Hence, the current review attempts to summarize the state of the science over the last three decades on neurocognitive markers as predictors of later substance use.

1. Typical neurodevelopment during adolescence

Between the ages of 13-25 years, individuals experience significant psychological, physiological, social, and neural remodeling.[12,13] The intricate changes in the frontal lobes

continue into young adulthood as the prefrontal cortex is the last region to fully develop.[20] Advanced cognitive efficiency is attained during neuromaturation by synaptic refinement in the gray matter of the frontal lobe, also known as "synaptic pruning".[13,21] Synaptic pruning eliminates hundreds of billions of these superfluous, unnecessary nerve cell connections (synapses) during adolescent years. The experiences adolescents and young adults go through influence this process and can promote corresponding cognitive efficiency.[13,20,22,23] White matter, which consists of myelinated axons, is highly associated with improved and efficient cognitive control, and emotional development.[13] As gray matter volume decreases during neurodevelopment,[21,23] white matter organization increases.[13,17,24]

Through use of animal models and neuroimaging data, we understand that the regions involved in motivation and reward develop earlier than the cortical circuits involved in cognitive control.[14,25] Previous research on adolescent neurobiology[14,26-28] has supported the theory that adolescent neural development is marked by a tension between early "bottom-up" systems (that are responsible, in part, for the expression of enhanced reactivity to motivational stimuli) and "top down" cortical cognitive circuits that mature later.[25] As neural development progresses through adolescence and young adulthood there is a gradual decline of the competitive edge of the "bottom-up" system comprising regions like the ventral striatum[25] with the progressively emerging "top-down" cognitive regulation of the prefrontal cortex eventually taking control. Accordingly, sensitivity to reward and incentive seeking peaks during adolescence, followed by a gradual decline into adulthood. This allows for effective cognitive control associated with reasoning and decision making to dominate in adulthood.[17]

In summary, the absence of mature cognitive control capabilities combined with increased sensitivity to reward renders adolescents more susceptible to risk taking behaviors.

Hence, it is not surprising that initiation and experimentation with drugs and alcohol more frequently begins during adolescence as compared to any other period.[14,29]

2. Cognitive control and neurocognitive domains

The structural and functional development of the prefrontal cortex is crucial for efficient cognitive control, also referred to as executive cognitive functions (ECF).[14,30] The increase of white matter volume throughout development from early adolescence to young adulthood happens in a posterior to anterior fashion.[20,31] That is, myelination which is responsible for increased efficiency of brain circuits, first begins in cortical areas toward the back of the brain and then progresses to the frontal lobe.[20,31] Hence, these higher order neurocognitive abilities develop throughout adolescence and into young adulthood, exhibiting prolonged development[32] and characterize mature cognition.[18] ECF is essential for adaptive responses and goal-directed behavior.[18,19] It influences memory and supports the flexibility to inhibit automatic responses under uncertainty and allocates mental resources (such as abstract reasoning, attention, emotion control) to plans/goals that influence behavior.[19] Below we briefly introduce some of the more prominent components of ECF.

Working memory can be defined as the ability to retain information, both simple and complex representational contents in our mind, manipulate such information and act accordingly.[18,33] It is thought to peak in functioning at about 30 years of age.[32,34] **Verbal memory** is defined as the memory of verbal information- recalling words, their meaning and other conceptions that involve speech/language.[35] **Visuospatial memory** is defined as the ability to recall visual forms (images and structures in more than one dimension), and manipulate and track them via spatial navigation and distance/depth perception.[36] Verbal and visuospatial memory are thought to peak in young adulthood (ages 18-25).[37]

Another important domain integral to executive control is **impulsivity**.[38] Impulsivity is described as the susceptibility towards fast, unplanned reactions to stimuli without adequate consideration or thought to possible consequences of the action, mainly driven by the pursuit of immediate/short-term reward.[38,39] However, according to different personality theories and the field of cognitive neuroscience there are distinctive traits and behavioral processes that underlie impulsivity making it a multifaceted umbrella domain[40] including the sub-domains of **sensation seeking, positive and negative urgency, response inhibition and delay discounting**.[38,41] **Sensation seeking** and emotion driven **positive and negative urgency** fall into the trait facet of impulsivity where the former is defined as the predisposition towards novelty seeking, which often includes risky behaviors[38,42] and the latter is referred to as a propensity to behave or act recklessly when in an elevated positive or negative emotional state.[38,40,43]

Included in the behavioral facet of impulsivity are response inhibition and delay discounting. **Response inhibition** is defined as exercising self-regulation and self-control to respond appropriately to a situation by choice while resisting impulsive behaviors (often inappropriate in nature),[18] hence poor response inhibition is a disposition to impulsive tendencies.[38] **Delay discounting** on the other hand is described as the propensity to prefer immediate outcomes over delayed reward, thus discounting the reward value.[40,44] **Cognitive flexibility** represents a related domain which is defined as the ability to make quick judgement/adjustments to changing situations and adapt behavior.[25]

Additional higher order constructs of ECF include decision making, reward processing, and emotional regulation.[45,46] The earlier development of ventral striatum versus prefrontal projections in adolescence[4] aligns with the heightened motivation and reward seeking nature in youth and the increased probability to engage in risky behaviors.[14,25] The dopamine receptors in

the ventral striatum and other neural areas of the reward pathway undergo pruning during adolescence.[47] Such changes in the developing brain have been deemed important to understand the foundation of reward motivated behaviors and likelihood of problematic substance use[48] especially given how most drugs of abuse elicit increased dopamine neurotransmission.[49] [47]

Decision making is a complex multidimensional construct guided by memory, evaluation, and motivational processes.[45] It encompasses the ability to recover information from memory and evaluate potential negative and positive repercussions of the decision then retaining and manipulating such information (working memory) to act accordingly while weighing ones' motivation for reward/gain versus potential for punishment.[45,50] **Reward processing** includes the anticipation, preparation, and response to both natural and conditioned rewarding stimuli such as food or money, which culminates in reward-motivated goal-directed actions/behaviors.[51] Decision making and reward processing are often measured together as the latter plays an integral role in learning the value or utility of each choice and thus guides the evaluation and motivational processes in making a decision.[52] **Emotional regulation** involves involuntary but effortful recognition, maintenance and modification of the quality and intensity of emotional states and responses.[46,53,54] Discordance in regulating affective responses during adolescence can pose as a vulnerability for early substance use, as adolescents with dysfunctional emotion and mood regulatory processes may lean towards using substances to cope with emotional distress.[46] Emotional regulation is typically assessed with self-report surveys and scales such as the Difficulties in Emotion Regulation Scale (DERS),[54] Ecological Momentary Assessment Moods (EMA surveys),[46,55] UPPS-P Impulsive Behavior Scale,[53] as opposed to task-based manipulations, and thus may be more susceptible to response bias.

3. Effects of substance use on neurocognitive functioning during adolescence

Research has examined the influence of early drug and alcohol use on cognitive capabilities.[11-16] Multiple studies support that substance use during the key neurodevelopmental period of adolescence leads to changes in a variety of neurocognitive abilities.[12-14,56] For example, heavy alcohol use (e.g., extreme binge drinking - 10+ drinks per occasion) during adolescence has been associated with poorer verbal learning and memory, as compared to moderate drinking (4 or less drinks per occasion).[5,57] The co-use of alcohol and cannabis has been associated with poorer academic performance when compared to non-drinking peers.[58] Neuroimaging studies reported that adolescent cannabis users show increased activation in right frontal and parietal brain regions during attention tasks, suggesting more effort is needed for self-regulation during performance.[13,59,60] Adults with polysubstance use disorder (three or more substances: alcohol, cocaine, cannabis, amphetamine, etc.) who reported early onset of drinking at age 14 and heavy drinking (>100 drinks/month) by age 22, demonstrated poorer inhibition, memory and decision-making ability compared to adults with only alcohol use disorder, despite similar early onsets and patterns of drinking as the polysubstance use disorder group.[15,61] Thus, exposure to psychoactive substances such as alcohol, cannabis, methamphetamine, cocaine and other illicit drugs during the ongoing neuromaturation in adolescence is thought to endanger the linear increase in cognitive control capacities from childhood to adulthood.[14]

4. Neurocognitive markers as predictors of future substance use

The aforementioned studies investigated the relationship considering substance use as a predictor of later neurocognitive abilities. Relative to those, fewer studies have looked at the reverse direction of neurocognitive constructs prospectively predicting later substance use behaviors. Within the small volume of research in this reverse direction, most investigations

have been conducted on impulsivity constructs. The broad domain of **impulsivity** has been persistently linked to prospective addictive behaviors and substance use disorder[62,63] but there is ongoing discussion on which specific facets of this multidimensional predisposition play integral roles in this association.[38]

Response Inhibition is primarily assessed with behavioral measures such as the Stroop Task[40,64], Go/No-Go task and the Stop-Signal task.[40,65] Heightened impulsivity in the form of poor response inhibition during adolescence has been reported to predict increasing use of cannabis, stimulants, concurrent substance use and prospective SUD symptoms by early young adulthood (ages 18-20) including alcohol use disorder in adulthood.[1] This is largely consistent with results from another meta-analysis which found weakened inhibitory control was related to problematic use of stimulants like methamphetamine, MDMA, in addition to alcohol and nicotine. However, no association was observed between response inhibition and later cannabis or opioid use.[40] Specific to alcohol use, studies are inconclusive. In some cases, response inhibition performance between the ages of 11-14 years-old prospectively predicted drinking behavior two to five years later but in other studies where the age range was 14-19 years-old, inhibition performances revealed no association to drinking one to two years later.[1] One possibility for the differences in the results could be due to the difference in age ranges of measurement (early adolescence vs late adolescence period), yet this remains to be tested.[1]

Even though there are mixed results on response inhibition predicting drinking initiation or escalating use of alcohol, the findings from a 2020 neuroimaging longitudinal study revealed that less blood oxygenation level dependent (BOLD) response in a cluster comprising the precentral gyri, insula, and inferior frontal gyri was able to predict a more rapid transition to risky frequent binge drinking in adolescent participants who were already involved in moderate

drinking. This suggests that there is value in looking at neurocognitive performance after onset of alcohol use as predictors of change in use.[66]

Delay discounting, another cognitive aspect in the impulsivity umbrella, is frequently measured with the Monetary Incentive Delay task (MID) which includes scenarios where participants have to choose between immediate smaller and delayed larger hypothetical monetary or other incentives.[40,67] The design allows for estimating how the value of the incentive reduces across extending delay periods.[67] For example, adolescents (ages 11-14 years) who exhibit increasing discounting of delayed rewards are found to be more prone to early initiation and progressive substance use some two to five years later.[1,68,69] Multiple reviews on this sub-domain of impulsivity in adolescent and adult populations have found consilience in the association between an increased rate of delay discounting and escalating substance use (both in frequency and quantity) as well as heightened addiction severity, so much so that delay discounting is deemed a potential marker for addictive disorders.[1,38,40,70]

Positive and negative urgency belong to the trait aspect of impulsivity and has also been associated with prospective problematic substance use.[40] Both urgency traits are typically assessed with self-report surveys such as Barratt Impulsivity Scale and UPPS-P Impulsive Behavior Scale.[38,40] Positive and negative urgency have been reported to be strongly correlated to problem drinking and alcohol use disorder as studies with adolescents consistently found that urgency traits in pre-adolescence strongly predict drinking onset and problematic alcohol use in mid-adolescence.[40,43] Negative urgency in particular has been proposed to be strongly associated to alcohol use disorder and seems more likely to endorse positive attitudes towards cigarette use, indicating that children and preadolescents exhibiting increased negative urgency maybe at a greater risk of initiating smoking by mid-adolescence.[40,53]

Sensation seeking, another impulsivity trait facet, is usually measured with self-report surveys like the UPPS-P Impulsive Behavior Scale or the Sensation Seeking Scale.[40] According to a meta-analysis on teenage alcohol use, heightened sensation seeking has been largely associated with cannabis use,[71] onset of alcohol use in early adolescence, as well as problematic drinking (binge and heavy alcohol use).[40] According to the impulsivity theory of addiction, overactivation of the ventral striatum in response to rewarding stimuli may increase susceptibility to problematic substance use in the future through a pathway of heightened sensation seeking and motivation to attain potential reward.[1,68]

To summarize the relation between the multifaceted impulsivity domain and prospective substance use, adolescents with heightened predisposition to novelty-seeking, rash behavior/reaction to rewarding stimuli, coupled with weakened inhibition and steeper discounting of delayed reward, when in an elevated emotional state (negative or positive), may be at greater risk for escalating and problematic substance use in the future.[40] The foundation we have provided on impulsivity sub-domains as predictors of substance use, sets the stage for the current review of the state of science on the neurocognitive domains as potential predictors of future drug and alcohol use behaviors.

Methods

Overview

Our scoping review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines[72-74] to systematically map out and summarize findings from human subject research studies examining neurocognitive markers as predictors of later drug and alcohol use, followed by identification of gaps in this research area and potential future directions.

Methodological Framework

Step1. Identifying the research question. For this scoping review, we took an iterative and wide approach in seeking answer to the following research question: What is the available state of science on both concurrent (cross-sectional) and predictive (prospective/longitudinal) associations of minimally reviewed neurocognitive domains with substance use behaviors in the youth and adult population?

Step 2. Search strategy and selection Criteria. We conducted a thorough search of the electronic database PubMed for published literature over the last three decades (1990-2022) on neurocognition influencing substance use.

Exclusion criteria: We omitted studies investigating impulsivity facets (response inhibition, urgency, sensation seeking, delay discounting) as predictors of later substance use given the recent reviews covering that topic,[38,40,64] and instead provided a summary of those reviews above. Other pre-defined exclusion criteria included: studies not in English language, duplicate publications and studies evaluating neurocognition among substance use disorder (SUD) participants only (not general substance use).

Inclusion criteria: We focused our systematic search on studies examining executive function domains (outside of impulsivity) and emotion regulation as they relate to prospective substance use outcomes (i.e., age of onset, future initiation, changes in use pattern/frequency, and abstinence). We set a broad publication date parameter from 1990 to present times on PubMed and searched using these key terms and their combinations: neurocognitive abilities, working memory, visuospatial ability, attention, emotional regulation, verbal memory, reward processing, planning, decision making, executive cognitive functions, neurocognitive markers, drug use, substance use, predict, predictors, alcohol, cannabis, smoking, adolescents, youth, and

young adults. Even though only original cross-sectional and longitudinal research articles were included in our review, publication format search criteria were open to review articles also as they were useful resources to identify important themes and trends in existing literature and further distill our search.

Step 3. Study Selection. After conducting a thorough search following our inclusion criteria, full research articles were saved and imported to EndNote 20 reference management software for further screening and review. Full-text review of the articles were conducted primary reviewer to confirm their eligibility based on the pre-defined inclusion and exclusion criteria.

Step 4. Charting the data. On completion of the selection of eligible studies, we charted key information from the research articles to aid in narrative synthesis. The charting process involved recording the article name, authors, publication year, name of substance(s) of investigation, neurocognitive domains and tasks, sample (youths or adults), study design (cross-sectional or longitudinal), and highlights of results.

Step 5. Collating, summarizing, and reporting results. The last step involved a synthesis of the findings from the selected/charted studies. Our search identified 32 neurobehavioral studies investigating higher order cognitive domains (outside of impulsivity facets) and emotional regulation for predictive associations with substance use (see Table 1.1), which are grouped by domains in the text below.

See Figure 1.1 for an illustration of the methodological framework (Steps 1-5)

Results

1.1. Working Memory

Cross sectional investigations on working memory and substance use

A metanalysis including 42 cross sectional studies investigating the association between cognitive deficits and binge drinking [binge drinkers (mean age 18.88±1.30) *vs.* non-binge drinkers (mean age 18.83±1.43)] reported non-significant relationships between working memory deficits and binge drinking in youth.[75] However, they did observe significant associations of binge drinking with deficient decision-making ability and inhibition, hinting towards higher impulsive tendencies.[75] In contrast, another cross-sectional investigation with 145 high school students (ages 16-17 years-old) at risk of delayed graduation due to problem behaviors and/or poor academic status, revealed that "drug-related associations in memory" (assessed with a word association task) are more potent predictors of tobacco smoking and alcohol use among at-risk adolescents with poor working memory than among the ones with better working memory functioning.[76]

Longitudinal investigations on working memory and substance use

A prospective longitudinal investigation with substance *naïve* adolescents at baseline observed a significant association between working memory and substance use onset in early adolescence.[77] This study of 294 males (ages 13-20) from low-income neighborhoods in Montreal found that poor working and short-term memory, but also high verbal IQ, assessed in early adolescence (ages 11-13 years-old), predicted earlier age of onset of cannabis use by 14 years. Poorer working memory was also found to predict escalating cannabis use frequency and use severity, suggestive of a bidirectional relationship between these constructs.

Two other prospective studies with substance *naïve* participants at baseline, used a visual working memory task (2,4, and 6-dot array trials) and reported that reduced frontoparietal brain response during the task performance at ages 12-16 years significantly predicted moderate to heavy alcohol use (3 to 29 drinks per occasion) 3-4 years later. [78,79] There were no behavioral response differences observed on the task. Despite that, the limited engagement of these neural regions during high working memory load in early adolescence (pre-onset of use) may suggest a neurodevelopmental course related to deficient cognitive control in later years,[75,79,80] considering the major influence of working memory on decision making ability,[81] and the vulnerability of frontoparietal regions to teenage substance use.[82]

Another prospective longitudinal study with 88 Dutch adolescents (ages 14-20 years-old) from low-level vocational schools and at risk of problem behaviors impeding graduation, reported that "implicit positive-arousal cognitions" were strong predictors of alcohol use at one month follow up for youth with poor working memory whereas "explicit positive arousal cognitions" were strong predictors of drinking after a month among those with better working memory functioning.[83] The study interpreted this as suggestive of at- risk youth with better working memory exhibit deliberate alcohol use behaviors while the ones with poor working memory ability lean towards impulsive drinking behaviors which may lead to problematic use. [83]

Other studies have also discussed the predictive effects of reduced working memory in early adolescence on substance use onset, use levels[84], and later development of SUDs.[69] A longitudinal study by Khurana and colleagues with 358 adolescents (mean age 11.4 years at baseline) assessed annually over four years reported that poor working memory at baseline was a significant predictor of concurrent drinking as well as escalating frequency of alcohol use over the 4 years of the study.[84] They proposed that early onset of alcohol use during adolescence

could be a repercussion of pre-existing poor working memory capacity as opposed to being a cause of such impairment. Another longitudinal study by Khurana and colleagues looked at working memory as a predictor of SUD in late adolescence, where they collected five consecutive waves of annual data from 387 adolescents (aged 11-13 years at baseline) with a final follow-up 2 years later at ages 18-20 years (wave 6).[69] Weak working memory at baseline, in association with impulsive tendencies of "acting without thinking" and delay discounting, significantly predicted SUD at final follow-up and the effect remained independent of early substance use patterns. This suggests that adolescents with poor working memory capacity may have more difficulty controlling impulsive urges, increasing the risk of early substance use and subsequent SUD.

Large sample longitudinal studies[44,85-87] reported that deficient working memory capacity between the ages of 11-14 years-old (early adolescence) significantly predicted use of cannabis,[86] nicotine addiction symptoms,[69] drinking onset,[85-87] and binge and heavy use of alcohol[44,87] by the ages of 14-18 years, and the effects remained significant independent of other important predictors of future substance use such as family history of use dependence, sociodemographic factors, and other behavioral problems (antisocial behavior). These data add more weight to the interpretation that early substance use initiation including problematic use through middle and late adolescence may be partly driven by pre-existing weak working memory functioning in early adolescence.

Beyond adolescent samples, longitudinal investigation with adult drinkers (ages 21-65) has observed a significant association between greater number of drinks per drinking day and later reduced working memory (after adjusting for baseline working memory),[88] suggesting that alcohol induced declines in working memory may impair one's ability to regulate later alcohol

consumption. Overall, there is consistency across longitudinal findings reporting a significant predictive effect of deficient working memory in early adolescence on later substance use initiation, escalating use frequency and problematic use across both substance *naïve* and substance engaged youth samples.

1.2. Planning Ability

Longitudinal investigations on planning and substance use

To date, planning ability has been investigated in only two prospective longitudinal studies, both of which predicted problematic alcohol drinking outcomes.[29,89] No cross-sectional studies were identified in our search. Mullan and colleagues (2011) studied 153 young adult female students (mean age = 20 years-old) who were administered a questionnaire to measure alcohol use one week after cognitive assessment of planning ability.[89] Reduced level of planning ability in these students was associated with binge drinking behavior at one week follow-up, as compared to those who reported moderate drinking. This suggests that planning skill aid in predetermining the intended number of alcoholic drinks one may consume per occasion without crossing the binge/problematic drinking threshold.

A contrasting interpretation regarding the planning-intention-behavior relationship was reported by another prospective study with 149 Australian adults (mean age 20.1$\pm$4.2) who were assessed on their planning ability and then their heavy drinking episodes 15 days later.[29] The results revealed that prolonged planning (i.e., more time spent planning) prospectively predicted more persistent "heavy episodic drinking" (>4 standard drinks on a single occasion).[29,90] They emphasized on the interactive effects of planning ability in the intention-behavior association such that prolonged planning signified a stronger association between intention and behavioral action and suggested that greater planning ability may help individuals with strong intentions to

transition into heavy alcohol use behavior.[29] This contradicts the conclusion from the previous study which linked longer planning with predetermined intention of not binge drinking[89] and hence raises confusion about the relationship between planning skill and alcohol use.

1.3. Attention

Studies focusing on the relationship between attention and later substance use have utilized event-related potentials (ERPs), or more specifically, the P300 component, or P3, as a neural marker of attention.[91-93] The P3 component is an ERP registered as a positive deflection in the electroencephalograph (EEG) approximately 300-600 milliseconds following task-based stimuli [93]. It has been demonstrated that P3 wave amplitude increases proportionately with the attentional demands of the target stimulus (e.g., the amount of attention needed during task performance) [91]. Hence, the P3 component can index an individual's extent of attentional control [91-93] and low P3 amplitude has been associated with hereditary risks for substance use especially in cases of familial history of problematic alcohol use.[92,93]

Cross sectional investigations on attention and substance use

Paternal alcoholism has been associated with small P3 amplitude in substance *naïve* male progeny[94] and lower P3 amplitude in turn has been linked to attention control problems (deficits/overactivity) and disinhibiting tendencies including substance abuse.[93] A correlational analysis examined this claim with data from the larger longitudinal Minnesota Twin Family Studies (MTFS). They included 93 boys age 17 years old, who were split into two groups of "psychophysiological high risk for substance abuse" as indexed by small P3 amplitudes during the rotating heads task and "psychophysiological low risk for substance use" as indexed by large P3 amplitudes during the task.[93] Results revealed that the high-risk group with small P3 amplitudes had significantly higher cases of substance use including problematic use of alcohol,

tobacco, and other illicit drugs, compared to the low-risk group with P3s of large amplitude. Additionally, the high-risk small P3 group contained more cases with antisocial behavior and childhood disorders such as Conduct disorder (CD), Oppositional Defiant Disorder (ODD) and Attention deficit/hyperactivity disorder (ADHD), than the large P3 low-risk group. This suggests that early attentional control problems could be a vulnerability marker for later externalizing behavior traits which includes substance use.

Longitudinal investigations on attention and substance use

A longitudinal study published in 1993 assessed P3 with a visual continuous performance task among a sample of 36 pre-adolescent boys (ages 9.6-14.8, with or without family history of alcohol use disorder) before any alcohol or drug use initiation. They followed up four years post P3 assessment with questionnaires on use of alcohol, cannabis, nicotine and other drugs (including cocaine, amphetamine, barbiturates, and LSD).[92] Their results revealed that lower P3 amplitudes for non-target stimuli during the ERP task at baseline significantly predicted substance use 4 years later in adolescence, and the predictive effect retained over and beyond family history of substance use disorder.

Hence, lower P3 amplitude during early adolescence which has been linked to attentional control problems, appear to be predictive of prospective substance use. If these relationships hold in future studies, early signs of attention deficits or overactivity could be used as a vulnerability marker for potential problematic drugs and alcohol use.

1.4. Visuospatial Ability

Visuospatial ability has been minimally investigated for its predictive effects on future substance use. A ***cross-sectional*** study including 140 undergraduate students (mean age= 19.10$\pm$1.76) failed to find any association between visuospatial functioning and problematic

alcohol use but did observe a relationship between better organization skills and heavy alcohol use.[95] Given the observed cross-sectional associations between alcohol use disorder and declining visuospatial ability in adult samples,[95-98] prospective studies on this topic are warranted.

1.5. Decision Making and Reward Processing

Studies on substance *naïve* adolescents have suggested that most teenagers have difficulty with cognitive control in situations when it is beneficial to suppress ones' response to reward-related cues.[14,99] In one such study, Figner and colleagues show that adolescents made more risky gambles on a gambling task compared to adults but only in emotionally charged trials with enhanced task-elicited arousal.[99] These trials were referred to as "hot trials" because players received immediate feedback on reward which gave them the opportunity to make stepwise decisions about turning over an additional card based on the feedback. This triggered affective decision making as opposed to the deliberate decision making in the "cold trials" where there was no immediate reward feedback, thus no chance to make incremental decisions. Adolescents who exhibited increased arousal had predicted risk-taking in the hot trials but not in the cold trials which involved deliberate executive function processes to make decisions. Thus, this study demonstrates teenagers' affective system dominating over the deliberative cognitive control system in emotionally aroused states[14,20,99] which aligns with their heightened motivation and reward seeking risk taking nature.[14,100]

Longitudinal investigations on decision making/reward processing and substance use

A prospective longitudinal study investigating neural substrates of decision making as predictors of later cannabis use in a sample of 32 heavy cannabis users and 41 controls (ages 18-25 years-old), found that increased brain response linked to win *vs.* loss evaluation in the orbitofrontal cortex, insula, and superior temporal gyrus during the Iowa gambling task at age 21 predicted increased cannabis use 6 months later.[45] The results also suggested that individuals with an inclination towards instant reward on this task have a higher likelihood of escalating substance use at 6-month follow-up. In another study with 47 adolescents (ages 14-15 years old), increased neural activity in the nucleus accumbens and specific cortical regions (occipital cortex, fusiform, precuneus) during the "high risk/reward" condition of the Wheel of Fortune (WOF) decision making task was strongly associated with binge drinking initiation 6 years later.[101] In line with this, increased bilateral reward response in the medial prefrontal cortex, superior frontal gyrus, and precentral gyrus during the monetary incentive delay (MID) task at age 14 was reported to predict binge drinking at age 16,[44] while greater activation in these neural regions during a card guessing game with a reward component predicted lifetime substance (alcohol, illicit drugs) use by the age of 16 years.[102] These effects remained significant despite controlling for important covariates such as sociodemographic variables and co-occurring mental health conditions.[1,44,102] There were no behavioral response differences observed on the respective task in all of these neuroimaging studies, suggesting that increased activity of the neural reward circuitry during decision making in the absence of overt behavioral differences represents a neurobiological vulnerability marker for earlier initiation and greater escalation of substance use.

Neuroimaging studies assessing reward anticipatory decision-making during childhood in relation to substance use also revealed similar observations. In a sample of substance *naïve* at-

risk children (majority of the sample had family history of drug and alcohol use disorder) increased activation of the nucleus accumbens during monetary reward gain expectancy at an average age of 10.5±1.2 significantly predicted the increased possibility of substance use (alcohol, tobacco, cannabis, and other drugs) onset in early adolescence, adjusting for behavioral issues and family history of SUD.[51] Additionally, increased ventral striatum activity due to elevated reward gain expectancy in childhood and adolescence revealed potent predictive value for several substance use initiations (such as nicotine, alcohol, other illicit drugs) 2-6 years later, independent of confounding factors such as history of antisocial behavior and family background of SUD. [47,51,103] In young adults, increased reward associated ventral striatal response (assessed on the blocked-design number guessing paradigm) concurrent to reduced risk associated amygdala reactivity (assessed on the alternating perceptual face processing task) in a stressful context predicted prospective stress-related problematic alcohol use (as in excessive drinking to cope with life stress).[104-106]

Some of the neuroimaging studies also observed sex differences regulating the association between reward anticipation and future substance use.[103,107] Increased medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex activation during the Monetary Incentive Delay (MID) task at the age of 16 years significantly predicted elevated alcohol use only among female participants at 18 years of age.[103] While another study reported that activation of anterior insula during reward expectancy in early adolescence (ages 13-14) predicted increased drinking frequency by 15 or 16 years for males but not female participants.[107] Together suggesting that activity of certain neural regions during reward processing in adolescence can predict later alcohol use behaviors distinctively for the two sexes.

Despite most studies reporting associations between heightened brain response during reward gain expectancy and prospective substance use, an interesting finding was reported by Büchel and colleagues in one of their studies with adolescents exhibiting increased sensation-seeking.[68] In this sample, blunted response in the midbrain, ventral striatum, and bilateral prefrontal cortex during the MID task at age 14 predicted prospective increasing of substance misuse (i.e., therapeutic use beyond prescribed dosage or indications)[8] after 2 years. Thus, heightened novelty-seeking tendency during adolescence has been linked with pre-existing limited neural response to rewarding stimuli which drives teenagers to seek out external motivations such as substance use to experience similar levels of reward anticipation.

1.6. Emotion Regulation

Cross sectional investigations on emotional regulation and substance use

One cross-sectional study with 435 college students (ages 18-25) found that a lack of inner resources/strategies to regulate emotional states was not directly associated with drinking but was significantly correlated with "alcohol-related problems" through coping motivations to alleviate depression, negative affect, and anxiety by drinking.[54] Another cross-sectional study with children ages 10 to 14 years, reported that children and adolescents exhibiting maladaptive emotion regulation as well as impulsive tendencies when in an elevated negative emotional state are more likely to promote "positive social facilitation smoking expectancies" (which is harboring beliefs about the socially positive outcomes from cigarette use), and hence are at a higher risk for engaging in experimental smoking and progressive cigarette use.[53]

A cross-sectional study with 489 middle school (mean age 12.2$\pm$.90) and 602 high school students (mean age 15.8$\pm$1.3) reported a positive association between poor emotion management and substance (alcohol, cannabis and tobacco) use, and revealed contemplating negative

emotions as one of the major indicators of poor management of emotions.[108] A cross-sectional study investigating 25,186 middle and high-school students (mean age 14.13±1.95) from 38 public schools in Kentucky reported that limited emotional regulation ability increased the likelihood of smoking behaviors ranging from low level cigarette experimentation to regular use.[109] Their results deem greater emotional lability a risk factor for progressive cigarette use and thus teenagers with maladaptive inner resources to regulate affective responses are more likely to engage in risky external activities like substance use to cope with distress and negative emotional states. The analyses also revealed that students exhibiting poor emotional regulation have greater probability of engaging in experimental cigarette use in schools with substandard involvement and disciplinary protocols (i.e., low student involvement in school issues with loosely enforced school rules and lax faculty discipline) as compared to schools with higher standard of disciplines and involvement with students, suggesting the importance of school context and environment in influencing students' cigarette use.

Longitudinal investigations on emotional regulation and substance use

A prospective study among 517 8th and 10th graders found that heightened "negative mood variability" at baseline predicted escalating cigarette use patterns in their adolescent sample (mean age 14.4±1.20).[46] Specifically, adolescents with longitudinal increases in cigarette use exhibited elevated baseline mood variability compared to adolescents in the non-progressing smoking experimentation group and adolescents who reported never smoking.[46] Hence, a high level of variable negative affective state during adolescence is deemed a promising predictor/risk factor for future increasing smoking behaviors among youth.

In the case of alcohol, results from a longitudinal randomized controlled trial with 4th – 6th grade students (ages 9-12) indicated that emotional regulation, assessed in pre-adolescence,

was a predictor of alcohol use initiation by 6th grade.[110] A 2020 longitudinal analysis investigated ideas of emotional stability and variability among 94 adolescents (ages 13-14) using a feedback control model and their results revealed model-based indicators of emotion regulation significantly predicted prospective substance (alcohol, cannabis and tobacco) use behaviors.[55] They observed significant relationships between increasing emotional regulation and reducing use of alcohol, cannabis and tobacco.

In summary, multiple studies have observed an association between increased mood variability (affect dysregulation) and escalating use of tobacco and alcohol use among adolescents and young adults. This suggests that mood variability is worth looking at in adolescence as it may be clinically relevant as an early measure to determine who will need intervention.

Discussion

Our review focused on studies assessing associations and prospective predictive relationships of ECF and emotion regulation factors on substance use behaviors, with special attention to higher order cognitive domains that have received less attention in the literature (i.e., working memory, attention, planning ability, visuospatial ability, reward processing and decision making). In total, we summarized literature on six neurocognitive domains (*see* Table 1.1) and the overview of findings indicate that most studies (30 out of 32) across all six domains show some evidence for predictive effects on substance use related outcomes ranging from prospective use initiation, age of onset, escalating use, and later problematic substance use behaviors.

Of the 18 studies assessing solely alcohol use outcomes (see Table 1.1), lower working memory capacities were associated with drinking behaviors (8 out of the 18 studies) with most

longitudinal investigations reporting the significant predictive effect of lower working memory functioning in early adolescence, prior to alcohol use onset, on alcohol use initiation, escalation, and even heavy use in later years through adolescence and young adulthood.[44,69,78,79,84,86-88] Increased activation of the neural reward circuitry during high risk/reward anticipatory decision-making task in early adolescence (by ages 14 or 15) was shown to predict elevated alcohol use and binge drinking initiation by age 16 or later (4 studies), indicative of a promising vulnerability marker for later problem drinking.[44,101] Maladaptive emotion regulation was linked to alcohol related problems in two studies, with drinking to cope with negative emotional states suggested as a potential risk pathway,[54,110] and attention control problems in early adolescence in two studies (indicated via lower P3 amplitudes), prospectively predicting problematic alcohol use.[92,93]

The relationship between planning ability and later alcohol use is less clear. Only two studies were found on the topic, and these had contrasting results.[29,89] One possibility for observing contrasting results could be the difference in the sample makeup between the studies, as one included only young adult female students while the other included both males and females from the general population.[29,89] Such instances call for more rigorous longitudinal investigations to clearly understand the mechanism and nature of the relationship between sample demographics, planning ability and alcohol use. Similarly, only one cross-sectional study was found assessing visuospatial ability, thus we are unable to make any general conclusions on this domain.

In comparison to alcohol studies, we found fewer investigations assessing tobacco/nicotine use or cannabis use outcomes. In 3 of the 4 studies solely looking at nicotine/tobacco use, maladaptive emotional regulation in early adolescence (ages 10-14) was

strongly associated with escalating smoking behavior (progressing from low level cigarette experimentation to regular use) over time.[46,53,109] Other than emotion regulation, poor working memory between the ages of 11-13 years was implicated in predicting nicotine addiction symptoms by the ages of 18-20 years.[69] Similarly deficient working memory capacity in early adolescence (ages 11-14 years) significantly predicted early onset of cannabis use (by age 14) and escalating frequency of use through adolescence (ages 14-18 years) in 2 of the 3 studies exclusively assessing cannabis use.[77,86]

We found only one study that assessed the potential for a bidirectional relationship between our ECF domains and substance use. This study reported onset of cannabis use by age 14 and elevated frequency of use through adolescence was in turn associated with declining working memory capacity over the later years into early adulthood.[77] The stark absence of bidirectional investigations (where neurocognition is examined as a predictor and an outcomes of substance use) is noteworthy since there is mounting evidence from the plethora of impulsivity studies[38,40,64], as well as studies on other domains reported here, that separately show significant, yet independent, associations supporting both directions.

The investigation of ECF during heavy use periods is important as poor working memory coupled with increased reward anticipatory neural response during win evaluations, post cannabis use onset and heavy use at age 21, predicted elevated use 6 months later.[45] Here we see the predictive effect of neurocognition on later cannabis use post initiation at heavy use stage, something that is scarcely investigated but appears to have effect when the brain is most taxed with heavy influence of cannabis.

Unfortunately, for many of the studies, there was a lack of clarity in specific substance use profiles such that most investigating multiple substances (6 out of the 32 studies) appeared to

assess alcohol, cannabis, and tobacco distinctly yet group all other substances as “illicit”, “other” or “hard” drugs. Thus, we are unable to determine the specific relationships between neurocognitive functioning and each of the substances independently.

Overall, among ECF domains broadly, only the multifaceted impulsivity construct has been robustly investigated as a predictor and marker of vulnerability for future substance use [1,38,40,64]. Following an extensive literature search on other ECF domains, working memory was the only other domain to reveal more than 10 studies on this relationship. Other subdomains of memory have not been assessed but could prove fruitful. For example, verbal memory, an episodic long-term memory which deals with recall experience of events [111], has been reported to be affected by heavy alcohol use [5,57] and may be bidirectionally associated with alcohol use onset and escalation.

Future directions

In addition to expanding investigation within the memory domain, other higher order domains such as visuospatial ability and attention call for more scope of research in this reverse direction of neurocognition predicting substance use. Even though we found promising results regarding the predictive power of attention (P3 measure) on prospective substance use, [92,93] we need more longitudinal investigations including assessments on different measures of attention, especially since childhood ADHD has been consistently reported to have significant associations with early substance use and increased substance use in adulthood.[112-114] Lastly, emotional regulation, which is a multidimensional complex construct, was assessed with self-report surveys and scales as opposed to task-based manipulations.[46,53-55,108-110] As a future direction, it could be beneficial to design more longitudinal investigations with appropriate neurobehavioral tasks

enabling assessment of behavioral and/or neural responses to aspects of emotion regulation such as negative affect/mood variability and their relation to prospective substance use.

In summary, our review of neurobehavioral studies assessing neurocognition as a predictor of later substance use revealed a common theme where cognitive processing in some higher order constructs such as working memory, attention, emotion regulation, and elevated activity of the neural reward circuitry during decision making in childhood and early adolescence predicted earlier onset, greater escalation of use, and even development of SUD in some instances. Hence, most of the less researched ECF domains reported here show great promise as neurobehavioral vulnerability markers that can be assessed at earlier ages, and during times of substance use, to predict substance use behaviors during adolescence and help to possibly prevent problematic use in the future.

Table 1.1. Studies examining neurocognitive markers as predictors of substance use

	Sample (*N*)	Age(years) Mean (SD) or Range	Follow-up period	Study Design	Substance Outcomes	Measure(s)
Working Memory						
Castellanous-Ryan et al., 2017	294	13-20	8 years	Prospective Longitudinal	+ Cannabis Use	Number Randomization (NR) Self-Ordered Pointing Task (SOPT) Conditional Association Task (CAT)
Khurana et al., 2017	387	11-20	6 waves (2005-2010, 2012)	Longitudinal	+Nicotine (smoking), Alcohol, Cannabis	Digit Span (backward sequencing) Corsi-block tapping Letter two-back Spatial Working Memory task
Lechner et al., 2016	41	21-65	3 sessions (Mean days between = 9.23)	Secondary Analysis (Longitudinal data)	+ Alcohol Use	Trails Making Test-B (TMT-B)
Grenard et al., 2008	145	16.71(.74)	-------	Cross-sectional	+Nicotine (smoking); +Alcohol Use	Self-ordered pointing task (SOPT)
Thush et al., 2008	88	14-20	1 mo.	Prospective Longitudinal	+ Alcohol Use	Self-ordered pointing task (SOPT)
Peeters et al., 2015	534	12-14	2 years	Longitudinal	+ Alcohol Use	Self-ordered pointing task (SOPT)
Morin et al, 2019	3,826	12.7(.50)	4 years	Longitudinal	+ Cannabis Use	"find the phone" task (based on SOPT) Cambridge Neuropsychological Test Automated Battery- subtest
Whelan et al., 2014	692	14.56(.42)	2 years	Prospective Longitudinal	*+Alcohol Use*	*Cambridge Neuropsychological Test Automated Battery* (CANTAB): Spatial working memory task
Khurana et al., 2013	358	11.4(.87)	4 years	Longitudinal Cohort	+Alcohol Use	Digit Span (backward sequencing) Corsi-block tapping Letter two-back Spatial Working Memory task
Squeglia et al., 2012 (Study 1)	40	15-19	-------	Cross-sectional	+Alcohol Use	Visual Working Memory task (2,4 & 6-dot array trials)
Squeglia et al., 2012 (Study 2)	40	12-16	3 years	Longitudinal	+Alcohol Use	Visual Working Memory task (2,4 & 6-dot array trials)
Squeglia et al., 2017	137	12-19	5 years	Longitudinal	+Alcohol Use	Visual Working Memory task (2,4 & 6-dot array trials)

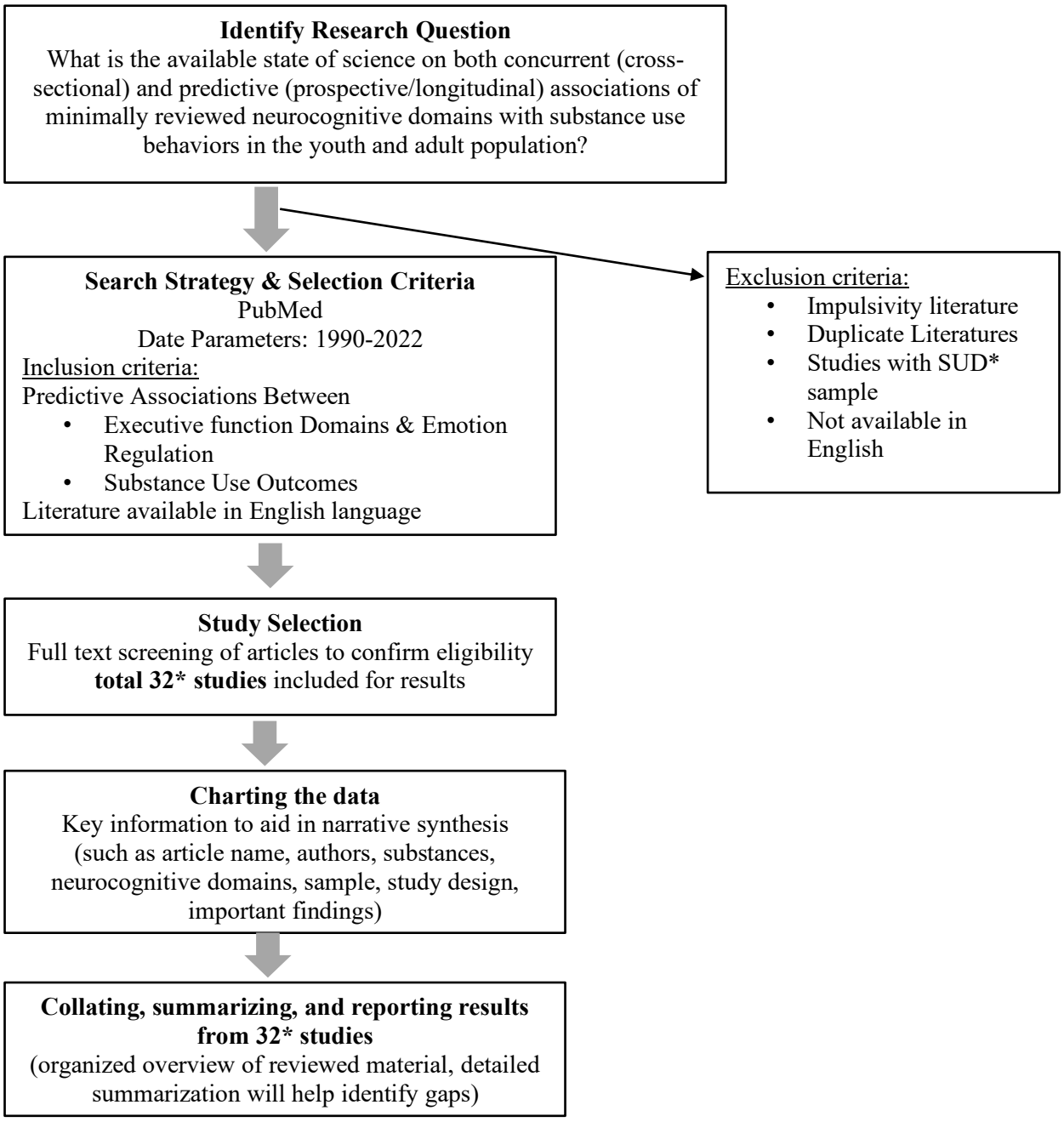
(Table 1.1 continued)

	Sample (*N*)	Age(years) Mean (SD) or Range	Follow-up period	Study Design	Substance Outcomes	Measure(s)
Planning Ability						
Black et al., 2017	401	25.89 (9.99)	15 days	Prospective Longitudinal	+Alcohol Use	Tower of London
Mullan et al., 2011	153	20.1(4.2)	1 week	Prospective Longitudinal	+Alcohol Use	The Tower of Hanoi (TOH)
Attention						
Berman et al., 1993	36	9.6-18.8	4 years	Longitudinal	(+) Alcohol, Cannabis, Nicotine, & Other Drugs Use (cocaine, LSD, amphetamine, barbiturates)	Visual Continuous Performance Task (CPT) (an Event-related Potential-ERP task)
Iacono et al., 1999	93	17	-------	Correlational Analysis	(+) Alcohol, Nicotine & Other Illicit Drugs	Rotating heads task
Visuospatial Ability						
Jia-Richards et al., 2021	140	19.10(1.76)	-------	Cross-sectional	-Alcohol Use	Behavior Rating Inventory for Executive Function—Adult (BRIEF-A) Rey-Osterrieth Complex Figure Task (ROCF)
Decision making & Reward Processing						
Cousijn et al., 2013	73	18-25	6 mos.	Prospective Longitudinal	+ Cannabis Use	Iowa Gambling Task (Monetary decision-making task)
Cope et al., 2019	34	8.2–12.9	*	Longitudinal	(+) Alcohol, Cannabis, Nicotine, & Other Drugs Use	Monetary Incentive Delay (MID) task (modified)
Büchel et al., 2015	144	14-16	2 years	Longitudinal	(+) Alcohol, Cannabis, Nicotine, & Other Illicit Drugs Use	Monetary Incentive Delay (MID) task
Morales et al., 2018	47	14-15	3 mos.	Longitudinal	+ Alcohol Use	Wheel of Fortune (WOF) (Computerized decision-making task)
Nikolova & Hariri, 2012	200	*	3 mos.	Longitudinal	+ Alcohol Use	Blocked-design number guessing paradigm (Ventral striatum reactivity paradigm) Paradigm of alternating perceptual face processing task & sensorimotor control task (Amygdala reactivity paradigm)
Swartz et al., 2020	262	16-18	2 years	Longitudinal	+ Alcohol Use	Monetary Incentive Delay (MID) task

(Table 1.1 continued)

	Sample (*N*)	Age(years) Mean (SD) or Range	Follow-up period	Study Design	Substance Outcomes	Measure(s)
Decision making & Reward Processing						
Waller et al., 2019	139	11-22	12 years	Longitudinal	(+) Alcohol, Nicotine &Other Drugs Use	Card guessing game (with monetary reward component)
Bertocci et al., 2017	73	9.89-17.71	24 mos.	Longitudinal	(+) Alcohol & Illicit Drugs Use	Card guessing game (with a reward component)
Elder et al., 2019	161	13-16	3 years	Longitudinal	+ Alcohol Use	Economic lottery choice task (involving uncertain monetary outcomes)
Whelan et al., 2014	692	14.56(.42)	2 years	Prospective Longitudinal	+ Alcohol Use	Monetary Incentive Delay (MID) task
Emotional Regulation						
Simons et al., 2017	435	18-25	-------	Cross-sectional	+ Alcohol Use	Difficulties in Emotion Regulation Scale (DERS)
Novak & Claython, 2001	25,186	14.13(1.95)	-------	Cross-sectional	+Nicotine (smoking)	Emotion Regulation Scale (9 items encompassing anger & extreme affect management, negative emotion regulation)
Weinstein et al., 2008	517	14.4(1.20)	6 mos. & 12 mos.	Longitudinal	+Nicotine (smoking)	Negative Affect Scale (Ecological Momentary Assessment- EMA)
Pentz et al., 2016 (Study 1)	709	9-12 (4^{th}-6^{th} grade)	3 years	Randomized Controlled Trial	+ Alcohol Use	Behavior Rating Inventory of Executive Function (BRIEF)- Self-Report
Pentz et al., 2016 (Study 2)	410	12.5*	-------	Cross-sectional Pilot Study	+ Alcohol Use	Behavior Rating Inventory of Executive Function (BRIEF)- Self-Report
McKee et al., 2020	94	13-14		Longitudinal	(+) Alcohol, Cannabis, Nicotine	Ecological Momentary Assessment Moods (EMA surveys)
Dir et al., 2016	61	10-14	-------	Cross-sectional	+Nicotine (smoking)	UPPS-PC (UPPS-P Impulsive Behavior Scale modified for children)
Wills et al., 2006 (Middle school sample)	489	12.2(.90)	-------	Cross-sectional	(+) Alcohol, Cannabis, Nicotine	Affective Lability Kendall-Wilcox Inventory Anger management scales
Wills et al., 2006 (High school sample)	602	15.8(1.3)	-------	Cross-sectional	(+) Alcohol, Cannabis, Nicotine	Affective Lability Kendall-Wilcox Inventory Anger management scales

(*) = Missing information in manuscript



*SUD = substance use disorder

Figure 1.1. Methodological framework of the scoping review adapted from the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines

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Chapter 2: Neurocognitive Markers during Maximum Alcohol Use in Late Adolescence as Predictors of Change in Later Drinking Behaviors

Abstract

***Background*:** The influence of alcohol use on later neurocognitive functioning is well researched, yet few studies have investigated whether neurocognition post-drinking initiation predicts changes in later alcohol use.

Objective: Investigate neurocognitive task performance during maximum alcohol use in late adolescence as predictors of drinking behaviors 3-7 years later.

***Methods*:** Analyses (*n=105*) were conducted on a longitudinal dataset involving adolescents (12-13 years-old) who were followed for 16 years. Time 1 (T1) was defined as the individuals' maximum drinking year within the first 10 study years and Time 2 (T2) was the first available data entry 3-7 years after T1. Four hierarchical linear regression models predicting change in follow-up alcohol use were estimated: drinking days, average drinks per drinking day, peak drinks, and binge episodes. All models included inhibition/cognitive flexibility, visuospatial ability, verbal memory, working memory, and their interactions with sex, while covarying for age at T1 and follow-up duration.

***Results*:** Better visuospatial ability (β= -.30) and working memory (β= -.25) at T1 predicted decreases in later binge episodes, whereas better verbal memory (β= .31) predicted an increase. Better inhibition/cognitive flexibility predicted increases in later drinks per drinking day (β= .24) and peak drinks (β= .21). Better verbal memory predicted an increase in drink days (β= .22) and interacted with sex to predict changes in peak drinks (β= .32).

***Conclusion*:** Findings suggest neurocognitive abilities during maximum drinking in late adolescence are useful as predictors of change in later alcohol use behaviors and could potentially inform intervention research targeting this age group.

Keywords: Alcohol, Neurocognition, Late Adolescence, Predictor, Drinking, Regression

Introduction

Adolescence is not only a period of rapid neuromaturation, but also a vulnerable time marked by the emergence of puberty and risk-taking behaviors such as experimentation with drugs[1,2] and maladaptive peer associations.[3] An estimated 20% of 8th graders have used alcohol within the past year, which more than doubles to 55% in 12th graders. Further, 4.5% of 8th graders and 16.8% of 12th graders reported engaging in binge drinking (> 5 drinks per occasion) during the past year.[4] Over the last 9-10 years, there has been a decline in the perceived harm/risk of alcohol experimentation and daily use among adolescents[5,6] which may contribute to increases in early experimentation with alcohol in the youth population.[6]

Executive functioning, essential for adaptive responses and goal-directed behavior, also peaks in late adolescence,[7,8] thus making this period especially vulnerable to neural insults. Higher order executive functions such as working memory, visuospatial ability,[9] and inhibition/cognitive flexibility exhibit prolonged development through adolescence and into young adulthood[8] and characterize mature cognition.[7] Exposure to potential toxins such as alcohol and other substances during this sensitive period of development may lead to long-term consequences on neural development,[10-15] including impeding the continued maturation of the prefrontal cortex and impairing the growth in cognitive control capacities from childhood to adulthood.[1]

Many studies have investigated the influence of alcohol and drug use on neurocognition during adolescence and reported deficits in a range of cognitive domains.[1,3,10,16-19] When compared to pre-drinking neurocognition, earlier age of first alcohol use has been associated with poorer performance in 'lower level' neurocognitive abilities of visual attention and psychomotor activity.[10,20] The progression to frequent, weekly alcohol use seems to exacerbate

deficits, as earlier age of initiation to frequent drinking has been associated to predict impairments in 'higher order' domains of working memory and inhibition/cognitive flexibility.[10,12] Heavy alcohol use during adolescence in the form of extreme binge drinking (10+ drinks per occasion) has been associated with deficits in verbal learning and recall memory.[11] The effects of heavy alcohol use are also evident in neuroimaging markers of the brain,[3] where adolescent heavy drinkers showed smaller hippocampal[13,14] and prefrontal cortex volume[15] than non-drinking control groups. Additional effects appear when looking at co-use of alcohol and cannabis which has been associated with poorer academic performance (lower GPA) when compared to non-drinking peers.[21]

Though much research has investigated the effect of alcohol use on subsequent neurocognition, very few studies have investigated whether neurocognitive abilities can serve as potential risk or protective factors of change in alcohol use over time. Of the few studies identified, the majority focused on response inhibition[22,23] and working memory[24,25] *prior to drinking initiation* as predictors of future alcohol use. Despite these studies finding support for poorer inhibitory control and reduced working memory capacity predicting drinking onset and heavy alcohol use behaviors in late adolescence, research on other neurocognitive domains remains scarce. Even more limited are longitudinal studies that have investigated the influence of neurocognitive ability on changes in alcohol use behaviors among adolescents who are already engaged in drinking. A recent study found that neural activation during a response inhibition task in adolescents who were already engaged in drinking predicted the transition from less frequent alcohol use to frequent binge drinking.[26] Although limited, these few studies highlight the potential for a bidirectional relationship between alcohol use and neurocognitive functioning and

suggest that transitioning into alcohol use in adolescence may cause additional alterations in neurocognitive functioning that, in turn, impact future alcohol use behaviors.

Due to the scarcity of investigation looking at the predictive capacity of earlier cognitive function, especially post-alcohol use onset, the nature of the directionality between neurocognitive functioning and later alcohol use remains largely untested. Thus, our aim is to investigate whether neurocognitive abilities vital for executive control (working and verbal memory, visuospatial ability, inhibition/cognitive flexibility) at the point of maximum alcohol use in late adolescence can serve as predictors of change in alcohol use behaviors 3 to 7 years later. The assessment of neurocognitive ability at the time of maximum alcohol use is important as past-month(s) peak use has been significantly associated with high motivations to change (reduce) substance use behavior.[27] High motivations can lead to better odds of change in drinking pattern and effective neurocognitive abilities can play an integral role in acting on such motivations and following through with regulating use behavior. Hence, it is important for our analyses to evaluate neurocognitive capacity at the maximum (peak) alcohol use stage in late adolescence as the main objective of our aim is to predict changes in later drinking behaviors.

We hypothesized that better performance in the neurocognitive measures of working memory, verbal memory, visuospatial ability, and inhibition/cognitive flexibility during maximum use will predict greater reductions in drinking at follow-up. Given that sex and gender differences are commonly observed in epidemiology[28-30] and physiology (blood alcohol concentration)[31] studies, we also investigated potential interactions between neurocognitive domains and sex in predicting changes in drinking behaviors over time.

Materials and Methods

Participants and procedures

We conducted secondary data analyses with data from the larger longitudinal substance use and neuroimaging study "Youth At Risk" (YAR) (NIAAA R01 AA13419). YAR followed adolescents (ages 12-14 years-old at baseline) for 16 years with repeated assessments on their alcohol and other drug use, neuropsychology/neuroimaging, and psychiatric symptoms and diagnoses. The eligibility criteria for enrollment in the parent study (YAR) was youths between the ages of 12-14 years with adequate English comprehension, no underlying mental health diagnoses, or psychiatric disorders, and less than or equal to one lifetime experience of alcohol use. Post baseline, participants were assessed every 6 months on alcohol and drug use, cognitive functioning, and changes in general health/social functioning.

For these analyses, the first time point (T1) was defined as the year of each participant's maximum drinking (i.e., the year participants reported the most drinking per occasion, on average) during the first 10 years of follow-up (ages 13-25 years). The second time point (T2) was defined as the first available report of alcohol use acquired 3-7 years after T1 (ages 21-27 years). Participants were included in the current sample if they reported any alcohol use during T1 (ages 13-25 years) and they had available neuropsychological assessment data at T1. Participants were excluded if they had missing alcohol use data on either timepoint. Out of the final baseline sample of 249 youths, data from 105 participants were included in the current secondary analysis. The final sample of 105 participants matched the baseline sample in terms of sex, race, and ethnicity distributions.

Measures

Demographics

Participants reported on demographic information (age, sex, race, etc.) and family history which were further corroborated by a guardian or biological parent. Follow-up (T2) income was considered in the present analyses as an indirect measure of general functioning and achievement given that most participants transitioned to their own income for financial support by this point.

Substance use

The Customary Drinking and Drug Use Record (CDDR), a structured interview to assess the pattern and severity of alcohol consumption and other drug use,[10,32,33] was administered at both time points. For the current analyses, data from four alcohol use change outcomes reported over the previous year were investigated: 1) Drink Days (DD) - total of alcohol drinking occasions; 2) Drinks per Drinking Days (DPDD) - number of standard alcoholic drinks, on average, consumed in a day when drinking occurred (24-hour period); 3) Peak Drinks (PeakDr) - maximum number of standard alcoholic drinks consumed in one occasion; 4) Binge - total number of binge drinking episodes (>5 drinks for males on one occasion and >4 drinks for females on one occasion).

Neurocognitive task domains

To assess cognitive functioning, a comprehensive neuropsychological battery was administered which included the Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference (CWI) subtest,[34] California Verbal Learning Test (CVLT)- Children's Version[35] and adult versions (CVLT-II; Wechsler, 1997),[36,37] Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and Wechsler Adult Intelligence Scale- Fourth Edition (WAIS-IV) Block Design subtests;[10,38] and Wechsler Intelligence Scale for Children- Third

Edition (Wechsler, 1991) and WAIS-IV Digit Span subtests.[10,39] Adult versions of applicable tests were administered at timepoints in which participants were ≥ 18 years old.

For the current secondary analyses, the primary predictors of interest were neurocognitive task scaled scores (age normed) from four domains: 1) CVLT Long Delay Free Recall (LDFR) scaled scores as a measure of verbal memory; 2) WASI and WAIS-IV Block Design scaled scores as a measure of visuospatial ability; 3) WAIS-IV Digit Span scaled scores as a measure of working memory; and 4) D-KEFS Color-Word Interference (CWI) Condition 4-Inhibition/Switching completion time scaled scores as a measure of cognitive flexibility and inhibition.[34,40]

Statistical analyses

SPSS (version 26) was used to conduct descriptive and multivariate analysis followed by post-hoc investigations. To examine neurocognitive markers as predictors of change in later alcohol use behaviors, hierarchical linear regression models were estimated with T1 age, follow-up duration (T2 minus T1 difference in years), and sex entered in the first step, T1 neurocognitive scores from four cognitive domains (verbal memory, working memory, visuospatial ability, inhibition/cognitive flexibility) entered in the second step, and interactions between sex and T1 neurocognitive scores entered in the third step. Four models were run to estimate the four alcohol use change outcomes (T2 minus T1): DD, DPDD, PeakDr, and Binge. Positive values on these change scores thus represent increases in alcohol use behaviors from T1 to T2, whereas negative values represent reductions in alcohol use behaviors at T2.

To address the appropriateness of change scores as outcome variables in the analyses, *post hoc* conservative hierarchical linear regression models controlling for T1 drinking were estimated including T1 drinking variables as covariates in Step 1 to predict T2 alcohol use

outcomes. We also ran models in which participants' T2 income was added as a covariate in Step 1 to test if youth income at follow-up has a moderating role in the significant relationships observed between primary predictors and outcomes.

Results

Description of sample

Age at maximum alcohol use at T1 was between 14.67 to 24.69 years with a mean age of 19.20 years. The age range at follow-up (T2) was 20 to 28 years with a mean age of 23.28 years. This sample was predominantly White non-Hispanic males (59% males, 70% White). The low representation of Non-White race/ethnicity precluded using race/ethnicity as a secondary predictor in our models. There was no significant difference in T1 neurocognitive tasks scaled scores (age normed) at peak alcohol use stage, in all four domains, between males and females [Block Design: t(103)= -.69, p=.487; LDFR: t(103)= -1.04, p=.301; Digit Span: t(103)=.94, p=.350; CWI: t(103)= -.25, p=.801]. Among self-reported alcohol use between the two time points, DD trended towards an increase at T2 [paired t(104)= 1.84, p=.07)] and the other three drinking outcomes showed a significant decrease at T2: DPDD [paired t(104)= -12.08, p<.001)], Binge [paired t(104)= -3.78, p<.001)], and PeakDr [paired t(104)= -4.86, p<.001)] (see Table 2.1). In our full sample, 56.2% reported no past year use of any other substance by T2 and the next most widely used substance at T2 was cocaine with 30 of the 105 subjects reporting past year use, 20 of whom reported $\leq$ 5 times total use in the last year. When it comes to cases of alcohol dependence in our sample, 11.5% reported alcohol use disorder at T2.

Neurocognitive effects

The addition of neurocognitive measures in Step 2 (main effects) accounted for an additional 10.7% variance in DPDD change (p= .03; Table 2.2) and an additional 16.4% variance in Binge change (p= .001, Table 2.3), over and above the Step 1 covariates (sex, T1 age, follow-up duration). The addition of neurocognitive measures accounted for an additional 5.2% variance in PeakDr change (p= .27) and an additional 6.2% variance in DD change (p= .14), although they did not reach our significance threshold (see Table 2.4 and Table 2.5). The addition of Step 3 (interactions with sex) did not substantially or significantly add to variance accounted for in any alcohol use outcome model (ps>.05). No multicollinearity was observed between the primary predictors, as none of the four neurocognitive domains were highly correlated (rs < .6).

With respect to individual variable effects within Step 3, only one neurocognitive measure significantly interacted with sex to predict alcohol outcomes - the interaction between sex and T1 verbal memory was found to predict change in PeakDr at T2 [females: β= .317, p= .03; males (reverse coded): β= -0.426, p= .03; Table 2.4]. Given the limited support for the interactions across outcomes, only main effects derived from Step 2 will be reported and interpreted below.

Within Step 2 of the models, inhibition/cognitive flexibility at T1 was observed to positively predict change in DPDD (Table 2.2; Figure 2.1) and PeakDr (Table 2.4 and Figure 2.5) at T2. Verbal memory at T1 was found to positively predict change in Binge (Table 2.3; Figure 2.2) and DD (Table 2.5) at T2. T1 visuospatial ability (Table 2.3; Figure 2.3) and working memory (Table 2.3; Figure 2.4) were found to negatively predict change in Binge at T2. These results were observed while controlling for Step 1 covariates. No other significant effects were observed at Step 2 for all alcohol outcomes.

A trend-level interaction between T1 working memory and youth income was suggestive of predicting change in Binge (β= .849, *p*=.05, CI: .000-.317), and no other significant interaction between follow-up youth income and neurocognitive abilities at T1 was observed. All main effects reported above were maintained when youth income was included as a covariate in the regression models. Results of the regression analyses controlling for T1 alcohol use (versus change scores) were largely consistent with the results mentioned above except for the main effects of verbal memory on Binge and working memory on DPDD and Binge, which fell below the p<.05 significance threshold in these models.

Discussion

The current study investigated whether neurocognitive task performance at maximum alcohol drinking in late adolescence (T1) could predict a change in alcohol use behaviors 3-7 years later (T2). Results suggest that executive functioning overall is a meaningful predictor of change in alcohol use outcomes. Including measures of visuospatial ability, working memory, verbal memory, and inhibition/cognitive flexibility in the models accounted for significant amounts of variance in the outcomes of changes in drinks per drinking day and binge episodes, beyond that of age and sex. Given that both outcomes are characterized by quantity of alcohol consumption in a single occasion, our results suggest that capacity in these neurocognitive domains may relate to one's ability to regulate alcohol consumption while in a drinking episode.

Our hypothesis that better performance in the four neurocognitive domains at T1 will predict decreases in alcohol use behaviors over follow-up was partially confirmed. Better visuospatial ability and working memory performance in late adolescence were found to predict reductions in binge drinking, and better working memory had a moderate effect (β= -.24) on

reductions in drinks per drinking day, 3-7 years later. Together, this suggests that youths exhibiting greater functioning in these domains at T1, at a time of maximal alcohol use, get better in modulating their alcohol consumption per drinking occasion into adulthood. Consistent with this theory, weak working memory in adolescence is hypothesized to make it more difficult to process complex information and control impulsive urges, increasing the risk of later problematic alcohol use.[25] Similarly, others have observed an association between reduced working memory from alcohol use and greater number of drinks per drinking day in adults, controlling for baseline working memory,[24] suggesting that alcohol induced declines in working memory may impair one's ability to regulate later alcohol consumption. However, when regression models were run controlling for T1 drinking, only the effect of visuospatial ability was retained from these results indicating that performance in the visuospatial domain may uniquely be able to predict who later reduces problematic alcohol use, regardless of their severity of drinking at the point of maximum use.

In the case of inhibition/cognitive flexibility and verbal memory, better performance in these domains at T1 were found to predict an increase in later alcohol use behaviors. Specifically, better inhibition/cognitive flexibility at maximum drinking predicted an increase in drinks per drinking day and peak drinks, and better verbal memory at maximum use predicted an increase in binge episodes and drinking days at T2. Typically, low level of inhibitory control and poorer verbal memory have been associated with greater drinking, especially binge consumption, in cross-sectional studies with young adults.[41,42] Although our results are seemingly inconsistent with these studies, it should be noted that the current sample generally reduced their alcohol use behaviors from T1 to T2 such that the predicted increases in alcohol use behaviors observed at T2 still fall under the National Institute on Alcohol Abuse and Alcoholism heavy drinking

limit.[43] Hence, overall better performance in these two neurocognitive domains at T1 seems to be associated with non-problematic drinking at follow-up. Another possible explanation for this could be that youth exhibiting better inhibition/cognitive flexibility and verbal declarative memory delayed increasing their alcohol use behaviors until later in life (captured in T2), at which point they were able to gauge the level of alcohol use that did not impede performance in their day-to-day life.

Only in the case of verbal memory did we find sex to be a consistent moderator of alcohol use outcomes. Specifically, females with better verbal memory at T1 exhibited a greater increase in peak drinks from T1 to T2, whereas males with better verbal memory ability showed a greater decrease in peak drinks from T1 to T2. Verbal memory may interact with sex on drinks per drinking day and drink days as well, although these effects did not reach our statistical threshold. Despite this positive relationship between verbal memory and peak drinks in females, it should be noted that the means for all drinking outcomes in females are still lower than that of males at both timepoints and show an overall reduction as compared to T1 levels (e.g., peak means at T1: 7.91 females, 11.44 males; peak means at T2: 5.84 females, 9.15 males). Thus, this interaction effect appears to represent small, yet still significant, increases in drinking for females with higher verbal memory scores. However, our data on this increasing alcohol use behavior among young adult females is in line with the alarming growing evidence that over the years women have narrowed the gender gap in alcohol consumption especially when it comes to problematic drinking, and this closing gap is most noticeable among the young adult population.[44,45]

This study has several strengths and limitations. A strength of our study lies in analyzing key neurocognitive and alcohol use markers during the important developmental shift from late

adolescence into young adulthood. Given this is a secondary analysis outside the main aims of the parent study, missing data on our variables of interest resulted in a relatively small study sample (*n=105*) and could have biased the sample towards less problematic alcohol use. However, the presence of data on several drinking variables indexing the amount and frequency of alcohol consumption allowed for a more nuanced examination of alcohol use behaviors. Also, the disproportionate makeup of our sample which includes predominantly Non-Latinx/Hispanic White participants restricted us from exploring any moderating roles of race/ethnicity in the relationship between neurocognition and alcohol use. Future studies will benefit from increased sampling of diverse youth populations to better understand and inform tailoring of interventions. Lastly, it should also be noted that although longitudinal, the acquired data is correlational which prohibits inferences of causality. For instance, it is possible that the changes in alcohol use behaviors observed are representative of additional, unmeasured variables such as advanced careers or other achievements that impose alcohol consumption limits on the participants. However, we did not observe significant moderating effects of youth income at T2, at least partially discounting that hypothesis. Further studies are needed to understand the role of socioeconomic status, race, and ethnicity as potential moderators of neurocognitive predictors of later drinking behavior.

Conclusion

This report is the first to our knowledge to investigate the role of neurocognitive markers at maximum alcohol use in late adolescents as predictors of later alcohol use. The investigation of neurocognitive abilities as predictors of change in later alcohol use is critical for the identification of risk or protective factors for future problematic alcohol use. This knowledge can

aide in the development of more efficacious prevention and intervention approaches (e.g., working memory training interventions)[24,46] and inform policy recommendations by providing insights on the outcomes of so-called "normative" substance use in adolescence/young adulthood.

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Table 2.1. Sample demographic characteristics at time point 1 (T1) and follow-up (T2) *(n= 105*)

Variables	Time Points	
	Mean (SD) or *n* (%)	
	Time Point 1 (T1)	**Follow-Up (T2)**
Age (years)	19.20 (1.6) Range: 14.67-24.69	23.28 (1.4) Range: 20-28
Follow-Up Duration (years)	4.1(1.0) Range: 3-7	
T2 Income	_____	$26,220 ($25,710)
Sex		
Male	62 (59%)	_____
Female	43 (41%)	_____
Race		
White or Caucasian	70 (66.7%)	_____
Other (*Not White*)	35 (33.3%)	_____
Ethnicity		
Latino/Hispanic	22 (21%)	_____
Non-Latino/Hispanic	81 (77.1%)	_____
Unknown	2 (1.9%)	_____
Alcohol Use (previous year)		
Drinks per Drinking Day	6.37 (3.8)	2.99 (1.9) ***
Binge Days	48.18 (70.5)	25.76 (47.1) ***
Drink Days	100.14 (121.6)	123.79 (109.6)
Peak Drinks	9.99 (5.8)	7.79 (5.1) ***
Neurocognitive Performance at Maximum Use		
LDFR	.28 (.9)	_____
Block	12.60 (2.0)	_____
Digit	10.86 (2.5)	_____
CWI	12.14 (2.2)	_____

(*) $p < .05$; (***) p<.001; LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility)

Table 2.2. Linear regression results for Drink Per Drinking Days- DPDD (*n= 105*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	***β***	**Sig.**	**95% CI (B)**	**B (SE)**	***β***	**Sig.**	**95% CI (B)**	**B (SE)**	***β***	**Sig.**	**95% CI (B)**
Step 1- Covariates												
T1 Age	-.08(.20)	-.04	.71	-.47-.32	-.14(.20)	-.08	.48	-.53-.25	.05(.20)	-.03	.81	-.45-.35
Follow-Up Duration (Years)	-.28(.32)	-.10	.37	-.90-.34	-.42(.33)	-.15	.21	-1.1-.23	-.47(.34)	-.17	.17	-1.15-.20
Sex	.37(.58)	.06	.52	-.76-1.5	.21(.57)	.04	.71	-.91-1.33	-.14(4.70)	-.02	.98	-9.35-9.08
Step 2- Main Effects												
LDFR					.26(.32)	.05	.43	-.39-.90	-.31(.43)	-.11	.47	-1.1-.53
Block					-.21(.16)	-.15	.20	-.52-.10	-.07(.25)	-.05	.78	-.56-.42
Digit					-.26(.13)	-.24	.06	-.52-.01	-.37(.14)	-.35	.01*	-.64-(-.10)
CWI					.31(.13)	.24	.02*	.05-.56	.36(.16)	.28	.03*	.03-.68
Step 3- Interactions												
CWI * Sex									-.04(.27)	-.08	.90	-.58-.51
LDFR*Sex									1.3 (.68)	.27	.06	-.03-2.7
Block*Sex									-.14(.32)	-.31	.70	-.77-.48
Digit* Sex									.20(.15)	.41	.18	-.09-.51
R^2		.01				.12				.19		
R^2 *Change*		.01				.11				.07		
***F* for change in R^2**		.44				2.96*				1.95		

(*) $p < .05$; LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility)

Table 2.3. Linear regression results for Binge Drinking (*n= 105*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	***β***	**Sig.**	**95% CI(B)**	**B (SE)**	***β***	**Sig.**	**95% CI(B)**	**B (SE)**	***β***	**Sig.**	**95% CI(B)**
Step 1- Covariates												
T1 Age	-5.36(4.20)	-.14	.20	-14-2.86	-6.65(4.0)	-.18	.10	-15-1.20	-6.12(4.20)	-.16	.14	-14.30-2.03
Follow-Up Duration (Years)	5.55(6.59)	.09	.40	-7.4-19	.35(6.60)	.01	.95	-12.60-13.27	.54(6.87)	.01	.94	-13-14.0
Sex	-6.28(12)	-.05	.60	-30-17.30	-11.2(11.5)	-.09	.33	-33.85-11.39	-131(92)	-1.06	.16	-313-50.70
Step 2- Main Effects												
LDFR					19.20(6.60)	.309	.004*	6.31-32	17(8.60)	.27	.05	.004-34
Block					-8.85(3.2)	-.297	.01*	-15 - (-2.65)	-12 (5.08)	-.41	.02*	-22-(-2.30)
Digit					-5.88(2.9)	-.26	.02*	-12 (-.09)	-6 (2.90)	-.30	.046*	-12-(-.09)
CWI					1.82(2.6)	.067	.49	-3.28-6.92	1.98(3.20)	.07	.54	-4.37-8.34
Step 3- Interactions												
CWI* Sex									1.72(4.80)	.18	.72	-7.92-11
LDFR*Sex									10(13.80)	.10	.47	-17-37
Block*Sex									7(6.60)	.75	.29	-5.94-20
Digit *Sex									.67(2.98)	.06	.83	-5.44-6.77
R^2		.04				.21				.24		
R^2 Change		.04				.16				.04		
***F* for change in R^2**		1.53				5.02*				1.08		

(*) $p < .05$; LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility)

Table 2.4. Linear regression results for Peak Drinks (*n= 105*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	***β***	**Sig.**	**95% CI(B)**	**B (SE)**	***β***	**Sig.**	**95% CI(B)**	**B (SE)**	***β***	**Sig.**	**95% CI(B)**
Step 1- Covariates												
T1 Age	-.31(.32)	-.11	.34	-.95-.33	-.37 (.33)	-.13	.26	-1.01-.28	-.21 (.33)	-.07	.54	-.87-.45
Follow-Up Duration (Years)	-.24(.51)	-.05	.64	-1.24-.76	-.30 (.53)	-.07	.57	-1.36-.75	-.36 (.55)	-.08	.52	-1.45-.73
Sex	.15(.93)	.02	.87	-1.66-1.97	.06(.94)	.01	.95	-1.80-1.91	.61(7.50)	.07	.94	-14 -15.50
Step 2- Main Effects												
LDFR					-.03 (.54)	-.01	.96	-1.08-1.03	-1.11(.70)	-.23	.12	-2.48-.27
Block					-0.18(.26)	-.08	.50	-.69 -.34	.16 (.41)	.07	.69	-.65-.97
Digit					-.22(.22)	-.13	.33	-.66-.23	-.40(.23)	-.23	.08	-.84 -.05
CWI					.43(.22)	.21	.045*	.01-.85	.45(.26)	.22	.09	-.07 -.97
Step 3- Interactions												
CWI * Sex									.06(.40)	.22	.09	-.07-.97
LDFR*Sex									2.48(1.12)	.32	.03*	.30-4.68
Block*Sex									-.41 (.54)	-.58	.44	-1.46-.64
Digit* Sex									.30(.22)	.38	.18	-.14-.75
R^2		.01				.06				.14		
R^2 Change		.01				.05				.08		
***F* for change in R^2**		.32				1.36				2.02		

(*) $p < .05$; LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility)

Table 2.5. Linear regression results for Drink Days (*n= 105*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	***β***	**Sig.**	**95% CI(B)**	**B (SE)**	***β***	**Sig.**	**95% CI(B)**	**B (SE)**	***β***	**Sig.**	**95% CI(B)**
Step 1- Covariates												
T1 Age	-24 (9)	-.30	.01*	-42-(-6.96)	-28(9)	-.34	.002*	-45-(-10)	-27 (9)	-.33	.003*	-45-(-9)
Follow-Up Duration (Years)	.99 (14)	.01	.94	-26-28	-7.21(14)	-.06	.62	-36-21	-5.68(15)	-.04	.70	-35-24
Sex	-18 (25)	-.07	.49	-68 -32	-29(26)	-.11	.26	-79-22	-112(199)	-.42	.57	-504-279
Step 2- Main Effects												
LDFR					30(15)	.22	.04*	1.34-59	13(19.20)	.10	.50	-25-51
Block					-.81(7)	-.01	.91	-15-13	-4.65(11)	-.07	.68	-27-17
Digit					-7.73(5)	-.16	.15	-18-2.76	-8.50(6)	-.17	.17	-21-3.70
CWI					2.40(6)	.04	.68	-9.05-14	6.71(7)	.11	.35	-7.25-21
Step 3- Interactions												
CWI *Sex									-6.24(10)	-.30	.54	-26.50-14
LDFR*Sex									51(30)	.23	.10	-9.03-110
Block*Sex									8.20(15)	.40	.58	-20.50-37
Digit *Sex									3.83(6)	.17	.52	-7.86-15.50
R^2		.09				.15				.21		
R^2 ***Change***		.09				.06				.05		
***F* for change in R^2**		3.42*				1.78				1.51		

(*) $p < .05$; LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility)

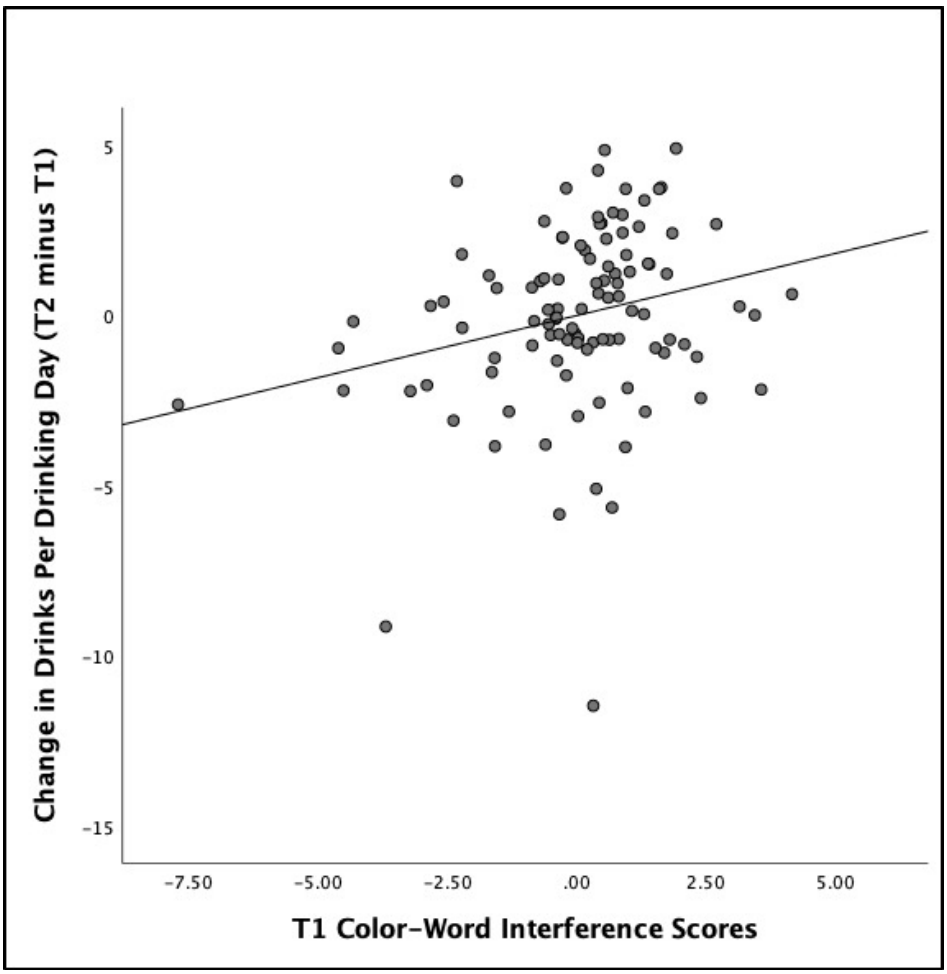

Figure 2.1. Partial regression plot showing the significant positive relationship between inhibition/cognitive flexibility at maximum drinking (T1 Color-Word Interference scores) and change in drinks per drinking day between T1 and T2

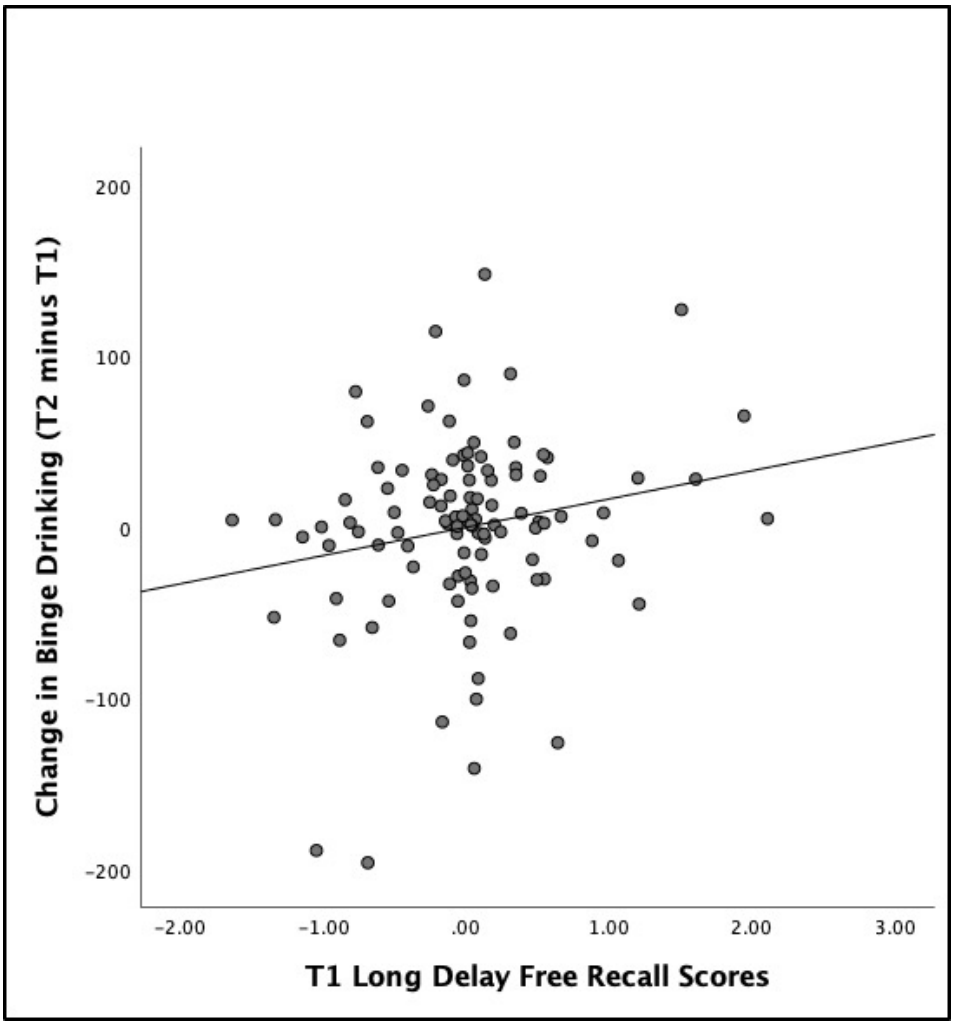

Figure 2.2. Partial regression plot showing the significant positive relationship between verbal memory at maximum drinking (T1 Long Delay Free Recall scores) and change in binge drinking between T1 and T2

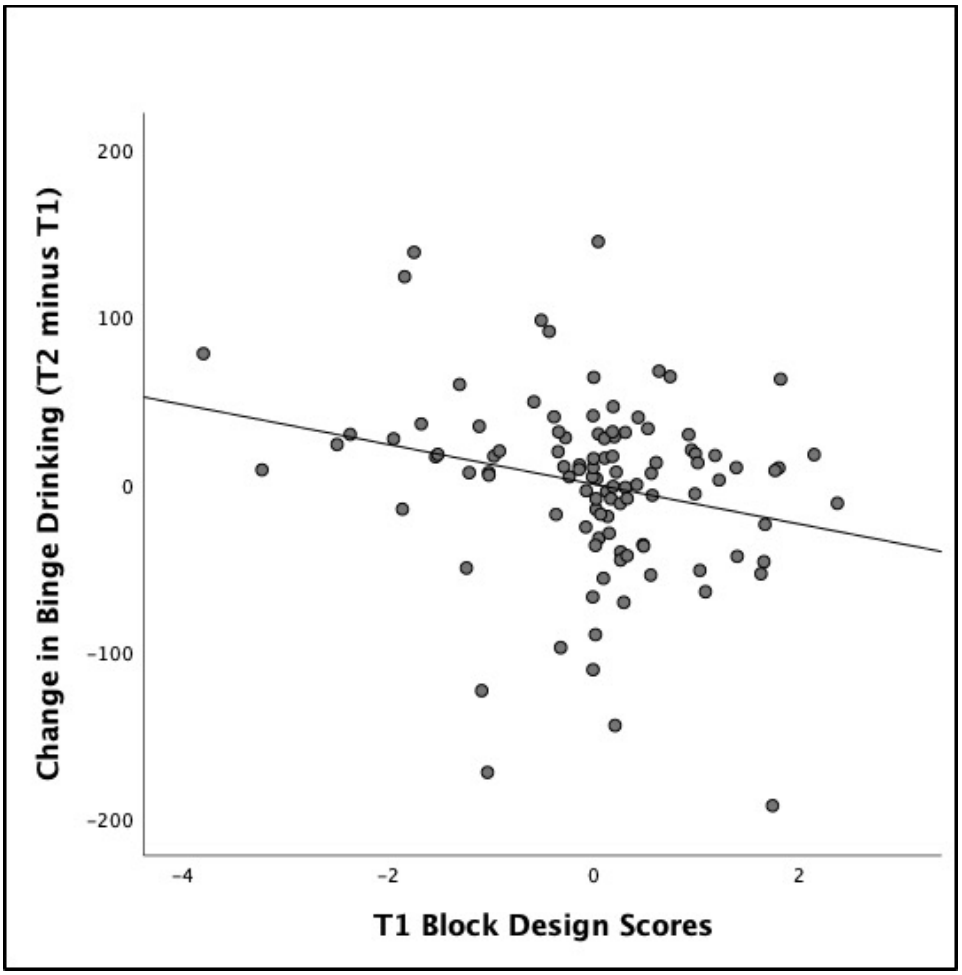

Figure 2.3. Partial regression plot showing the significant negative relationship between visuospatial ability at maximum drinking (T1 Block Design scores) and change in binge drinking between T1 and T2

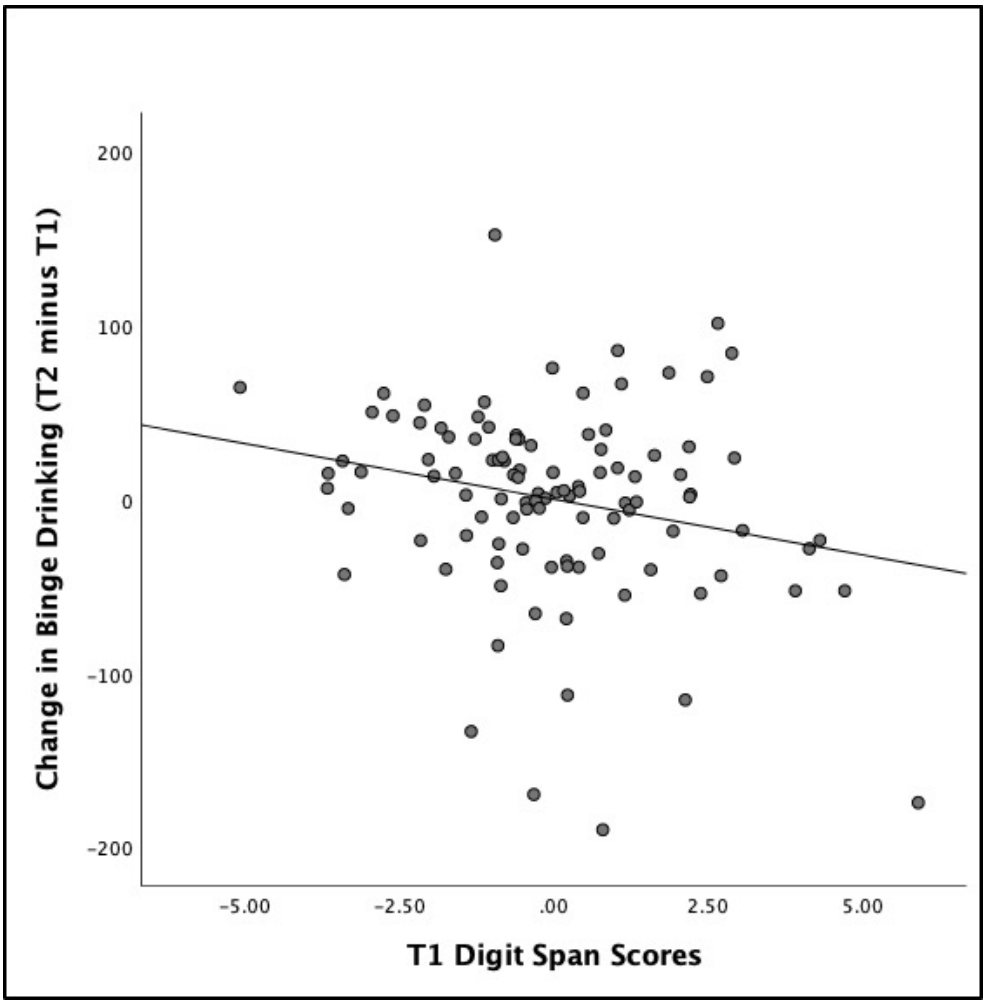

Figure 2.4. Partial regression plot showing the significant negative relationship between working memory at maximum drinking (T1 Digit Span scores) and change in binge drinking between T1 and T2

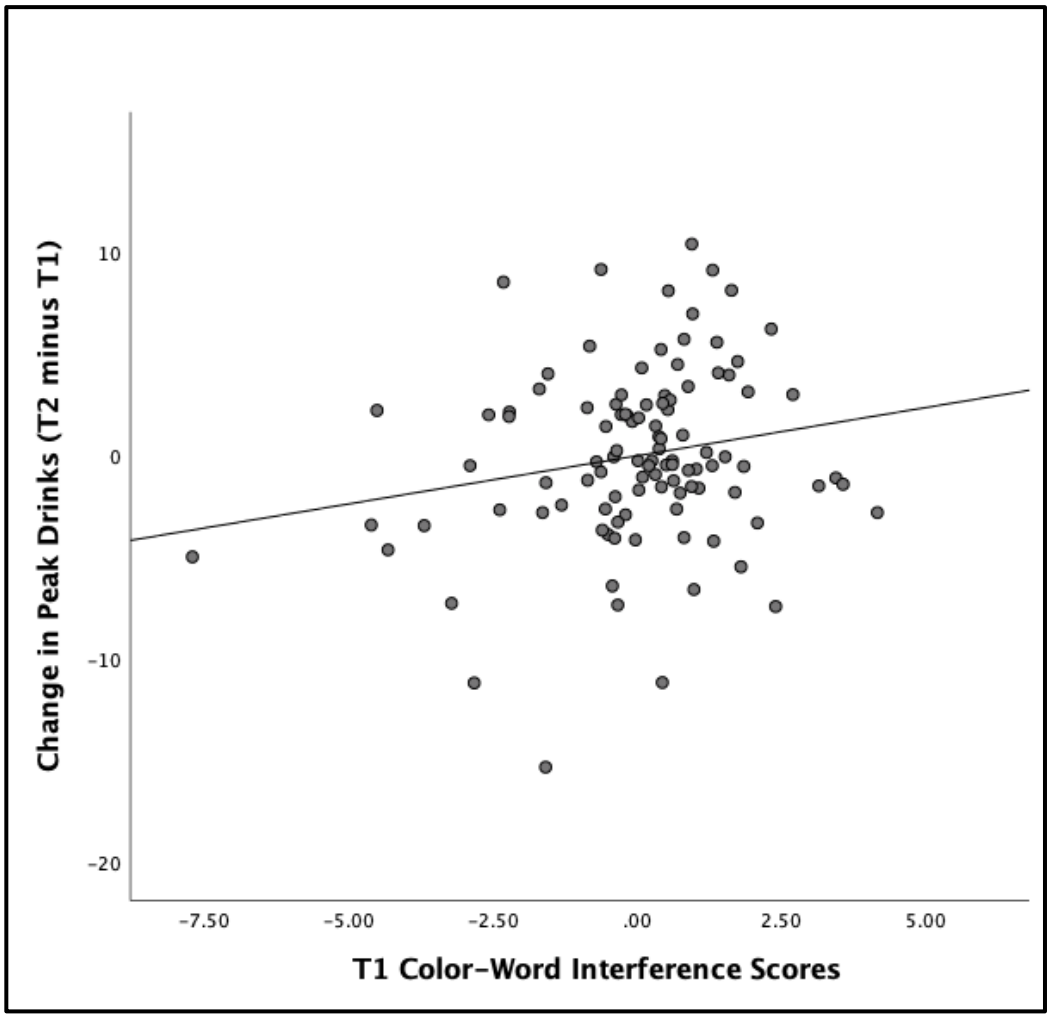

Figure 2.5. Partial regression plot showing the significant positive relationship between inhibition/cognitive flexibility at maximum drinking (T1 Color-Word Interference scores) and change in peak drinks between T1 and T2

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CHAPTER 3: Predictive Effects of Neurocognitive Markers during Maximum Substance Use in Late Adolescence on Changes in Later Substance Use Frequency

Abstract

Background: The influence of substance use (including alcohol, cannabis, nicotine) on later neurocognitive functioning has been robustly researched in the youth population, but the reverse direction of whether neurocognition, post-substance use onset and specifically at peak use, predicts changes in later use behaviors has been minimally investigated.

Objective: Investigate neurocognitive task performance during maximum substance use in late adolescence as predictors of use behaviors 3-7 years later.

***Methods*:** Secondary analyses (*n=71*) were conducted on a longitudinal dataset involving adolescents (12-13 years-old) who were followed for 16 years. Time 1 (T1) was defined as the year with the individuals' maximum substance (alcohol, cannabis, and/or nicotine) frequency index score within the first ten years of the study. Time 2 (T2) was defined as the individuals' first available data entry on substance use, 3-7 years after T1. Hierarchical linear regression models predicting change in follow-up overall use frequency index scores, and individual substance (alcohol, cannabis, and nicotine) use outcomes, were estimated. For follow-up analyses exploring the relationships between neurocognition and substance use within 3 groups of one-, co- and tri-substance users independently, overall substance use models for each group were run separately. If any main effects were observed, then individual substance use models were run for further break down. All models included inhibition/cognitive flexibility, visuospatial ability, verbal memory, working memory, and their interactions with sex, while covarying for age at T1 and follow-up duration.

***Results*:** Better inhibition/flexibility at T1 predicted increases in later nicotine (cigarette) use frequency with borderline significance (β= .24; *p*= .058) across the full sample (*n= 71*). In the exploratory follow-up analyses with the co-use group only (*n= 27*), better T1 visuospatial ability predicted increase in later overall use frequency index scores with borderline significance (β= .44; *p*= .055) and better working memory at T1 significantly predicted a reduction in overall substance use frequency at T2 (β= -.51; *p*= .018).

***Conclusion*:** Findings from our investigation across full sample and follow-up analyses within one-, co- and tri-substance use groups independently suggest neurocognitive abilities during maximum substance use in late adolescence are useful as predictors of change in use behaviors over time.

Keywords: Substance Use, Cannabis, Nicotine, Alcohol, Neurocognition, Late Adolescence, Predictor, Regression

Introduction

The period of adolescence through young adulthood is marked by the emergence of puberty, and substantial risk-taking behaviors such as experimentation with drugs and alcohol.[1,2] In addition to alcohol, cannabis and nicotine are the two most used substances by adolescents.[3-9] The high prevalence of concurrent use ($\geq$ 2 substances on different occasions) and/or simultaneous use ($\geq$ 2 substance administrations together or back to back on the same occasion) of nicotine with alcohol and cannabis, during the teenage developmental years has been reported by many epidemiological studies over the last two decades.[4,10-14] Reports have associated nicotine use (tobacco products) with increased probability of subsequent alcohol[7] and cannabis use onset,[15] and with the legalization of cannabis products across the US (for both medical and recreational purposes), there is higher likelihood of cannabis co-use with these substances in the youth population.[4]

A high school survey reported that 88% students who use cigarettes also use alcohol. Tobacco use has been linked to predicting subsequent drinking initiation. Smoking onset prior to the age of 17 years has been associated with a greater risk of developing an alcohol use disorder.[7] Data from the 2014 National Survey on Drug Use and Health (NSDUH) suggests that youths (ages 12 to 17) who reported past month cannabis use were 8.9 times more likely to report past-month smoking, 9.9 times more likely to report past month illicit drugs use and 15.8 times more likely to report past-month heavy use of alcohol.[16] According to the 2017 Monitoring the Future (MTF) National Survey reports, among 12th graders 20% endorsed simultaneous use of cannabis and alcohol in the past year.[4,11] More recently, 2021 MTF survey reports on past 30 days use among 12th graders revealed current use of alcohol (25.8%), cannabis (19.5%) and nicotine products including electronic vapes (10.5%), which is more than twice the percentage among 8th

graders (7.3% alcohol, 4.1% cannabis, and 4.8% nicotine products).[17] In the case of young adult population (ages 19-30), MTF reported some noteworthy significant changes in alcohol, cannabis and nicotine use in the year 2021.[18] Among young adults, cannabis use in the past 12 months (42.6%) and past 30-days (28.5%) reached an all-time high since 1988, binge drinking (5+ drinks on one occasion for consecutive 2 weeks) reported by 32% in 2021 was an significant increase from 2020, and past 30-day prevalence of nicotine vaping approximately increased 3 times between 2017 and 2021.[18]

Given that most teenagers begin using one or more of these substances during sensitive neurodevelopmental period in adolescence and young adulthood,[3-9] their use places them at high risk of developing substance use disorder later in life.[4] The structural and functional development of the prefrontal cortex is crucial for efficient cognitive control, also regarded as executive control or ECF.[1,19] Cognitive control influences memory, emotion, abstract reasoning, and is essential for adaptive responses and goal-directed behavior.[20,21] Working memory, verbal memory, visuospatial ability and inhibition/cognitive flexibility are all vital components of ECF. These neurocognitive abilities develop throughout adolescence and into young adulthood, exhibiting prolonged development[22] and characterize mature cognition.[20]

The earlier development of ventral striatum versus prefrontal projections in adolescence aligns with the heightened motivation and reward seeking nature in adolescents and the increased probability to engage in risky behaviors.[1,23] The tendency for many youth to experiment with drugs and alcohol during this sensitive period can have long term consequences because exposure to potential toxins such as alcohol, cannabis, tobacco products, and other illicit drugs can interfere the continued maturation of the pre-frontal cortex and endanger the linear increase in cognitive control capacities from childhood to adulthood.[1,24]

Hence, the influence of substance use on neurocognition has been robustly studied over many years,[1,25-29] with studies reporting various changes in cognitive abilities because of teenage substance use.[1,25,26,30] One such longitudinal study collected data from 662 youths across 10 years from 2003-2013, to explore the use of multiple substances (which included cigarette, cannabis, alcohol and illicit drugs) and examine transitions to co-use and poly-use as participants step into young adulthood from adolescence.[3] The study had three distinct substance use profiles: alcohol only, co-user (alcohol plus cannabis), and poly-user (alcohol, cannabis, cigarette and other drugs). Results revealed that the probability to remain a poly-user was the most stable between waves and most transitions happened from co-use class to poly-use class,[3,31] suggesting that as teenagers emerge into young adulthood, most transition from co-use of substances to poly-use.[3] Such early onset of polysubstance use likely has more profound harmful consequences on the developing brain and significantly affect memory, inhibition and other executive abilities.[25]

Even though much research has investigated the effect of substances on neurocognition, very few studies have investigated the reverse direction where cognitive markers are looked at as potential factors to predict risk and/or pattern of substance use over time.[32-36] Even more limited are longitudinal research studies that have investigated the influence of neurocognitive ability on drug and alcohol use pattern when adolescents are already engaged in substance use. Previously we addressed and focused on this scarcely researched area with our scoping review in Chapter 1 and our investigation of neurocognitive markers prospectively predicting alcohol use outcomes in Chapter 2 of this dissertation, but it is evident from youth substance use reports that alcohol is seldom used in isolation and the co- or tri-use of alcohol with cannabis and nicotine is well-documented in this population.[3-9] Hence, in this current investigation we examined the

predictive power of vital executive cognitive markers (working and verbal memory, visuospatial ability, inhibition/cognitive flexibility) on overall use of these three substances together and independently, to obtain the full picture of how neurocognition may influence later use behaviors.

We focused on neurocognitive functioning at the age of maximum use frequency of alcohol, cannabis, and/or nicotine (cigarette smoking) to determine if cognitive performance under maximum influence of substance(s) predicts changes in substance use behaviors (increases or decreases) over time. Studies have yet to look at the predictive utility of cognitive functioning during peak use of potential toxins like alcohol, cannabis, and nicotine which are known to interfere with neuronal communication and affect brain structure.[1,25] The assessment of neurocognitive functioning at the time of peak substance use is important as many adolescents concurrently use these substances,[4] and past-month(s) peak use has been significantly associated with high motivations to change (reduce) substance use behavior.[37] High motivations can lead to better odds of changes in alcohol/cannabis/nicotine use patterns and effective cognitive abilities can play an integral role in acting on motivations to regulate substance use behaviors. Thus, it is important for our analyses to evaluate neurocognitive capacity at the maximum substance use stage in late adolescence as the main objective of our aim is to predict changes in later use behaviors.

Based on observations reported in the existing (but limited) literature on the reverse direction[32-36] and the peak substance use-motivation association,[37] we hypothesized that better performance in the neurocognitive measures of memory, inhibition, and cognitive flexibility at time of maximum substance use will predict greater reductions in overall substance use at follow-up. In the current study, we also examined sex as an exploratory secondary predictor

given that sex/gender substance use differences are consistently reported in epidemiological research,[38-41] and physiology studies (including blood alcohol concentration)[42]. We tested for potential interactions between sex and neurocognitive markers in predicting changes in later substance use (alcohol, cannabis, and/or nicotine).

Materials and Methods

Participants and procedures

We performed a secondary analysis on data from the larger longitudinal substance use and neuroimaging study "Youth At Risk" (YAR) (NIAAA R01 AA13419). The YAR study recruited adolescents ages 12-14 years-old at baseline and followed them for 16 years with annual measures on neuropsychology and neuroimaging, and 6-month measures on substance use, psychiatric diagnoses, and changes in general health/social functioning. Inclusion criteria for the parent study (YAR) were adolescents between the ages of 12-14 years with no underlying mental health conditions or psychiatric disorders, ample English language comprehension, and ≤ to one lifetime alcohol use experience.

Secondary analysis timepoints and eligibility criteria

We defined the first time point (T1) as the year of each participant's maximum substance use during the first 10 years of follow-up (ages 13-25 years). T1 was determined by first calculating each subject's overall substance use (alcohol, cannabis, and/or nicotine) frequency index scores (a sum of frequencies for each substance) for each assessment year and then selecting the year with maximum index score within the first ten years. We defined the second time point (T2) as the first available report of overall substance use (alcohol, cannabis, and/or nicotine) acquired 3-7 years after T1 (ages 21-27 years) to account for the overlap in the years

and ages between the two time points. [see *Measures* section for details on operationalization of substance use variables and index scores for both timepoints].

Participants were eligible for the current study if they reported any alcohol, nicotine (cigarette smoking), and/or cannabis use during the T1 time period (ages 13-25 years) and had available neurocognitive assessment data at T1. Participants were excluded if their substance use data was missing at either timepoint. Out of the final baseline sample of 249 youths, data from 71 eligible participants were included in the current secondary analysis. The final sample of 71 participants matched the baseline sample in terms of sex, race, and ethnicity distributions.

Measures

Demographics

Demographic information including age, sex, race, ethnicity, and family history were self-reported by participants and were further verified by biological parent(s) or a guardian.

Substance use

To assess the pattern, frequency and severity of alcohol and other substance use, participants were administered the established structured interview- Customary Drinking and Drug Use Record (CDDR) at both time points.[43-45] The number of substance use days for alcohol, nicotine (cigarettes), and cannabis reported over the previous 3 months at each timepoint was used to allow for cross substance use frequency comparability. For the main analyses, we looked at the overall combined use frequency of these three substances by computing an index variable for each participant.

To evaluate the predictive effect of neurocognition on changes in later substance use behaviors, four substance use change outcomes (T2 minus T1) were investigated in our analysis models: 1) change in overall substance use (alcohol, cannabis, and/or nicotine) frequency index

scores; 2) change in alcohol use frequency (drink days in past 3 months); 3) change in cannabis use frequency (number of days used in past 3 months); and 4) change in nicotine (cigarette) use frequency (number Of days smoked in past 3 months). Positive values on these change scores thus represent increases in substance use behaviors from T1 to T2, whereas negative values represent reductions in use behaviors at T2 compared to T1.

Since not everyone in the sample reported use of all three substances, the index score represented the use of any singular or combined substance. Therefore, to better understand our sample's (*n=71*) substance use profiles, we created 3 groups: I) tri-substance use group (reported use of all three substances at T1), II) co-substance use group (reported use of two of the three substances at T1, in any combination), and III) one-substance use group (reported use of one of the three substances at T1). These grouping were used in exploratory follow-up analyses as described below.

Neurocognitive task domains

A comprehensive neuropsychological battery was administered to participants to assess their neurocognitive functioning which included the California Verbal Learning Test (CVLT)-Children's Version[46] and adult versions (CVLT-II; Wechsler, 1997);[47,48] the Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference (CWI) subtest;[49] Wechsler Intelligence Scale for Children- Third Edition (Wechsler, 1991) and WAIS-IV Digit Span subtests;[43,50] and Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and Wechsler Adult Intelligence Scale- Fourth Edition (WAIS-IV) Block Design subtests.[43,51] Adult versions of applicable tests were administered at timepoints in which participants were $\geq$ 18 years-old.

The primary predictors of interest for the current secondary analyses were neurocognitive task scaled scores (age normed) from four domains: 1) CVLT Long Delay Free Recall (LDFR) scaled scores as a measure of verbal memory; 2) WASI and WAIS-IV Block Design scaled scores as a measure of visuospatial ability; 3) WAIS-IV Digit Span scaled scores as a measure of working memory; and 4) D-KEFS Color-Word Interference (CWI) Condition 4-Inhibition/Switching completion time scaled scores as a measure of cognitive flexibility and inhibition.[49,52]

Statistical analyses

We used SPSS (version 26) to conduct descriptive, univariate, and multivariate analysis followed by post-hoc investigations.

Main Analysis

First, to examine neurocognitive markers as predictors of change in overall substance use (alcohol, cannabis, and/or nicotine) frequency index scores in the full sample (N=71), a hierarchical linear regression model was estimated with T1 age, follow-up duration (T2 minus T1 difference in years), and sex entered in the first step, T1 neurocognitive scores from four cognitive domains (verbal memory, working memory, visuospatial ability, inhibition/cognitive flexibility) entered in the second step, and interactions between sex and T1 neurocognitive scores entered in the third step. After running the general model estimating overall substance use change outcome, we ran three additional separate models to estimate the effects of each of the three substances independently: alcohol, cannabis, and nicotine use frequency change outcomes (T2 minus T1).

Follow-up analyses by substance use groups

Potential mean differences in T1 neurocognitive performance across the three substance use groups (tri-, co-, and one-substance use) were tested by running a univariate analysis of variance (One-Way ANOVA) while controlling for sex and baseline age. To explore the relationships between neurocognitive performance and substance use within the three substance use groups independently, we ran overall use hierarchical linear regression models with each sample: one-, co- and tri-users (using the same primary neurocognitive predictors, covariates and substance use change outcomes). If any main effects were observed, then individual substance use outcome models were run for further break down.

Results

Description of sample

Age at maximum substance use (T1) was between 17.04-24.69 years with a mean age of 20.19 years. The age range at follow-up (T2) was between 20.40-28.01 years with a mean age of 24.06 years. Our sample was predominantly White non-Hispanic males (70.4% White, 71.8% males), and the low representation of Non-White race/ethnicity precluded using race/ethnicity as a secondary predictor in our models. There was no significant difference in T1 neurocognitive task scaled scores (age normed) at maximum use stage, in all four domains, between males and females [Block Design: t(69)=.53, p=.599; LDFR: t(69)=.57, p=.571; Digit Span: t(69)=1.49, p=.141; CWI: t(69)=1.66, p=.101]. Among self-reported substance use between the two time points, there was a significant decrease in use frequency of all three substances at T2: Alcohol [paired t(70)= -3.14, p=.002)], Cannabis [paired t(70)= -3.65, p<.001)], and Nicotine [paired t(70)= -4.74, p<.001)] (see Table 3.1). In the full sample, 54.9% reported no past year use of any

other substance by T2 and the next most widely used substance at T2 was cocaine with 23 of the 71 subjects reporting past year use, 12 of whom reported ≤ 5 times total use in the last year. When it comes to cases of alcohol and drug dependence in our sample, 15.4% reported alcohol use disorder and 14.1% reported substance use disorder at T2.

Neurocognitive effects

In the primary regression models estimating changes in use frequency across the full sample (*n=71*), the addition of neurocognitive measures in Step 2 (main effects) accounted for an additional 6.2% variance in overall substance use (alcohol, nicotine, and/or cannabis) frequency index scores change (p= .33; Table 3.3), 2.7% variance in alcohol use frequency change (p= .74, Table 3.4), 4.1% variance in cannabis use frequency change (p= .57; Table 3.5), and 5.5% variance in nicotine (cigarette) use frequency change (p= .38; Table 3.6), over and above the Step 1 covariates (sex, T1 age, follow-up duration), although they did not reach our significance threshold (p<.05). The addition of Step 3 (interactions with sex) also did not substantially or significantly add to variance accounted for in any of the substance use outcome models (ps>.05). No multicollinearity was observed in the regression models as none of the four neurocognitive domains (primary predictors) were highly correlated (rs < .6).

Within Step 2 of the general model with the full sample, only inhibition/cognitive flexibility at T1 was observed to positively predict change in overall substance use (alcohol, nicotine, and/or cannabis) frequency index scores with approaching significance (β=.22; p =.088; Table 3.3), while controlling for Step 1 covariates. No other significant predictive effect of T1 neurocognitive abilities on changes in overall use frequency were observed at Step 2 of the general model (ps>.05).

Given the trending significant effect of T1 inhibition/ cognitive flexibility predicting overall use frequency index, additional models estimating changes in alcohol, cannabis, and nicotine use frequency independently were run. Within Step 2 of the independent substance use models, T1 inhibition/ cognitive flexibility was found to positively predict change only in nicotine (cigarette) use frequency at T2 across all subjects with borderline significance (p= .058; Table 3.6; Figure 3.2). With respect to individual variable effects within Step 3 of these models, only one neurocognitive measure significantly interacted with sex to predict substance use outcomes - the interaction between sex and T1 working memory was found to predict change in cannabis use frequency at T2 across all subjects [females: β= 1.44, p= .028; males (reverse coded): β= -1.68, p= .028; Table 3.5; Figure 3.3]. These results were observed while controlling for Step 1 covariates.

Exploratory follow-up analyses by substance use groups

Out of the 71 study participants, 29 (40.8%) participants were in the tri-substance use group, 27 (38.1%) were in the co-substance use group, and the remaining 15 (21.1%) were in the one-substance use group (see Table 3.2). Within the co-substance use group, 59.3% reported co-use of alcohol and cannabis, 37% reported co-use of alcohol and nicotine (cigarette smoking), and only 3.7% (1 subject) reported co-use of cannabis and nicotine. In the case of one-substance use group, alcohol use was predominant (93%) with only 1 subject reporting cigarette smoking.

Baseline neurocognitive performance across the substance use groups

Between the three substance use groups, co-users appeared to have lower scores in all four neurocognitive tasks (Long Delay Free Recall, Block Design, Digit Span, and DKEFS Color-Word Interference) when compared to both one-substance and tri-substance using participants (see Table 3.2), yet the only statistically significant difference was observed between

the one-substance use and the co-substance use group on T1 Color-Word Interference mean scores (index for inhibition/switching) [F(2,66)= 3.37, *p*=.040; Figure 3.1].

Predictive neurocognitive models across substance use groups

Regression models estimating predictive power of neurocognitive markers on later use within one-, co- and tri- substance use groups independently, revealed effects within the co-use group only. Specifically, within Step 2 (main effects) of the models with co-use sample only (*n=27*), working memory at T1 was found to negatively predict change in overall substance use (alcohol, cannabis, nicotine) frequency index scores at T2 with statistical significance (Table 3.8; Figure 3.5), and T1 visuospatial ability was observed to negatively predict change at T2 with borderline significance (Table 3.8; Figure 3.4). A trend-level significant main effect was observed between working memory at T1 and later cannabis use, suggestive of working memory negatively predicting change in cannabis use frequency at T2 (Table 3.10).

With respect to individual variable effects within Step 3 of the models with co-use sample only (*n=27*), trend-level interactions observed between: I) T1 visuospatial ability and sex, and II) T1 working memory and sex on predicting change in overall use frequency index scores (Table 3.8). Further probe with individual substance outcome models revealed: I) a significant interaction between T1 visuospatial ability and sex in predicting change in alcohol use frequency at T2 [females: β= -15.1, *p*= .027; males (reverse coded): β= 18.1, p= .027; Table 3.9; Figure 3.6]; II) a significant interaction between T1 verbal memory and sex predicting change in alcohol use at T2 [females: β= -3.08, *p*= .035; males (reverse coded): β= 8.26, p= .035; Table 3.9; Figure 3.7]; and III) an approaching interaction between T1 working memory and sex, suggestive of predicting change in later alcohol use frequency (p= .064; Table 3.9). All these

results were observed while controlling for Step 1 covariates and no other main or interactive effects were observed within the co-use sample.

No main effects were observed in the models with one-substance use sample only (*n=15*) [Table 3.7], and tri-use sample only (*n=29*) [Table 3.12].

Discussion

We investigated whether neurocognitive task performance at the point of maximum substance (alcohol, cannabis, and/nicotine) use in late adolescence (T1) could predict a change in use behaviors 3-7 years later (T2). Results from our investigation across full sample and follow-up analyses within one-, co- and tri-substance use groups independently suggest that executive cognitive domains of working memory, verbal memory, visuospatial ability, and inhibition/cognitive flexibility are useful predictors of change in substance (alcohol, cannabis, and/or nicotine) use frequency outcomes, with sex surfacing as an important moderator in some cases (working and verbal memory, visuospatial ability).

Our observations from the main analyses across full sample did not align with our hypothesis that better performance in the four neurocognitive domains at T1 will predict decreases in use behaviors over follow-up. However, our hypothesis was partially supported by the exploratory follow-up results within the co-substance use group (Tables 3.8 & 3.10; Figure 3.5).

The borderline significant effect of inhibition/cognitive flexibility where better performance in this domain predicted an increase in cigarette use frequency from T1 to T2 across our full sample of youth (Table 3.6; Figure 3.2) is one such case of deflection from our hypothesis. This finding also seemingly contradicts previous research reporting associations

between weakened inhibitory control (response inhibition) and problematic use of tobacco products.[53,54] These differences may be an artifact of our relatively small sample size (*N=71*); however, the current sample generally reduced their use of cigarettes from T1 to T2 with an average of 10 days out of the 90 days (see Table 3.1). Thus, the predicted relationship between better inhibition/cognitive flexibility and increased cigarette use observed at T2, despite being opposite to previous study reports, must be couched by the fact that the overall usage of this sample is still well below the threshold of daily/regular smoking.[55-57]

In the exploratory follow-up analyses with the co-use group only, we observed some support for better performance in T1 visuospatial ability as a predictor of increases in overall use frequency index scores at T2 (Table 3.8; Figure 3.4). This not only deviates from our hypothesis but also from the data we presented in the second chapter of this dissertation (aim 2 with alcohol use outcomes) where better visuospatial ability was found to predict reduction in later binge drinking, an effect that remained even after controlling for T1 drinking (Table 2.3; Figure 2.3).Despite the contradiction, the positive predicted relationship in our current sample of co-users, who exhibit better visuospatial ability at a taxing time of maximum use, is suggestive of their superior cognitive control and the ability to delay increase in substance use until later in life and even then, gauge it to a safe level to stay under the problematic use threshold (see Table 3.1).

Again, the inconsistency we observed with the borderline effect of visuospatial ability in our current analysis could be an error from the small sample size of co-users we analyzed (*n=27*). It should also be noted that, in addition to alcohol, this group of co-users are using another substance (cannabis 59.3% or nicotine 37%) at T1 so that can factor into the different outcome we see with visuospatial ability in this aim. Use of any one substance may be associated

with escalating use of other substances over time; for example, teenage nicotine exposure can promote long lasting increase in alcohol consumption later into adulthood.[7]

Given the many reports of the association between alcohol use disorder and declining visuospatial ability in adult samples,[58-61] this domain warrants more attention as a vulnerability marker for prospective substance use, especially alcohol use. As a potent predictor of later alcohol use behavior, it can be beneficial to assess visuospatial ability early on to predict who may be at risk of problematic alcohol use and who may reduce or increase consumption over time.

The significant main effect observed within the co-use group supports our hypothesis in that better T1 working memory was found to predict a reduction in overall substance use frequency at T2 (Table 3.8; Figure 3.5). Weak working memory in early adolescence has been reported to predict use onset and escalating use of all three of our substances: alcohol,[35,62-68] nicotine,[35] and cannabis[63,69]. Hence, our result corroborates with exiting literature and show that better working memory performance during maximum use in late adolescence predicts a decrease in overall use frequency in the future, suggesting efficiency in this domain regardless of the severity at their maximum use, makes youths better at modulating their use behaviors later in life.

In our analyses predicting independent substance use outcomes, only in the case of working memory did we find sex to be a consistent moderator of cannabis use frequency in our full sample (Table 3.5; Figure 3.3). Specifically, females with better working memory at T1 exhibited a greater increase in cannabis use frequency from T1 to T2, whereas males with better working memory ability showed a greater decrease in cannabis use from T1 to T2 (Figure 3.3). Despite the positive relationship between working memory and cannabis use frequency in

females, it should be noted that overall females in the sample reduced their cannabis use by 73% between T1 and T2 whereas males reduced their cannabis use by only 43% between the two time points (e.g., cannabis use means at T1: 12.05 females, 9.88 males; cannabis use means at T2: 3.3 females, 5.55 males). Thus, this interaction effect appears to represent small, yet still significant, increases in cannabis use frequency for females with higher working memory scores.

In our exploratory follow-up analyses within the co-use group, we observed two significant interactions between T1 neurocognitive markers (visuospatial ability, verbal memory) and sex predicting change in alcohol use frequency (Figure 3.6 & 3.7). In both cases, females with better visuospatial ability and verbal memory at T1 exhibited a greater decrease in alcohol use frequency from T1 to T2, whereas males with better visuospatial ability and verbal memory showed a greater increase in alcohol use from T1 to T2 (Table 3.9; Figure 3.6 & 3.7). Despite the positive relationship between these two neurocognitive domains and alcohol use in males, it should be noted that the current sample generally reduced their alcohol use behaviors from T1 to T2 (Table 3.1), including the male participants (e.g., alcohol use means: 16.2 at T1 to 11.3 at T2), such that the predicted increases in alcohol use behaviors observed at T2 still fall under the National Institute on Alcohol Abuse and Alcoholism heavy drinking limit.[70]

This current study embodies several strengths and limitations. A strength of our study lies in analyzing key neurocognitive domains and three separate substance use behaviors (alcohol, nicotine, and cannabis frequency) with follow-up exploratory insight into one-, co- and tri-substance users in the current sample, during the important developmental shift from late adolescence into young adulthood. However, given this is a secondary analysis conducted outside the primary aims of the parent study, missing data on our variables of interest culminated in a relatively small study sample and hence less power. The small sample size also could have

biased the sample towards less problematic substance use. Despite the sample size, the presence of data on several substance use variables indexing the amount and frequency of alcohol, cannabis and nicotine use allowed for a nuanced examination of substance use behaviors across our participants. The makeup of our sample allowed for investigating moderating roles of sex in the association between neurocognition and substance use; yet the predominantly Non-Latinx/Hispanic White participants restricted us from exploring any moderating roles of race/ethnicity. Future studies with larger more diverse youth sample will be beneficial for better understanding of effects within each substance use group (one-, co- and tri- use) and for informing prevention/intervention development. Although longitudinal, the nature of the study prohibits inferences of causality. As a future direction, the moderating role of follow-up (T2) youth income can be explored as an indirect measure of general functioning and achievement, given that most participants transitioned to their own income for financial support by this point.

Conclusion

The current study is first to our knowledge to investigate the predictive utility of neurocognition during the point of maximum substance use in late adolescence on substance use changes 3-7 years later and explore this effect across one-, co- and tri-users independently. The results from this study will shed light on the influences of neurocognitive markers on co- and tri-substance use behaviors specifically when it comes to alcohol, cannabis, and nicotine use, and inform intervention research of cognitive vulnerability markers for concurrent/simultaneous use of two or more substances. Our data may aid in development of efficacious assessments and approaches: e.g., cognitive remediation interventions or cognitive skill development training curriculums could be worthwhile for future investigations to address such risk factors early in the youth population and prevent problematic use in the future.

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Table 3.1. Sample demographic characteristics at time point 1 (T1) and follow-up (T2) *(n= 71)*

Variables	Time Points	
	Mean (SD) or *n* (%)	
	Time Point 1 (T1)	Follow-Up (T2)
Age (years)	20.19 (1.6) Range: 17.04-24.69	24.06 (1.6) Range: 20.40-28.01
Follow-Up Duration (years)	3.86 (.79) Range: 3-7	
Sex		
Male	51 (71.8%)	_____
Female	20 (28.2%)	_____
Race		
White or Caucasian	50 (70.4%)	_____
Other (*Not White*)	21 (29.5%)	_____
Ethnicity		
Latino/Hispanic	13 (18.3%)	_____
Non-Latino/Hispanic	56 (78.9%)	_____
Unknown	2 (2.8%)	_____
Substance Use (no. of days used past 3 months)		
Alcohol	16.15 (14.0)	10.58 (10.6) *
Cannabis	10.49 (15.3)	4.92 (8.7) ***
Nicotine (cigarette use)	24.21 (33.7)	10.52 (24.9) ***
Neurocognitive Performance at Maximum Use		
LDFR	.23 (.9)	_____
Block	12.86 (2.1)	_____
Digit	10.83 (2.6)	_____
CWI	12.46 (2.1)	_____

(*) $p < .05$; (***) p<.001; LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility)

Table 3.2. Baseline age, gender and neurocognitive performance scaled scores by substance use groups

Variables	Substance Use Groups		
	Mean (SD) or *n* (%)		
	One-substance use (*n*=15)	**Co-substance use (*n*=27)**	**Tri-substance use (*n*=29)**
Age	20.70 (2.0)	20.37 (1.3)	19.78 (1.7)
Sex			
Male	9 (60)	20 (74.1)	22 (75.9)
Female	6 (40)	7 (25.9)	7 (24.1)
Neurocognitive Task Scaled Scores			
LDFR	.53 (.70)	.07 (.90)	.21 (1.04)
Block	13.60 (2.5)	12.33 (2.1)	12.96 (1.7)
Digit	11.87 (2.5)	10.18 (2.7)	10.89 (2.4)
CWI	13.53 (1.5) [a]	12.07 (2.5) [a]	12.28 (1.9)

LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); [a] Group mean difference $p < .05$

Table 3.3. Results of linear regression predicting change in overall substance use (alcohol, cannabis, nicotine) frequency index scores across all subjects (*n*= *71*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)
Step 1- Covariates												
T1 Age	.68 (.71)	.12	.34	-.74 (2.09)	.56 (.72)	.09	.436	-.87-1.99	.72 (.74)	.13	.337	-.77-2.20
Follow-Up Duration (Years)	-3.38 (1.5)	-.28	.02	-6.29-(-.46)	-3.99 (1.5)	-.34	.009	-6.95-(-1.03)	-3.43 (1.6)	-.29	.036	-6.63-(-.24)
Sex	-.70 (2.4)	-.03	.774	-5.54-4.14	-.46 (2.5)	-.02	.855	-5.42-4.51	-14.1 (20.2)	-.68	.487	-54.4-26.3
Step 2- Main Effects												
Block					.33 (.61)	.07	.592	-.89-1.55	.76 (.86)	.17	.378	-.95-2.47
LDFR					-.26 (1.3)	-.03	.842	-2.86-2.34	-.51 (1.5)	-.05	.739	-3.57-2.55
CWI					.98 (.56)	.22	.088	-.15-2.10	.48 (.77)	.11	.531	-1.05-2.02
Digit					-.61 (.45)	-.17	.178	-1.51-.29	-.90 (.53)	-.25	.093	-1.96-.15
Step 3- Interactions												
Block*Sex									-.66 (1.3)	-.41	.608	-3.24-1.91
LDFR*Sex									.29 (3.3)	.01	.931	-6.38-6.96
CWI*Sex									.80 (1.2)	.47	.507	-1.60-3.20
Digit*Sex									1.19 (1.3)	.59	.364	-1.41-3.79
R^2			.12				.18				.21	
R^2 *Change*			.12				.06				.03	
F for change in R^2			3.00*				1.19				.50	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

Table 3.4. Results of linear regression predicting change in alcohol use frequency (drink days in past 3 months) across all subjects (*n= 71*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)
Step 1- Covariates												
T1 Age	-2.87 (1.1)	-.32	.012	-5.11-(-.64)	-3.03 (1.2)	-.33	.011	-5.34-(-.73)	-3.01 (1.2)	-.33	.014	-5.39-(-.63)
Follow-Up Duration (Years)	-5.37 (2.3)	-.29	.023	-9.97-(-.78)	-5.76 (2.3)	-.31	.019	-10.53-(-.10)	-5.97 (2.6)	-.32	.023	-11.11-(-.84)
Sex	-4.03 (3.8)	-.12	.296	-11.67-3.61	-4.86 (3.9)	-.15	.229	-12.85-3.13	-34.54(32.4)	-1.05	.291	-99.35-30.28
Step 2- Main Effects												
Block					.87 (.98)	.12	.376	-1.09-2.83	.03 (1.4)	.004	.985	-2.72-2.78
LDFR					-.05 (2.1)	-.003	.983	-4.23-4.13	.25 (2.5)	.02	.919	-4.66-5.16
CWI					-.08 (.91)	-.01	.933	-1.89-1.74	-.67 (1.2)	-.095	.59	-3.13-1.79
Digit					-.89 (.72)	-.16	.222	-2.33-.55	-.59 (.85)	-.104	.486	-2.29-1.10
Step 3- Interactions												
Block*Sex									1.60 (2.1)	.63	.442	-2.53-5.74
LDFR*Sex									1.79 (5.4)	.05	.74	-8.92-12.5
CWI*Sex									1.52 (1.9)	.56	.434	-2.34-5.38
Digit*Sex									-.91 (2.1)	-.29	.665	-5.08-3.27
R^2			.12				.15				.18	
R^2 *Change*			.12				.03				.03	
F for change in R^2			3.11*				.50				.57	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

Table 3.5. Results of linear regression predicting change in cannabis use frequency (no. of days used in past 3 months) across all subjects (*n= 71*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)
Step 1- Covariates												
T1 Age	1.94 (.98)	.25	.054	-0.03-3.9	1.71 (1.0)	.22	.095	-0.31-3.73	1.90 (.10)	.24	.06	-0.08-3.88
Follow-Up Duration (Years)	2.62 (2.0)	.16	.201	-1.43-6.66	2.21 (2.1)	.14	.292	-1.95-6.38	4.06 (2.1)	.25	.062	-0.22-8.34
Sex	-3.34 (3.4)	-.12	.325	-10.1-3.38	-4.06 (3.5)	-.14	.248	-11.06-2.91	-4.36 (27)	-.15	.872	-58.35-49.6
Step 2- Main Effects												
Block					.101 (.86)	.02	.907	-1.61-1.81	1.61 (1.1)	.26	.164	-0.68-3.9
LDFR					1.35 (1.8)	.097	.462	-2.30-5.01	-0.63 (2.0)	-.05	.758	-4.73-3.46
CWI					0.22 (.79)	.04	.78	-1.36-1.81	0.24 (1.0)	.04	.818	-1.81-2.30
Digit					-1.01 (.63)	-.20	.116	-2.27-.25	-2.0 (.71)	-.41	.006*	-3.41-(-.59)
Step 3- Interactions												
Block*Sex									-2.34 (1.7)	-1.07	.178	-5.79-1.1
LDFR*Sex									3.97 (4.5)	.13	.377	-4.95-12.90
CWI*Sex									-.92 (1.6)	-.39	.569	-4.13-2.3
Digit*Sex									3.93 (1.7)	1.44	.028*	.45-7.41
R^2			.08				.12				.23	
R^2 *Change*			.08				.04				.11	
F for change in R^2			2.01				.75				2.11	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

Table 3.6. Results of linear regression predicting change in nicotine (cigarette) use frequency (no. of days smoked in past 3 months) across all subjects (*n= 71*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)
Step 1- Covariates												
T1 Age	2.97 (1.8)	.20	.105	-0.63-6.57	3.01 (1.8)	.20	.105	-0.65-6.67	3.26 (1.9)	.22	.093	-0.56-7.07
Follow-Up Duration (Years)	-7.37 (3.7)	-.24	.051	-14.78-.04	-8.43 (3.8)	-.28	.029	-15.98-(-.87)	-8.39 (4.1)	-.27	.046	-16.62-(-.16)
Sex	5.27 (6.2)	.10	.396	-7.05-17.60	7.57 (6.3)	.14	.237	-5.10-20.23	-3.41 (52)	-.06	.948	-107.3-100.5
Step 2- Main Effects												
Block					.01 (1.6)	.001	.995	-3.10-3.12	.64 (2.2)	.06	.772	-3.76-5.05
LDFR					-2.09 (3.3)	-.08	.531	-8.71-4.54	-1.15 (3.9)	-.04	.771	-9.02-6.72
CWI					2.78 (1.4)	.24	.058	-0.09-5.65	1.88 (1.9)	.17	.344	-2.07-5.82
Digit					.07 (1.1)	.01	.955	-2.22-2.35	-.11 (1.4)	-.01	.937	-2.82-2.61
Step 3- Interactions												
Block*Sex									-1.25 (3.3)	-.30	.707	-7.87-5.38
LDFR*Sex									-4.89 (8.6)	-.09	.571	-22.05-12.27
CWI*Sex									1.80 (3.1)	.41	.562	-4.38-7.99
Digit*Sex									.55 (3.3)	.11	.871	-6.15-7.24
R^2			.14				.19				.21	
R^2 *Change*			.14				.06				.013	
F for change in R^2			3.58*				1.08				.23	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

Table 3.7. Results of linear regression predicting change in overall substance use (alcohol, cannabis, nicotine) frequency index scores within the one-substance use group only (*n=15*)

Model	Step 1				Step 2				Step 3			
Variables	**B (SE)**	**ß**	**Sig.**	**95%CI(B)**	**B (SE)**	**ß**	**Sig.**	**95%CI(B)**	**B (SE)**	**ß**	**Sig.**	**95%CI(B)**
Step 1- Covariates												
T1 Age	-.39(.37)	-.33	.316	-1.21-.43	-.39(.48)	-.33	.445	-1.52-.75	-1.07(.48)	-.92	.106	-2.60-.43
Follow-Up Duration (Years)	.74(.92)	.25	.437	-1.28-2.76	.79(1.1)	.27	.509	-1.89-3.47	.53(.93)	.18	.608	-2.43-3.5
Sex	1.15(1.3)	.24	.378	-1.60-3.9	1.24(1.6)	.26	.468	-2.59-5.07	-31.4(19.7)	-6.67	.208	-94.1-31.2
Step 2- Main Effects												
Block					-.04(.36)	-.04	.918	-.88-.81	.20(.64)	.21	.777	-1.85-2.25
LDFR					-.17(1.2)	-.05	.892	-3.01-2.67	-.57(1.2)	-.17	.657	-4.28-3.14
CWI					-.34(.50)	-.21	.522	-1.52-.85	-.44(.44)	-.27	.385	-1.82-.94
Digit					.23(.33)	.24	.516	-.56-1.01	.37(.47)	.39	.485	-1.12-1.86
Step 3- Interactions												
Block*Sex									-.52(.73)	-1.6	.528	-2.84-1.81
LDFR*Sex									4.37(3.1)	.82	.25	-5.40-14.1
CWI*Sex									5.8(2.3)	16.5	.089	-1.63-13.3
Digit*Sex									-3.55(1.4)	-8.72	.084	-7.97-.89
R^2			.35				.42				.86	
R^2 *Change*			.35				.07				.44	
***F* for change in R^2**			1.97				.21				2.30	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

Table 3.8. Results of linear regression predicting change in overall substance use (alcohol, cannabis, nicotine) frequency index scores within the co-substance use group only (*n=27*)

Model	Step 1				Step 2				Step 3			
Variables	**B (SE)**	**ß**	**Sig.**	**95%CI(B)**	**B (SE)**	**ß**	**Sig.**	**95%CI(B)**	**B (SE)**	**ß**	**Sig.**	**95%CI(B)**
Step 1- Covariates												
T1 Age	-.32 (1.0)	-.07	.753	-2.41-1.77	.21 (.90)	.04	.817	-1.68-2.1	-.06 (.98)	-.01	.953	-2.14-2.02
Follow-Up Duration (Years)	-3.33 (2.1)	-.33	.12	-7.60-.93	-6.05 (2.1)	-.59	.01	-10.5-(-1.62)	-7.18 (2.5)	-.70	.011	-12.5-(-1.9)
Sex	-2.97 (2.8)	-.21	.301	-8.76-2.83	-1.72 (2.6)	-.12	.514	-7.13-3.69	98.2 (56.6)	6.99	.103	-22.4-218.8
Step 2- Main Effects												
Block					1.28 (.62)	.44	.055	-0.03-2.58	1.76 (.78)	.60	.039*	.10-3.43
LDFR					-.61 (1.4)	-.09	.668	-3.53-2.31	-1.56 (1.7)	-.22	.375	-5.21-2.08
CWI					.47 (.52)	.19	.377	-0.62-1.56	.47 (.70)	.19	.509	-1.02-1.97
Digit					-1.17 (.45)	-.51	.018*	-2.11-(-.23)	-1.36 (.48)	-.59	.013*	-2.40-(-.33)
Step 3- Interactions												
Block*Sex									-14.6 (7.6)	-11.7	.074	-30.8-1.61
LDFR*Sex									-46.9 (26.8)	-2.3	.10	-104-10.15
CWI*Sex									-.57 (1.1)	-.47	.61	-2.88-1.75
Digit*Sex									6.33 (3.4)	4.66	.085	-0.99-13.65
R^2			.13				.46				.58	
R^2 *Change*			.13				.33				.12	
***F* for change in R^2**			1.18				2.87				1.08	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

Table 3.9. Results of linear regression predicting change in alcohol use frequency (drink days in past 3 months) within the co-substance use group only (*n=27*)

Model	Step 1				Step 2				Step 3			
Variables	**B (SE)**	**ß**	**Sig.**	**95%CI(B)**	**B (SE)**	**ß**	**Sig.**	**95%CI(B)**	**B (SE)**	**ß**	**Sig.**	**95%CI(B)**
Step 1- Covariates												
T1 Age	-2.19 (2.5)	-.17	.386	-7.31-2.94	-1.25 (2.5)	-.10	.622	-6.47-3.97	-2.27(2.6)	-.18	.389	-7.74-3.19
Follow-Up Duration (Years)	-10.0 (5.1)	-.38	.059	-20.5-.44	-14.8(5.9)	-.55	.021	-27-(-2.53)	-21.9(6.5)	-.82	.004	-35.86-(-8.13)
Sex	-11.5 (6.9)	-.31	.108	-25.7-2.71	-12.8 (7.2)	-.35	.09	-27.7-2.21	346(149)	9.49	.034	29.7-663.2
Step 2- Main Effects												
Block					1.20 (1.7)	.16	.495	-2.41-4.82	1.81 (2.1)	.24	.391	-2.56-6.18
LDFR					-5.17 (3.9)	-.28	.197	-13.3-2.92	-5.99(4.5)	-.33	.203	-15.56-3.59
CWI					.43 (1.4)	.07	.771	-2.60-3.44	.60(1.8)	.09	.75	-3.33-4.52
Digit					-2.09 (1.2)	-.35	.11	-4.70-.52	-2.06(1.3)	-.35	.125	-4.76-.64
Step 3- Interactions												
Block*Sex									-49 (19.9)	-15.1	.027*	-91.5-(-6.52)
LDFR*Sex									-163(70.3)	-3.08	.035*	-313.2-(-13.5)
CWI*Sex									-1.24 (2.9)	-.40	.67	-7.32-4.84
Digit*Sex									18.0 (9.0)	5.1	.064	-1.18-37.3
R^2			.23				.39				.57	
R^2 *Change*			.23				.16				.19	
F for change in R^2			2.30				1.21				1.62	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

Table 3.10. Results of linear regression predicting change in cannabis use frequency (no. of days used in past 3 months) within the co-substance use group only (*n=27*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)	B (SE)	ß	Sig.	95% CI(B)
Step 1- Covariates												
T1 Age	.09 (1.9)	.01	.962	-3.76-3.94	.85 (1.9)	.10	.66	-3.13-4.83	1.02 (1.9)	.12	.598	-3.01-5.04
Follow-Up Duration (Years)	-.65 (3.8)	-.04	.865	-8.51-7.21	-4.26 (4.5)	-.24	.352	-13.6-5.09	1.27 (4.8)	.07	.794	-8.93-11.5
Sex	-.84 (5.2)	-.04	.871	-11.5-9.83	-1.19 (5.5)	-.05	.83	-12.6-10.2	-96.4 (109)	-4.0	.392	-329.5-137
Step 2- Main Effects												
Block					.85 (1.3)	.17	.527	-1.91-3.6	2.3 (1.5)	.46	.148	-0.92-5.52
LDFR					-1.47 (2.9)	-.12	.625	-7.63-4.7	-4.95(3.3)	-.41	.155	-12-2.09
CWI					.42 (1.1)	.10	.704	-1.88-2.72	.29 (1.4)	.07	.833	-2.60-3.18
Digit					-1.83 (.95)	-.47	.069	-3.82-.16	-2.71 (.93)	-.69	.011*	-4.6-(-.72)
Step 3- Interactions												
Block*Sex									10.2 (14.7)	4.78	.497	-21.1-41.5
LDFR*Sex									46.1 (51.7)	1.32	.387	-64.2-156.3
CWI*Sex									-0.57 (2.1)	-.27	.791	-5.04-3.91
Digit*Sex									-.43 (6.6)	-.18	.949	-14.6-13.7
R^2			.002				.18				.47	
R^2 *Change*			.002				.18				.28	
F for change in R^2			.02				1.06				2.01	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

Table 3.11. Results of linear regression predicting change in nicotine (cigarette) use frequency (no. of days smoked in past 3 months) within the co-substance use group only (*n=27*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	ß	Sig.	95%CI(B)	B (SE)	ß	Sig.	95%CI(B)	B (SE)	ß	Sig.	95%CI(B)
Step 1- Covariates												
T1 Age	1.13 (2.2)	.11	.608	-3.36-5.61	1.03 (2.0)	.10	.606	-3.1-5.16	1.08 (2.4)	.11	.656	-3.98-6.14
Follow-Up Duration (Years)	.66 (4.4)	.03	.882	-8.49-9.82	.91 (4.6)	.04	.846	-8.78-10.6	-.82 (6.0)	-.04	.893	-13.7-12.0
Sex	3.43 (6.0)	.12	.574	-9-15.85	8.80 (5.6)	.31	.136	-3.03-20.6	44.6 (138)	1.57	.75	-249-338
Step 2- Main Effects												
Block					1.77 (1.4)	.30	.21	-1.08-4.63	1.18 (1.9)	.20	.545	-2.87-5.22
LDFR					4.81 (3.1)	.33	.132	-1.58-11.2	6.25 (4.2)	.43	.154	-2.62-15.1
CWI					.57 (1.1)	.11	.625	-1.82-2.95	.54 (1.7)	.11	.758	-3.1-4.17
Digit					.42 (.98)	.09	.673	-1.64-2.48	.68 (1.2)	.15	.57	-1.82-3.19
Step 3- Interactions												
Block*Sex									-4.9 (18.5)	-1.94	.794	-44.3-34.5
LDFR*Sex									-23.4 (65.1)	-.57	.725	-162.1-115.4
CWI*Sex									.11 (2.6)	.04	.968	-5.52-5.73
Digit*Sex									1.37 (8.4)	.50	.872	-16.4-19.18
R^2			.03				.37				.40	
R^2 *Change*			.03				.34				.03	
F for change in R^2			.25				2.58				.16	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

Table 3.12. Results of linear regression predicting change in overall substance use (alcohol, cannabis, nicotine) frequency index scores within the tri-substance use group only (*n=29*)

Model Variables	Step 1				Step 2				Step 3			
	B (SE)	ß	Sig.	95%CI(B)	B (SE)	ß	Sig.	95%CI(B)	B (SE)	ß	Sig.	95%CI(B)
Step 1- Covariates												
T1 Age	1.01 (1.3)	.16	.425	-1.56-3.59	.99 (1.5)	.15	.526	-2.19-4.17	.94 (1.7)	.15	.579	-2.55-4.43
Follow-Up Duration (Years)	-4.46 (2.1)	-.39	.045	-8.81-(-.12)	-4.20 (2.2)	-.36	.075	-8.85-.46	-5.22 (2.9)	-.45	.087	-11.27-.84
Sex	-1.88 (4.7)	-.08	.695	-11.62-7.86	-2.12 (6.1)	-.09	.73	-14.75-10.51	11.8 (73)	.47	.873	-142.2-165.9
Step 2- Main Effects												
Block					-.55 (1.5)	-.09	.723	-3.73-2.63	-.83 (2.0)	-.13	.686	-5.08-3.42
LDFR					-1.91 (2.2)	-.18	.389	-6.42-2.61	-2.07 (2.6)	-.20	.442	-7.65-3.5
CWI					1.25 (1.3)	.22	.354	-1.48-3.98	.72 (1.8)	.12	.70	-3.13-4.56
Digit					-0.78 (1.1)	-.18	.47	-2.99-1.43	-.44 (1.2)	-.10	.728	-3.06-2.18
Step 3- Interactions												
Block*Sex									-.34 (4.0)	-.18	.934	-8.84-8.16
LDFR*Sex									1.49 (5.7)	.07	.797	-10.51-13.48
CWI*Sex									2.34 (3.3)	1.08	.482	-4.53-9.21
Digit*Sex									-3.88 (5.9)	-1.45	.518	-16.30-8.53
R^2			.23				.30				.34	
R^2 *Change*			.23				.07				.05	
F for change in R^2			2.41				.55				.29	

(*) $p < .05$; Block= Wechsler Adult Intelligence Scale Block Design (index for visuospatial ability); LDFR= California Verbal Learning Test Long Delay Free Recall (index for verbal memory); CWI= Delis-Kaplan Executive Function System Color-Word Interference (index for inhibition/cognitive flexibility); Digit= Wechsler Adult Intelligence Scale Digit Span (index for working memory)

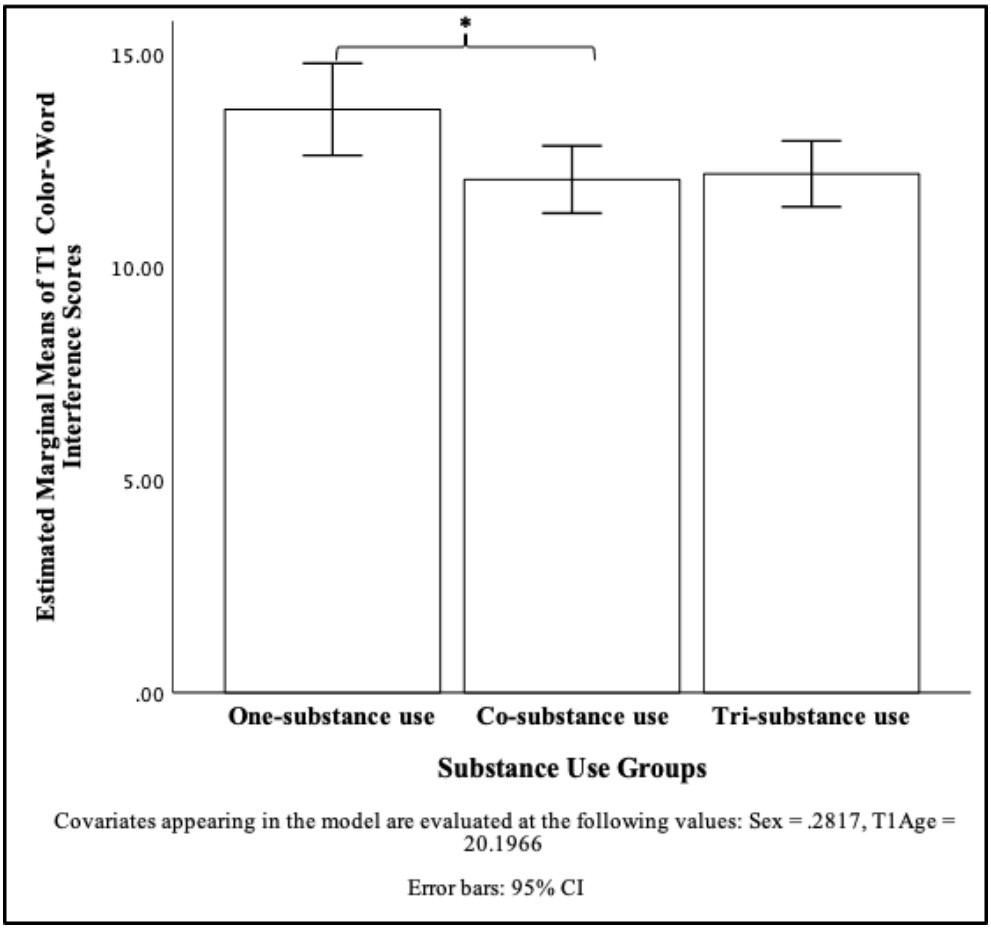


Figure 3.1. Bar graph illustrating a significant mean difference (p <.05) in baseline inhibition/cognitive flexibility performance (T1 Color-Word Interference scores) between one-substance use and co-substance use groups

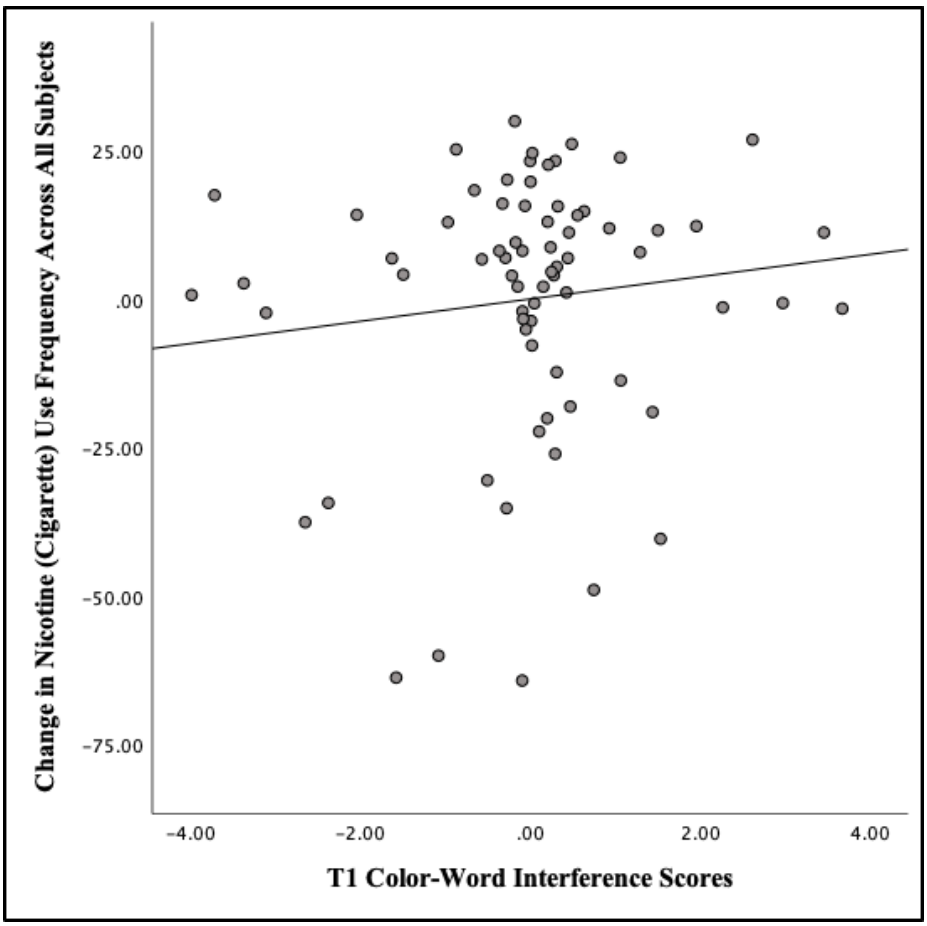
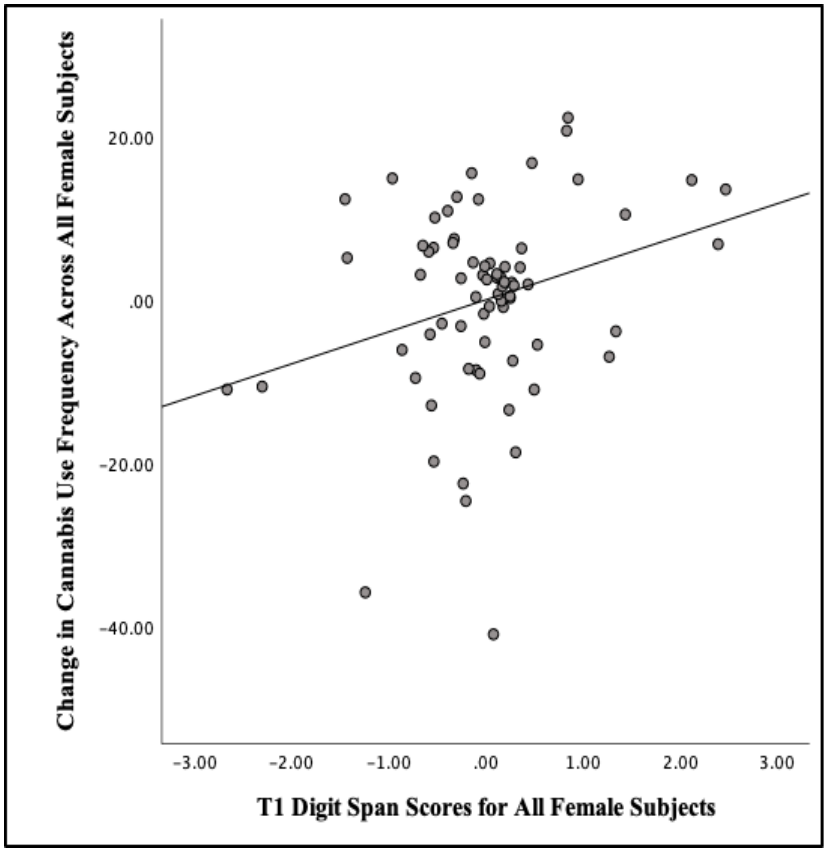


Figure 3.2. Partial regression plot showing borderline significant positive relationship between inhibition/cognitive flexibility at maximum substance use (T1 Color-Word Interference scores) and change in nicotine (cigarette) use frequency (no. of days smoked in past 3 months) across all subjects; (*n= 71*)



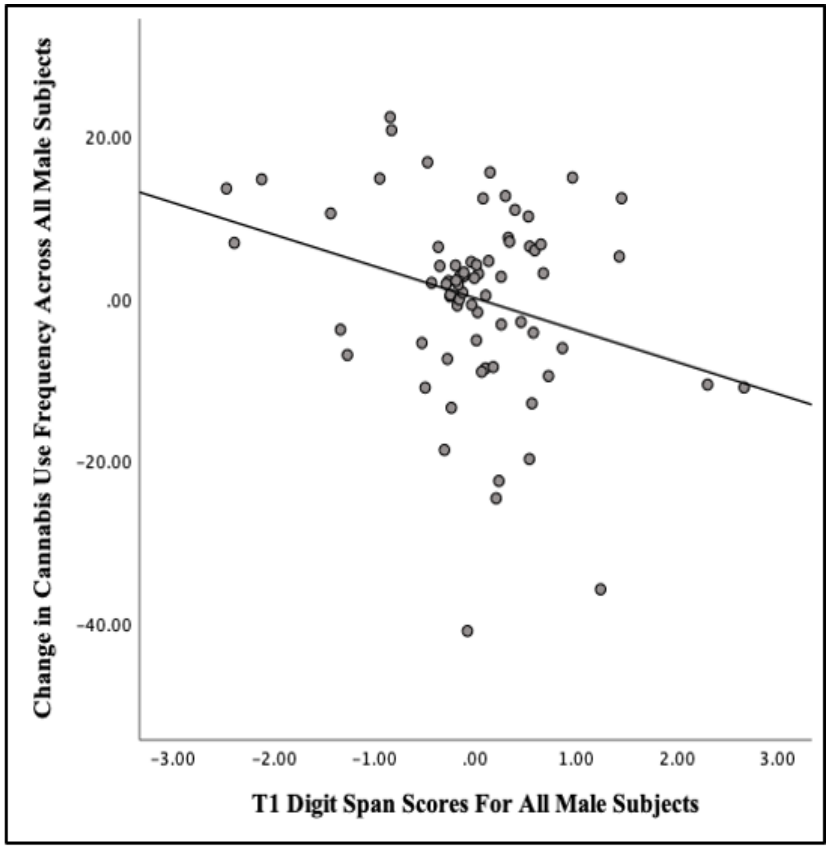


Figure 3.3. (left) Partial regression plot showing the significant positive relationship between working memory at maximum substance use (T1 Digit Span scores) and change in cannabis use frequency (no. of days used in past 3 months) among all female subjects; (right) Partial regression plot showing the significant negative relationship between working memory at maximum substance use (T1 Digit Span scores) and change in cannabis use frequency (no. of days used in past 3 months) among all male subjects; (*n= 71*)

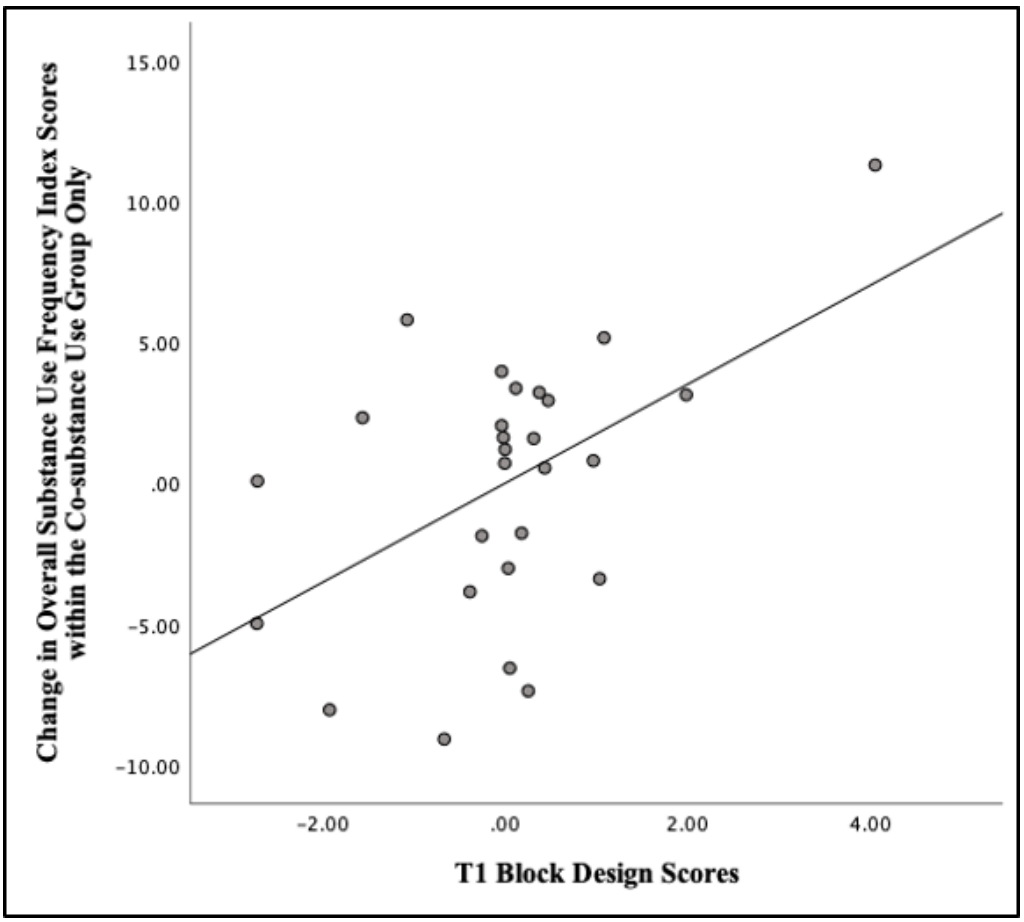


Figure 3.4. Partial regression plot showing borderline positive relationship between visuospatial ability at maximum substance use (T1 Block Design scores) and change in overall substance use (alcohol, cannabis, nicotine) frequency index scores, within the co-substance use group only; (*n=27*)

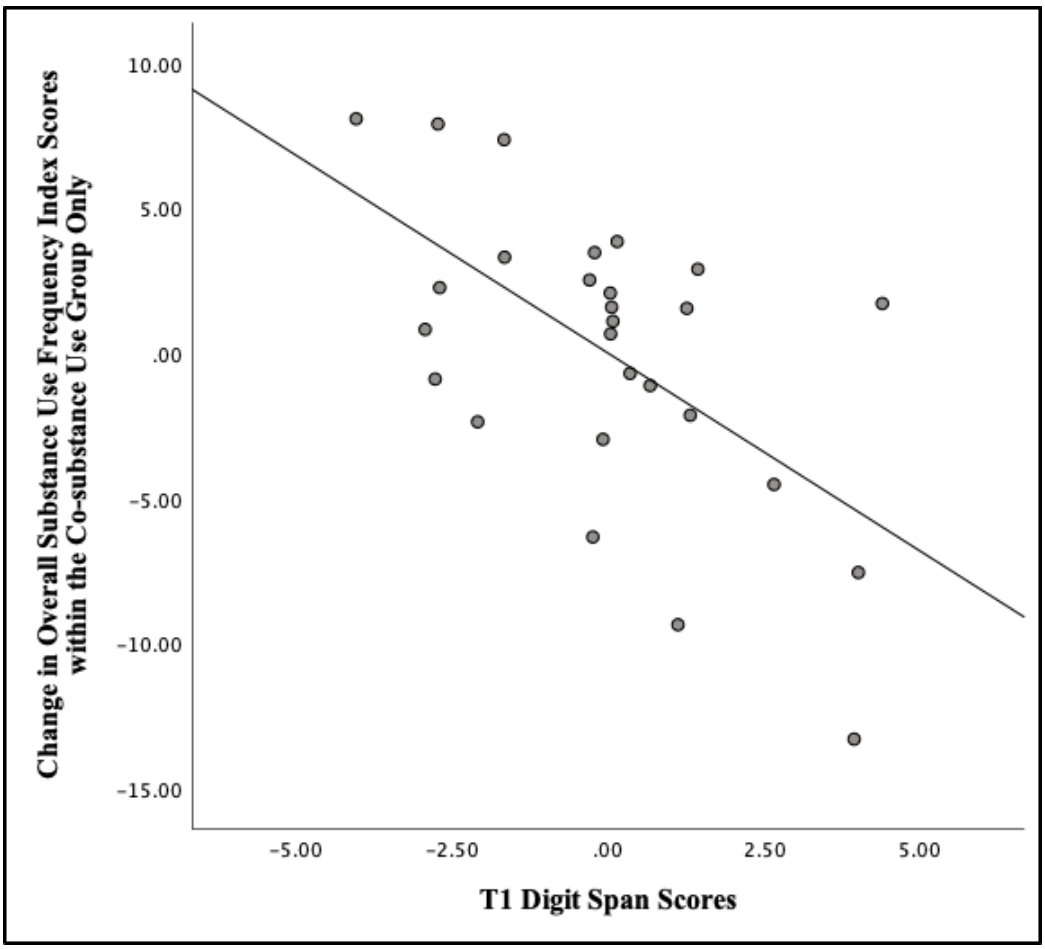
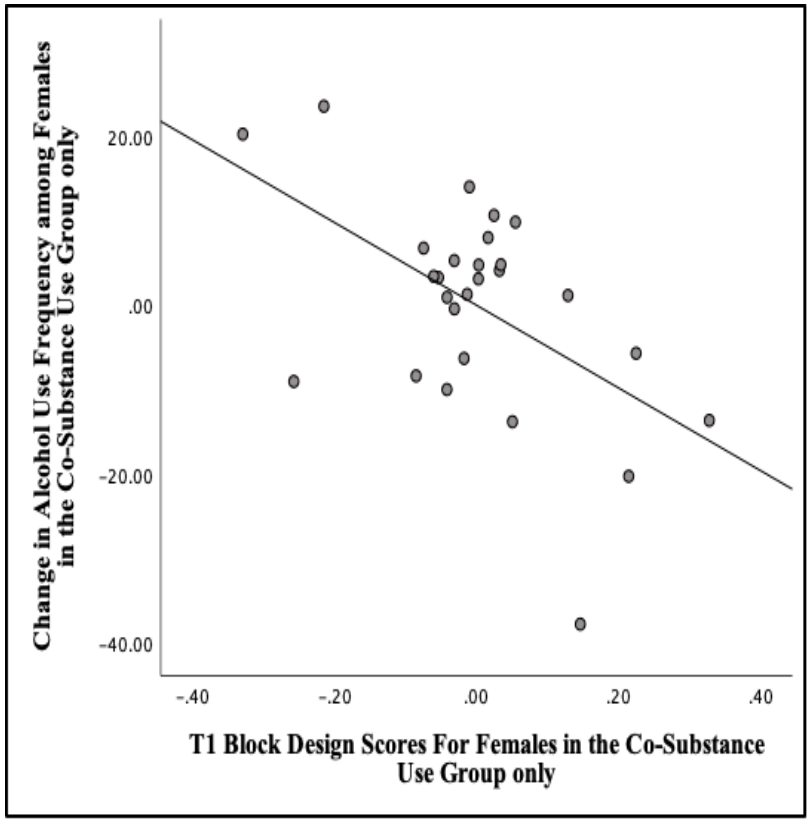


Figure 3.5. Partial regression plot showing the significant negative relationship between working memory at maximum substance use (T1 Digit Span scores) and change in overall substance use (alcohol, cannabis, nicotine) frequency index scores, within the co-substance use group only; (*n=27*)



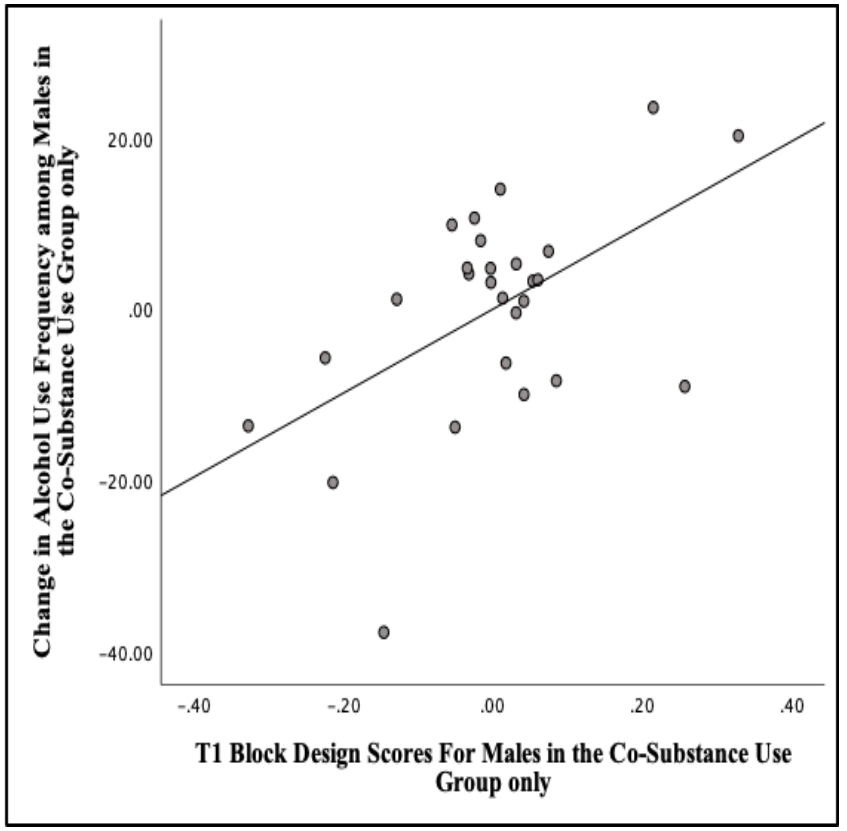
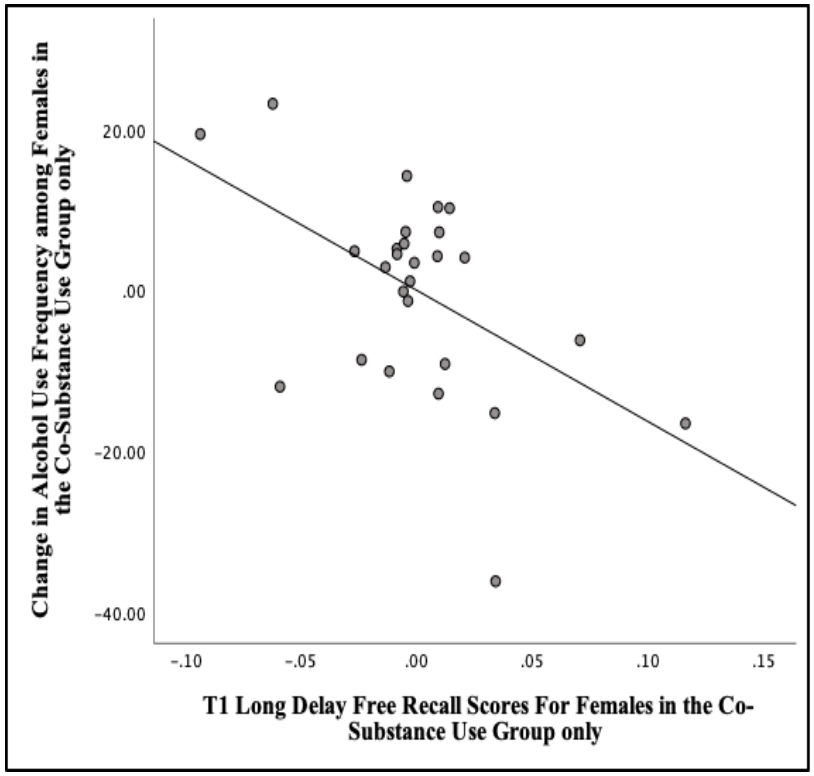


Figure 3.6. (left) Partial regression plot showing the significant negative relationship between visuospatial ability at maximum substance use (T1 Block Design scores) and change in alcohol use frequency (drink days in past 3 months) among females within the co-substance use group only. (right) Partial regression plot showing the significant positive relationship between visuospatial ability at maximum substance use (T1 Block Design scores) and change in alcohol use frequency (drink days in past 3 months) among males within the co-substance use group only; (*n=27*)



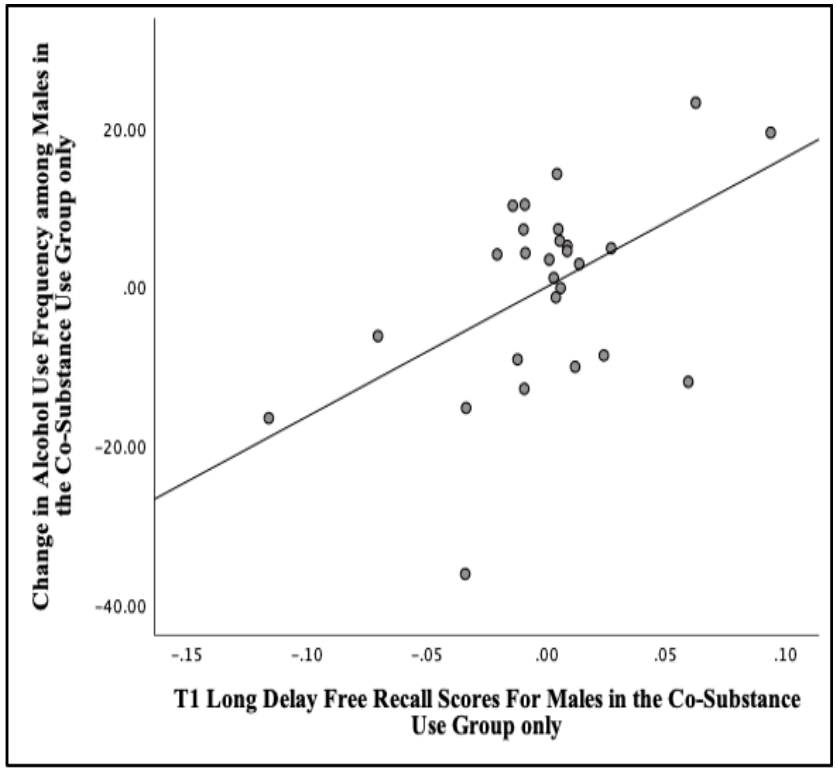


Figure 3.7. (left) Partial regression plot showing the significant negative relationship between verbal memory at maximum substance use (T1 Long Delay Free Recall scores) and change in alcohol use frequency (drink days in past 3 months) among females within the co-substance use group only. (right) Partial regression plot showing the significant positive relationship between verbal memory at maximum substance use (T1 Long Delay Free Recall scores) and change in alcohol use frequency (drink days in past 3 months) among males within the co-substance use group only; (*n=27*)

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Overall Findings and Conclusion

The current dissertation project highlights the research done on the executive neurocognitive domains which have not previously been reviewed and in a scoping review format summarize the existing literature investigating their predictive associations with prospective substance use. The dissertation also includes 2 analytical aims that comprehensively investigates neurocognitive domains (working memory, visuospatial ability, verbal memory, and inhibition/cognitive flexibility) during peak use stage in late adolescence as predictors of later substance use behaviors (alcohol, cannabis, and nicotine).

Our scoping review revealed a common theme where deficient working memory and attention, maladaptive emotion regulation and heightened reward-related neural response during decision making in early adolescence were largely predictive of substance (alcohol, cannabis, tobacco smoking, and other drugs) use onset, as well as greater frequency of use and problematic use through adolescence and into young adulthood (Table 1.1). Results from our two analytical aims (secondary analyses) reveal that the neurocognitive markers in the domains of working memory, verbal memory, visuospatial ability, and inhibition/cognitive flexibility at maximum substance (alcohol, cannabis, and nicotine) use in late adolescence are useful as prospective predictors of change in substance use behaviors over time.

Hence, broadening the scope of longitudinal neurobehavioral research on these constructs could aid in identification of early risk factors and preventive measures for future drug and alcohol use among youth. The findings from this dissertation project can potentially inform policy recommendations as well as intervention research targeting this age group. Even though data from our sample suggests that most late adolescents reduce their use over time regardless of neurocognitive performance, the reported knowledge of cognitive vulnerability markers in

childhood, preadolescence, and adolescence (post onset and at maximum use) maybe a steppingstone for researchers to further investigate into efficacious intervention strategies targeting these constructs to prevent prospective youth substance use. Investigating potential cognitive remediation approaches[1] or cognitive skill training curriculums (e.g., working memory training,[2-4] decision making exercises[5]) as intervention strategies could be a worthwhile future direction.

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