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Delay Discounting and Neurocognitive Performance in Young Adults with Differential Patterns
of Substance Use: Findings from the Human Connectome Project

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Abstract

A large proportion of individuals who use psychoactive substances regularly use more than one substance. This pattern of behavior, termed polysubstance use, is associated with greater risks than when consuming only single substance. The present study examined delay discounting, neurocognitive functioning, and demographic indicators among a large, racially and socioeconomically diverse sample of young adults drawn from the Human Connectome Project who reported either non, mono, or dual use of alcohol, tobacco and/or cannabis. Univariate and multivariate tests suggested individuals who reported using multiple substances were more likely to be male, experienced higher rates of alcohol use disorder, and, when reporting both alcohol use and cannabis involvement, scored lower on a measure of inhibitory control relative to those who reported mono or dual use of alcohol and/or cigarettes. Individuals who reported currently smoking cigarettes exhibited the steepest discounting irrespective of other substances used; however, we observed additive effects for alcohol use and, to a lesser extent, cannabis involvement. Specifically, steeper discounting occurred when individuals who reported either regular alcohol use or >100 lifetime instances of cannabis use also reported smoking cigarettes. We discuss several hypotheses for this finding related to the diversity of the sample and substances assessed as well as directions for future programmatic lines of research.

Key Words: Addiction, polysubstance use, behavioral economics, delay discounting, neurocognitive performance

Introduction

Approximately 80 percent of people who use substances will regularly consume more than one substance (Batel et al., 1995; Kalman et al., 2005). This pattern of behavior, known as polysubstance use, is associated with greater risk of developing a substance use disorder than when consuming only a single substance (Hayaki et al., 2016; Stinson et al., 2006). There is a rich literature implicating maladaptive decision making as a shared mechanism across substance use disorders (Amlung et al., 2017; Bickel et al., 2012; MacKillop et al., 2011; Reynolds, 2006), with delay discounting among the most widely studied paradigms. Delay discounting is a process wherein outcomes become less subjectively valuable as a function of increasing delay to receipt. Relatively steeper discounting of delayed outcomes is observed among people who report heavy use of tobacco (Bickel et al., 1999), alcohol (Petry, 2001), heroin (Kirby et al., 1999), cocaine (Coffey et al., 2003; Heil et al., 2006; Johnson et al., 2015), and methamphetamine (Hoffman et al., 2006; Monterosso et al., 2007), among other substances. Interestingly, findings for cannabis are mixed, with studies reporting only minimal differences between cannabis users and non-using controls (Johnson et al., 2010), or small-magnitude associations between discounting and cannabis misuse that are generally accounted for by other substance use (Patel & Amlung, 2020; see review and meta-analysis by Strickland et al., 2020).

Studies examining relations between polysubstance use and delay discounting have been scarce with somewhat discordant results. Businelle et al. (2010) found that individuals who were heavy smokers and those who were heavy smokers with a comorbid alcohol or substance use disorder did not differ in the degree to which they discounted future monetary rewards. A limitation of this study, however, was that Businelle et al. combined all drugs and alcohol into a single substance use disorder category, thereby precluding an evaluation of the unique impact of

specific drugs. This is important since a majority (78%) of the participants in the comorbid group met use disorder criteria for more than one substance (in addition to nicotine). Moreover, the authors noted that small group sizes may have been underpowered to detect an effect ($n = 20 - 36$), suggesting differences in delay discounting as a function of polysubstance use may emerge with a sufficiently powered sample. Moallem and Ray (2012) addressed several of these issues by examining the roles of alcohol and tobacco use on delay discounting in a larger sample and found that individuals who heavily drink alcohol and smoke cigarettes ($n = 213$) discounted small rewards more than individuals who were solely heavy drinkers ($n = 107$) or smokers ($n = 67$). Although this additive effect was not observed across medium and large rewards, results suggested use of more than one substance may indeed be associated with steeper delay discounting. Moody et al. (2016) expanded on this research by assessing differences in delay discounting among individuals who were either mono-, dual-, or tri-dependent on cigarettes, alcohol, and/or cocaine (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*; DSM-IV; American Psychiatric Association, 1994) drawn from separate study protocols across a 5-year span. Like those reported by Moallem and Ray (2012), results indicated that individuals dependent on cigarettes who were also dependent on more than one substance discounted future monetary rewards more than individuals dependent on cigarettes alone. Although dependence on additional substances was associated with steeper discounting than dependence on cigarettes alone, there were no differences as a function of the number of additional substances used, suggesting larger differences emerge when a second substance is involved and may be accompanied by a ceiling effect. Of note, individuals with cocaine dependence exhibited the steepest discounting, largely accounting for the observed ceiling effect,

as was evident by the fact that additional dependences among this group were not associated with steeper discounting.

Although current research on delay discounting of monetary rewards as a function of polysubstance use is relatively scarce, there is an established literature on neurocognitive performance among individuals who use multiple substances, specifically with respect to domains such as inhibitory control. For instance, in addition to assessing the impact of heavy drinking and/or cigarette smoking on delay discounting, Moallem and Ray (2012) examined performance on neurocognitive assessments measuring response inhibition (*Stop Signal Task*) and risky decision making (*Balloon Analog Risk Task*; Lejuez et al., 2002) and found no additive effects of heavy drinking and cigarette smoking (cf. Abroms et al., 2003 for an examination of acute effects). The authors offered that while both of these neurocognitive measures previously differentiated individuals who use substances from controls (Lejuez et al., 2003; Li et al., 2009), the tasks may not be as sensitive in differentiating between specific substance groups (cf. Verdejo-García et al., 2010). In an analysis of studies that assessed inhibitory control among mono and polysubstance users, Liu et al. (2019) found that after controlling for age and education, lifetime cannabis use was the only variable associated with reduced inhibitory control.

Taken together, the extant research on the associations between use of multiple substances, delay discounting, and neurocognitive performance is unclear. First, there is inconsistency in whether combined use of substances is associated with steeper discounting. Second, a number of the previous studies have been underpowered due to relatively small sample sizes (Businelle et al., 2010) or have only examined a limited number of substances (e.g., alcohol and cigarettes; Moallem and Ray, 2012). Given these two gaps in the literature, the purpose of the present study was to examine delay discounting (across \$200 and \$40,000 reward

magnitudes) and to compare several key domains of neurocognitive functioning among non, mono, and dual users of alcohol, cigarettes, and/or cannabis in a large, open-access dataset of adults from the Human Connectome Project.

Methods

Participants and Setting

We extracted data for use in the current study from the 1200 subjects release of the Human Connectome Project (HCP; release date 03/01/2017) with all procedures adhering to the HCP Data Use Terms for Open Access and Restricted Data (see <https://www.humanconnectome.org/study/hcp-young-adult/data-use-terms>). The HCP is a large-scale collaboration sponsored by the National Institutes of Health with the goal of building a "network map" (connectome) to better understand structural and functional connectivity within the healthy human brain as well as to facilitate research through an extensive repository of neural and behavioral data (Van Essen et al. 2013). Healthy young adults ranging in age from 22 – 35 years served as participants in the initial HCP study from which these data were drawn. Exclusion criteria for the initial HCP study consisted of diagnoses of the following: severe neurodevelopmental disorders, pre-existing psychiatric or neuropsychiatric disorders (except substance use), other illnesses that could confound neuroimaging data, as well as premature birth (see full recruitment and screening procedures in Van Essen et al., 2013). Of note, another study by Petker et al. (2019) used HCP data to examine associations between cannabis involvement, neuropsychological performance, and delay discounting. However, Petker et al. did not examine any variables related to combined use of multiple substances as was the focus of the current study.

Substance Use Groups

Self-reported use of alcohol, cigarettes, and cannabis on the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview led to the identification of three participant groups (see below). To be coded as an alcohol user, participants had to report drinking alcohol at least 1 day per week over the past 12 months (i.e., HCP variable SSAGA_Alc_12_Frq $\leq$ 4). This was to ensure a broad range of alcohol involvement and thus to be more representative of the general population, which is a strength of the HCP (see Table 1 for rates of substance use disorders and patterns of use). To be coded as a cigarette smoker, participants had to report smoking at least 100 cigarettes in their lifetime (i.e., HCP variable SSAGA_TB_Smoking_History = 3; coded as “regular smoker”) and report that they are still smoking (i.e., HCP variable SSAGA_TB_Still_Smoking = 1). To be coded for cannabis involvement, participants had to report using cannabis more than 100 times in their lifetime (i.e., HCP variable SSAGA_MJ_Times_Used $\geq$ 4). Participants who did not surpass any of these thresholds constituted non user status. This scheme resulted in the following groups: non (n = 412); mono (n = 407; comprised of alcohol [n = 323; 79.36%], cigarettes [n = 52; 12.78%], and cannabis [n = 32; 7.86%]); and dual (n = 116; comprised of alcohol-cigarettes [n = 54; 46.55%], alcohol-cannabis [n = 40; 34.48%], and cigarettes-cannabis [n = 22; 18.97%]). The number of individuals coded for tri use (n = 29) were too few to constitute a standalone group and were therefore omitted from the analyses reported here. Table 1 presents the full sample (final N = 935) characteristics (see *Data Analytic Approach* for participant exclusions).

Measures

All neurocognitive and individual differences measures were administered in person via computer. Complete details of the HCP study visits are provided in Barch et al. (2013). See below for a summary of measures included in the present analyses.

Delay Discounting

Participants completed two adjusting-amount delay discounting tasks (Du et al., 2002) across \$200 and \$40,000 magnitudes. In these assessments the value of the adjusting (immediate) alternative began at half the value of the fixed (delayed) alternative and, on the second trial, either increased or decreased by 50 percent of its initial value (depending on whether the participant chose the fixed or adjusting option, respectively). For the remaining trials, the adjusting option increased or decreased by 50 percent of the previous adjustment until the sixth choice, at which point the procedure started again on the next delay block. Repeating this procedure produced a series of indifference points, representing the point at which the value of the adjusting and fixed options was subjectively equal. Delays to the fixed alternative included *1 month, 6 months, 1 year, 3 years, 5 years, and 10 years*. As the primary measure of discounting, we used area under-the-curve (AUC) values for each reward magnitude provided in the HCP Open Access data release. The AUC metric is a model-free index of the degree to which an individual discounts delayed outcomes, with smaller AUC values reflecting steeper discounting (Myerson et al., 2001).

NIH-Toolbox Cognition Battery Tests

We examined performance on five neurocognitive measures from the NIH-Toolbox Cognition Battery (www.nihtoolbox.org; see also Gershon et al. 2013, Heaton et al. 2014). Each of these tasks produced raw scores that were then adjusted for age. These tests have largely shown good-to-excellent test-retest reliability as well as good convergent and divergent construct validity (Carlozzi et al., 2015; Tulsky et al., 2014; Weintraub et al., 2014; Zelazo et al., 2014).

Flanker Inhibitory Control and Attention Test (Executive Function/Attention). In this test individuals indicate the direction a centrally positioned arrow is facing while bordered

(i.e., flanked) on either side by similar stimuli facing the same direction (congruent trials) or the opposing direction (incongruent trials). The purpose is to direct visual attention toward the target stimulus while inhibiting attention toward extraneous dimensions of the task. The Flanker task involves 40 trials and produces a score incorporating accuracy and reaction time. The task has excellent test-retest reliability and has shown good and acceptable convergent and discriminant validity, respectively (Zelazo et al., 2014).

Dimensional Change Card Sort Test (Executive Function/ Set Shifting). This test measures the ability to shift attention between different dimensions of a matching task. Individuals view pairs of stimuli on the computer screen and must match a target stimulus to one of the two choices based on shape or color. The relevant matching dimension appears on the screen for each trial. An individual's score integrates accuracy and reaction time across 40 trials and, similar to the Flanker, the test has excellent test-retest reliability and good convergent and discriminant validity (Heaton et al., 2014)

List Sorting Working Memory Test (Working Memory). For this test, individuals view a series of stimuli on a computer screen and must then repeat, in order of size from smallest to largest, the name of each stimulus. The first condition features items from a single category (e.g., animals). In the second, items are drawn from separate categories (e.g., animals and food) and the individual must recall those from the first category in order of size and then do so for the second category. Each trial features an increasing number of items until the individual fails two trials of the same length, at which point the test is over. The total number of correct items across trials comprise an individual's raw score. Although this test is related to aspects of executive functioning that include response inhibition, cognitive flexibility, perseveration, and processing

speed, the test has good convergent validity with criterion measures of working memory and has excellent test-retest reliability (Tulsky et al., 2014).

Picture Sequence Memory Test (Episodic Memory). The goal of this test is to reposition pictures of thematically related objects and activities into a computer-demonstrated sequence. At the start of each trial pictures (ranging from 6 to 18, according to the participant's age) move sequentially from the center of the screen to an ordered position while accompanied by an audio description of the depicted object or activity. Pictures then return to the center of the screen in a randomized sequence and the task is to move them to the previously demonstrated spatial order. An individual's raw score is comprised of the total number of correctly recalled adjacent pairs across the three trials. The test has both excellent test-retest reliability and discriminant validity and strong associations with gold standard measures of episodic memory (Dikmen et al., 2014).

Pattern Comparison Processing Speed Test (Processing Speed). This test measures choice reaction time and involves identifying whether a pair of visual patterns are or not the same. Patterns appear on the computer screen in pairs and keying the "Yes" button records a response as "the same" while keying the "No" button records a response as "not the same". Scores are derived from the sum of correct responses. As is common in serial cognitive assessments, performance on this test tends to improve with repeated administration (Duff et al., 2007; McCaffrey et al., 2000).

Data Analytic Approach

Participants with missing data for delay discounting ($n = 8$; 0.66%), neurocognitive functioning ($n = 4$; 0.33%), or relevant substance-use screening ($n = 63$; 5.22%) resulted in listwise exclusion. Inconsistent delay discounting indifference points were defined according to

the methods in Petker et al. (2019; personal communication with second author, October 2020), with any point higher than the previous flagged as inconsistent. Individuals with three or more inconsistencies across the two magnitudes resulted in listwise exclusion ($n = 57$; 5.58%). Finally, participants classified as non users with any history of use disorder ($n = 42$; 4.1%) were also omitted listwise. We winsorized univariate outliers according to methods described in Tabachnick and Fidell (2007), with values greater than 3.29 standard deviations recoded as one unit greater than the highest non-outlier. This occurred for AUC₂₀₀ ($n = 11$) and the Dimensional Change Card Sort Test ($n = 6$). Examining the Mahalanobis distance, which reflects each participant's multivariate distance from the data centroid (i.e., multivariate mean; Tabachnick & Fidell, 2007), confirmed no multivariate outliers among the set of neurocognitive functioning tasks. Distributions were examined for normality and AUC₂₀₀ values were transformed prior to linear modeling by taking the natural logarithm to correct for positive skewness.

We conducted statistical analyses of sample characteristics at two levels. First, we analyzed differences in gender, income, age, or education between the three use groups (non use, mono use, and dual use). Second, we analyzed differences within groups (e.g., between the three mono use profiles or between the three dual use profiles). Pearson chi-squared tests examined differences in use disorder and dependence by primary use group, with alcohol use disorder (composite abuse and dependence scores) and cannabis dependence defined according to DSM-IV criteria and tobacco dependence according to the Fagerström Test for Nicotine Dependence (scores ≥ 4 ; Heatherton et al., 1991). Subsequent statistical comparisons involved a two-stage analytic approach where differences in delay discounting and then neurocognitive functioning were first examined by substance(s) endorsed and then as a function of the specific use profile. We used Pearson chi-squared tests to examine categorical variables and performed post hoc

testing using the adjusted standardized residuals to calculate p values based on a chi-squared distribution. Univariate and multivariate general linear modeling techniques were used for continuous variables and non-parametric Kruskal-Wallis tests for ordinal variables or when data transformations did conform to statistical assumptions about the distribution. Where appropriate, we adjusted significance values using the Benjamini-Hochberg false discovery rate (FDR) to control for expected proportions of Type I errors.

Results

Sample Characteristics

Sex. We identified significant sex differences between the use groups ($\chi^2[2, N = 935] = 31.27, p < .001$), with more female participants among non users ($p < .001$) and more male participants in the dual-use group ($p < .001$) than expected by chance. The proportion of females and males did not significantly differ within the three mono- ($\chi^2[2, N = 407] = 3.90, p = .14$) or dual-use profiles ($\chi^2[2, N = 116] = .57, p = .75$).

Age. There were no differences in age between use groups ($F[2,932] = .71, p = .49, \eta_p^2 = .002$), however, differences emerged within the mono-use group ($F[2,404] = 4.49, p = .01, \eta_p^2 = .02$), where individuals in the cigarettes-only profile were slightly older than those in the alcohol- ($p = .003$) and cannabis-only profiles ($p = .046$). Differences in age were also present in the dual-use group ($F[2,113] = 4.40, p = .01, \eta_p^2 = .07$), with the alcohol-cigarettes profile being slightly older than the alcohol-cannabis profile ($p = .004$).

Race. Differences in racial composition were significant, $\chi^2(6, N = 893) = 14.67, p = .02$. Specifically, individuals identifying as African American or Black were disproportionately represented in the dual-use group ($p = .009$), being more likely to endorse lifetime cannabis involvement along with either current alcohol use (27.50% of the alcohol-cannabis profile) or

cigarette smoking (36.36% of the cigarettes-cannabis profile). The racial composition of the remaining use groups and profiles (that provided data on race) did not differ from that expected by chance ($ps > .05$).

Education. Numerous differences in years of education also emerged ($\chi^2[2] = 44.28, p < .001$), with non users reporting slightly fewer years than the mono-use group ($p = .004$) and the dual-use group reporting fewer years than both of these groups ($ps < .001$). Years of education also differed within the mono-use group ($\chi^2[2] = 56.68, p < .001$), where the alcohol-only profile reported more years than the cigarettes- ($p < .001$) and cannabis-only profiles ($p < .001$); differences within the dual-use group ($\chi^2[2] = 11.18, p = .004$) occurred between the cigarettes-cannabis profile, who reported the fewest years in the present study ($m = 12.77$; $SD = 1.77$), and the alcohol-cigarettes ($p = .003$) and alcohol-cannabis profiles ($p = .002$).

Income. Annual income also differed between use groups, $\chi^2(2) = 12.77, p = .002$. Individuals in the dual-use group reported lower income than non users ($p = .004$) and the mono-use group ($p < .001$). There were also differences among the mono-use profiles, $\chi^2(2) = 22.68, p < .001$. Here, the alcohol-only profile reported higher income than the cigarettes- ($p < .001$) and cannabis-only profiles ($p = .006$). Differences among the dual-use profiles ($\chi^2[2] = 7.10, p = .03$) occurred between the alcohol-cigarettes profile and the cigarettes-cannabis profile ($p = .01$), with the latter reporting lower income.

Bivariate Associations

Table 2 contains Spearman rank correlations between demographic variables, delay discounting, and neurocognitive tests, a subset of which we report here. There were small positive associations between education and delay discounting across the \$200 ($r_s = .19, p < .001$) and \$40,000 ($r_s = .23, p < .001$) magnitudes; income was also modestly associated with

each magnitude, $AUC_{200}: r_s = .15, p < .001$; $AUC_{40k}: r_s = .14, p < .001$. Neurocognitive tests were associated with education ($r_s = .07 - .22$) and income ($r_s = .08 - .17$) and the only significant association between these tests and delay discounting occurred for the Picture Sequence Memory- ($AUC_{200}: r_s = .11, p = .001$; $AUC_{40k}: r_s = .08, p = .02$) and List Sorting Working Memory tests ($AUC_{200}: r_s = .11, p = .001$; $AUC_{40k}: r_s = .09, p = .01$).

Prevalence of Use Disorders

We found significant differences in the frequency of alcohol use disorder among alcohol-use groups, $\chi^2(2, N = 421) = 14.88, p = .001$. Post hoc tests (conducted as described earlier) indicated significantly higher rates for dual-use (alcohol-cigarettes [$p = .009$]; alcohol-cannabis [$p = .01$]) groups than expected by chance. There were no differences in nicotine dependence among tobacco-using groups ($\chi^2(2, N = 134) = 2.05, p = .36$) nor were there differences in cannabis use disorder among cannabis involvement groups ($\chi^2(2, N = 100) = 1.15, p = .56$).

Delay Discounting

Results indicated significantly lower AUC values (i.e., steeper discounting) for the \$200 magnitude as a function of cigarette smoking ($F[1,910] = 9.92, p = .002, \eta_p^2 = .01$), yet not of alcohol use ($F[1,910] = 1.51, p = .22, \eta_p^2 = .002$) or cannabis involvement ($F[1,910] = .09, p = .76, \eta_p^2 < .001$). There was, however, a significant alcohol $\times$ cigarettes interaction ($F[1,910] = 7.55, p = .006, \eta_p^2 = .01$), such that dual use of alcohol and cigarettes were associated with steeper discounting than use of alcohol alone. When controlling for education ($F(1,907) = 16.68, p < .001, \eta_p^2 = .02$), income ($F(1,907) = 2.80, p = .10, \eta_p^2 = .003$), and race¹ ($F(1,907) = 11.14, p$

¹ Primary and secondary delay discounting and neurocognitive performance analyses were restricted to individuals who provided data on race ($n = 917$; 98% of sample).

= .001, $\eta_p^2 = .01$), the main effect of cigarette smoking remained significant ($F(1,907) = 4.34, p = .04, \eta_p^2 = .01$), as did the alcohol $\times$ cigarettes interaction ($F(1,907) = 8.42, p = .004, \eta_p^2 = .01$).

A subsequent model with the specific substance profile as a between-subjects factor ($F(6,910) = 7.04, p < .001, \eta_p^2 = .04$) corroborated these results. Specifically, individuals endorsing mono use of cigarettes exhibited significantly steeper discounting than all profiles ($ps < .01$) with the exception of the cigarettes-cannabis profile ($p = .17$). Among those endorsing alcohol use, only the alcohol-cigarette profile exhibited steeper discounting than non users ($p = .007$). When controlling for education, income, and race, results for the cigarettes-only profile remained significant (all $ps < .01$) although differences between the alcohol-cigarettes profile and non users fell outside the threshold of significance after applying the FDR correction ($p = .017$; adjusted $\alpha = .014$). An analysis of the \$40,000 reward magnitude revealed no significant main effects of alcohol use ($F[1,910] = 3.01, p = .08, \eta_p^2 = .003$), cigarette smoking ($F[1,910] = 3.07, p = .08, \eta_p^2 = .003$), or cannabis involvement ($F[1,910] = .44, p = .51, \eta_p^2 < .001$). Results did, however, reveal significant alcohol $\times$ cigarettes ($F[1,907] = 4.43, p = .04, \eta_p^2 = .01$) and cannabis $\times$ cigarettes ($F[1,907] = 5.55, p = .02, \eta_p^2 = .01$) interactions, such that alcohol use or cannabis involvement were associated with significantly steeper discounting only among current cigarette smokers. Again, a secondary analysis controlled for education ($F[1,907] = 25.13, p < .001, \eta_p^2 = .03$), income ($F[1,907] = .93, p = .33, \eta_p^2 = .001$), and race ($F[1,907] = 7.36, p = .007, \eta_p^2 = .01$), with results remaining significant for both the alcohol $\times$ cigarettes ($F[1,907] = 5.20, p = .023, \eta_p^2 = .01$) and cannabis $\times$ cigarettes ($F[1,907] = 6.77, p = .009, \eta_p^2 = .01$) interactions.

There was also a significant main effect of substance profile ($F[6,910] = 5.60, p < .001, \eta_p^2 = .04$), where the cigarettes-only profile exhibited steeper discounting than non users and the

alcohol-only profile ($ps < .001$). Differences between these profiles remained significant ($ps < .01$) when controlling for education, income, and race.

Neurocognitive Performance

A multivariate analysis of variance (MANOVA) indicated significant effects of cannabis involvement ($\lambda = .98$, $F[5,906] = 4.06$, $p = .001$, $\eta_p^2 = .02$) on neurocognitive task performance, yet not of alcohol ($\lambda = .98$, $F[5,906] = 2.15$, $p = .06$, $\eta_p^2 = .01$) or cigarette use ($\lambda = .98$, $F[5,906] = 1.36$, $p = .24$, $\eta_p^2 = .01$). Univariate tests indicated cannabis involvement was associated with lower scores on the Flanker task (measuring inhibitory control; $F[1,910] = 9.43$, $p = .002$, $\eta_p^2 = .01$) and modestly with lower scores on the Picture Sequence Memory test (measuring episodic memory; $F[1,910] = 4.09$, $p = .04$, $\eta_p^2 = .004$). There was also a significant alcohol $\times$ cannabis interaction ($\lambda = .99$, $F[5,906] = 2.29$, $p = .04$, $\eta_p^2 = .01$) that occurred primarily for the Flanker task ($F[1,910] = 6.57$, $p = .01$, $\eta_p^2 = .01$). Specifically, individuals endorsing both alcohol use and cannabis involvement scored lower on response inhibition than those who endorsed only alcohol use ($t[358] = -3.51$, $p < .001$, $d = -.60$) or only cannabis involvement ($t[68] = -2.23$, $p = .02$, $d = -.54$). Controlling for education ($\lambda = .95$, $F[5,903] = 10.02$, $p < .001$, $\eta_p^2 = .05$), income ($\lambda = .98$, $F[5,903] = 3.12$, $p = .01$, $\eta_p^2 = .02$), and race ($\lambda = .99$, $F[5,903] = 1.94$, $p = .09$, $\eta_p^2 = .01$) retained the significant effect of cannabis involvement ($\lambda = .98$, $F[5,903] = 3.53$, $p = .004$, $\eta_p^2 = .02$) while tempering the alcohol $\times$ cannabis interaction ($F[5,903] = 2.16$, $p = .06$, $\eta_p^2 = .01$). Univariate tests confirmed the association between cannabis involvement and scores on the Flanker task ($F[1,907] = 7.01$, $p = .008$, $\eta_p^2 = .01$), while associations with those on the Picture Sequence Memory test were no longer significant ($F[1,907] = .76$, $p = .38$, $\eta_p^2 = .001$). A separate MANOVA revealed a significant role of substance profile ($\lambda = .95$, $F[30,3626] = 1.74$,

$p = .008$, $\eta_p^2 = .01$) which was observed primarily for the Flanker task ($F[6,910] = 2.65$, $p = .02$, $\eta_p^2 = .01$). Univariate tests indicated that individuals in the alcohol-cannabis profile produced lower scores than all other profiles ($ps < .05$) with the exception of the cannabis-only ($p = .02$; FDR adjusted $\alpha = .01$) and cigarettes-cannabis ($p = .28$) profiles. Although controlling for education, income, and race resulted in a non-significant multivariate effect of substance profile ($\lambda = .96$, $F[30,4507] = .10$, $\eta_p^2 = .01$), univariate comparisons with the FDR correction indicated individuals in the alcohol-cannabis profile scored lower on the Flanker task than non users ($p = .003$) as well as the alcohol-only ($p = .001$), cigarettes-only ($p = .002$), and alcohol-cigarettes ($p = .004$) profiles. There were no significant differences between the alcohol-cannabis and cannabis-only profiles ($p = .02$; FDR adjusted $\alpha = .01$) or the alcohol-cannabis and cigarettes-cannabis ($p = .19$) profiles.

Discussion

This study examined delay discounting and neurocognitive performance associated with non, mono, or dual use of alcohol, cigarettes, and/or cannabis in large sample of adults drawn from the HCP. Steeper discounting associated with use of multiple substances occurred only when individuals endorsed cigarette smoking in addition to either alcohol use or cannabis involvement; however, discounting associated with cigarette smoking was not significantly impacted by dual use of alcohol or cannabis. There are several hypotheses as to why we observed no evidence of the type of additive effects reported in Moallem and Ray (2012) and Moody et al. (2016). First, all substance-using groups in these studies met criteria for heavy use or dependence, whereas only a subset of the participants in the present study met these criteria. Second, Moody et al. included individuals with cocaine dependence and found that cocaine use was associated with the steepest discounting irrespective of mono-, dual-, or tri-substance group

status, raising the question as to whether additive effects reported by Moody et al. may have been driven largely by the steep discounting associated with cocaine dependence relative to dependence on alcohol or cigarettes only (see also García-Rodríguez et al., 2013). In the present study, individuals who smoked cigarettes exhibited the steepest discounting, potentially resulting in a similar ceiling effect where, unlike for those who endorsed alcohol use or cannabis involvement, discounting did not differ as a function using multiple substances.

Among neurocognitive measures individuals who endorsed both alcohol use and cannabis involvement scored lower on inhibitory control (as measured by the Flanker task) compared to individuals who endorsed alcohol use or cannabis involvement alone. Moallem and Ray (2012) found no differences in inhibitory control among individuals who engaged in mono or dual use of alcohol and/or cigarettes, highlighting the role of cannabis involvement in the present investigation as an important consideration when examining response inhibition. Indeed, the results reported here align with those reported by Liu et al. (2019) who found that, across studies measuring inhibitory control among individuals who engaged in substance use, lifetime cannabis use was the strongest predictor of task performance. Research on the acute effects of combined alcohol and cannabis provides evidence of a pharmacodynamic interaction that impacts performance on tasks measuring inhibitory control. Ramaekers et al. (2011) found that adult heavy cannabis users could develop tolerance to the impairing effects of cannabis during neurocognitive tasks, yet the presence of alcohol resulted in significant declines in response inhibition (as well as critical tracking and divided-attention tasks). Although response inhibition in the present study was not assessed in the context of acute alcohol or cannabis administration, it is plausible that residual effects of recent combined alcohol and cannabis use may have

contributed to lowered inhibitory control. Further research is needed to clarify the residual and long-term effects of combined alcohol and cannabis use on neurocognitive functioning.

The present results suggest that, in this sample, the combination of alcohol use and cannabis involvement was associated with higher prevalence of alcohol use disorder than use of alcohol alone, a finding that aligns with previous research reporting greater risk of alcohol use disorder among individuals who use both alcohol and cannabis (Hayaki et al., 2016; Stinson et al., 2006). Toward this end, heavier alcohol use combined with greater lifetime cannabis use may have moderated the additive effects on inhibitory control observed in the present investigation. Future studies should assess lifetime as well as current frequency of alcohol and cannabis consumption when used singly or in combination. Such research would help to illuminate the distinct and shared contributions of each substance to performance on tasks measuring inhibitory control and would add to the surmounting evidence implicating dual use of alcohol and cannabis as a marker of maladaptive behavioral and psychological processes.

These results align with previous studies (e.g., Businelle et al., 2010; García-Rodríguez et al., 2013; Moallem and Ray, 2012; Moody et al., 2016) that reported a systematic association between demographic variables and the specific substance use profiles. In the present study years of education, income, and race accounted for significant variance in rates of discounting; however, associations remained largely the same when controlling for these variables, providing stronger support for role of particular substance use patterns in delay discounting. Among neurocognitive measures, years of education and income were significantly associated with task performance. Although the modest association between reported cannabis involvement and episodic memory (measured using the Picture Sequence Memory test) was no longer significant

when controlling for these demographic variables, cannabis involvement remained a significant predictor of performance on the Flanker task across each of the models.

The promise of these results must be qualified in light of several limitations. First, due to constraints of the data collected as part of the HCP assessments, there was variability in the timeframes used to classify regular use or drug involvement. For example, alcohol use was measured as frequency during the past 12 months, whereas cannabis involvement was measured by number of lifetime uses. This limited our ability to confirm that participants were current cannabis users, precluding a more thorough analysis of the unique contributions of each substance to delay discounting and performance on tests of inhibitory control. Second, inclusion criteria of the HCP specified participants could have no pre-existing psychiatric or neuropsychiatric disorders, thereby limiting the degree to which these results may generalize to the larger population. Third, although cognitive assessments comprising the NIH Toolbox are valid and reliable measures (Heaton et al., 2014; Tulsky et al., 2014), they may not have been as capable of detecting subtle differences between substance-use profiles as more comprehensive neuropsychological tests (Meredith et al., 2020). Fourth, we acknowledge that although we corrected for false discoveries when conducting multiple statistical comparisons, there existed the possibility of committing Type I errors due to repeated tests. Finally, the number of participants comprising several of the dual-use profiles was low relative to that of the mono-use profiles (e.g., tobacco-cannabis vs. alcohol-only) and may have been underpowered to detect an effect, raising the possibility that group differences reported here may have been more pronounced with balanced profile sizes. Further research will determine the degree to which these findings are replicable.

In sum, these data suggest individuals who use multiple substances may be more likely to experience alcohol use disorder and, when endorsing both alcohol use and cannabis involvement, tend to score lower on a measure of inhibitory control relative to individuals who engage in either mono or dual use of alcohol and/or cigarettes. Findings for the discounting measures point to a central role of cigarette smoking in steep discounting seen among individuals who report using multiple substances. Future research should further examine factors that may differentiate individuals who consume multiple psychoactive substances, which may in turn inform efforts to treat and prevent polysubstance use.

Author Note

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Table 1. Sample Characteristics, Delay Discounting, and Neurocognitive Performance for Use Groups and Profiles (N = 935)

Variable	Non (n = 412)	Mono (n = 407)			Dual (n = 116)		
	n/a	Alcohol (n = 323)	Cigarettes (n = 52)	Cannabis (n = 32)	Alc-Cig (n = 54)	Alc-Can (n = 40)	Cig-Can (n = 22)
Variable	n (%)	n (%* Profile)			n (%* Profile)		
Sex (female)	267 (64.81)	167 (51.70)	34 (65.38)	15 (46.88)	21 (38.89)	13 (32.50)	9 (40.91)
Mean age ± SD, years	28.90 (3.87)	28.43 (3.42)	29.98 (3.58)	28.41 (4.05)	29.87 (3.41)	27.63 (3.82)	29.14 (3.85)
Race							
Caucasian/White	295 (71.60)	262 (81.11)	36 (69.23)	16 (50.00)	41 (76.79)	26 (65.00)	13 (59.09)
African American/Black	65 (15.78)	32 (9.91)	11 (21.15)	9 (28.13)	8 (14.81)	11 (27.50)	8 (36.36)
Asian/Native Hawaiian/Pacific Islander	32 (7.77)	20 (6.19)	2 (3.85)	1 (3.13)	3 (5.56)	0	0
Native American/Alaskan Native	0	1 (0.31)	0	1 (3.13)	0	0	0
More than one	7 (1.70)	6 (1.86)	2 (3.85)	4 (12.50)	2 (3.70)	2 (5.00)	1 (4.55)
Unknown or not reported	13 (3.16)	2 (0.62)	1 (1.92)	1 (3.13)	0	1 (2.50)	0
Hispanic/Latino?							
Yes	41 (9.95)	29 (7.62)	2 (3.85)	1 (3.13)	2 (3.70)	2 (5.00)	1 (4.55)
Unknown or not reported	3 (0.73)	0	0	1 (3.13)	0	2 (5.00)	1 (4.55)
Median income per year, \$	50k–74,999	50k–74,999	30k–39,000	20k–29,999	40k–49,000	30k–39,000	25k–34,999
Mean education ± SD, years	14.91 (1.80)	15.57 (1.52)	13.87 (1.70)	14.44 (1.66)	14.20 (1.79)	14.38 (1.93)	12.77 (1.77)
Drinking frequency (past 12 months)							
1–2 days per week		227 (70.28)			32 (59.26)	21 (52.50)	
3 days per week		78 (24.15)			17 (31.48)	12 (30.00)	
4–7 days per week		18 (5.57)			5 (9.26)	7 (17.50)	
Alcohol use disorder (DSM-IV)		77 (23.84)			22 (40.74)	18 (45.00)	
Cigarette smoking frequency (per regular day)							
1–5			26 (50.00)		28 (51.85)		8 (36.36)
6–10			16 (30.77)		14 (25.93)		11 (50.00)
11–15			5 (9.62)		6 (11.11)		1 (4.55)
16–20			1 (1.92)		5 (9.26)		2 (9.09)
>20			4 (7.69)		1 (1.85)		0
Nicotine dependence (FTND)			11 (21.15)		12 (22.22)		9 (40.91)
Cannabis involvement (lifetime instances)							
101–999				18 (56.25)		20 (50.00)	12 (54.55)
>1000				14 (43.75)		20 (50.00)	10 (45.45)
Cannabis dependence (DSM-IV)				11 (34.38)		18 (45.00)	8 (36.36)
Delay discounting (mean, ±SEM)							
AUC-\$200	0.27 (0.01)	0.25 (0.01)	0.16 (0.02)	0.24 (0.03)	0.21 (0.02)	0.25 (0.04)	0.17 (0.03)
AUC-\$40k	0.53 (0.01)	0.53 (0.01)	0.34 (0.04)	0.41 (0.05)	0.46 (0.04)	0.44 (0.04)	0.43 (0.07)
Neurocognitive performance (mean, ±SEM)							
Flanker (executive function/attention)	101.19 (0.49)	102.20 (0.57)	102.52 (1.25)	101.93 (1.53)	102.11 (1.32)	96.19 (1.86)	98.80 (1.76)
Card sort (executive function/set shifting)	101.64 (0.46)	103.41 (0.53)	100.04 (1.33)	101.99 (2.26)	101.99 (1.31)	101.58 (1.56)	103.59 (2.53)
List sort (working memory)	103.60 (0.67)	103.99 (0.74)	102.42 (1.96)	99.10 (2.26)	102.98 (1.76)	101.52 (2.11)	100.85 (2.18)
Picture sequence (episodic memory)	105.26 (0.80)	106.44 (0.91)	102.53 (2.74)	106.70 (3.54)	105.50 (2.01)	100.26 (2.74)	97.76 (3.94)
Pattern comparison (processing speed)	103.04 (1.04)	105.79 (1.10)	99.36 (2.38)	104.11 (2.77)	104.41 (2.18)	103.69 (3.07)	96.46 (4.58)

Note. * = Unless otherwise noted; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.); FTND = Fagerström Test for Nicotine Dependence; AUC = Area Under the Curve

Table 2. *Spearman Rank Correlations Between Demographic Variables, Delay Discounting, and Neurocognitive Tests*

Variable	1	2	3	4	5	6	7	8	9
1 Age									
2 Education	.125**								
3 Income	.258**	.368**							
4 AUC - \$200	-.019	.193**	.147**						
5 AUC - \$40,000	-.043	.225**	.144**	.726**					
6 Flanker	-.047	.068*	.076*	.013	.05				
7 Card sort	.035	.135**	.147**	.03	.059	.519**			
8 List sort	.012	.197**	.174**	.084*	.077*	.128**	.182**		
9 Picture sequence	.035	.215**	.150**	.108**	.070*	.167**	.207**	.322**	
10 Pattern comparison	.001	.132**	.116**	.035	.068*	.401**	.406**	.164**	.200**

Note. AUC = Area Under the Curve; * $p < .05$; ** $p < .01$