Insights from behavioral economics to characterize substance use involvement in adolescents: a cluster analysis

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Abstract
Reinforcement pathology (RP), a framework rooted in behavioral economics, has contributed to advances in the etiology and treatment of substance use. Drug demand and delay discounting (DD) have gained considerable interest, as they inform on the risk for escalation to substance use as well as treatment-specific targets. No prior study conducted in Spain has explored the interplay of demand and DD in adolescents. This study was aimed to: 1) identify whether DD and alcohol demand can yield empirically driven subgroups, and 2) examine differences in substance use involvement. The sample comprised 107 (% females = 54.2) adolescents (M=15.46, SD=1.25) from a high school in Asturias (Spain). Participants filled out an ad-hoc survey on substance use over the prior 30 days and one year. A 20-item alcohol purchase task (APT) was used to assess the reinforcing value of alcohol. The 21-item Monetary Choice Questionnaire evaluated impulsive choice. Two subgroups emerged: Cluster 1 (n = 72) and Cluster 2 (n = 35). Participants in C2 consistently showed higher impulsivity and demand for alcohol, signifying lower responsiveness to alcohol pricing. As compared to C1, those in C2 had a higher prevalence of past-month substance use [C1: 26/72 (36.1%) vs. C2: 33/35 (94.3%), p < .001], and a greater frequency of drunkenness [p < .001] and binge drinking episodes [p < .001]. RP differentiate between subgroups of adolescent substance users with patterns of more versus less substance use involvement. The existence of specific drug use subpopulations should be considered when designing environmental preventive policies.

Keywords: Adolescents; Behavioral Economics; Alcohol Demand; Delay Discounting.

Resumen
La economía conductual para caracterizar el uso de drogas en adolescentes: análisis de cluster. La patología del refuerzo (PR), basada en la economía conductual, ha contribuido al avance de la etiología y el tratamiento de drogas. La demanda y el descuento por demora (DD) informan sobre el incremento en el consumo y los objetivos de tratamiento. Ningún estudio realizado en España ha examinado la interacción entre ambas variables en adolescentes. Los objetivos fueron: 1) identificar si el DD y la demanda de alcohol pueden identificar distintos subgrupos y, 2) examinar sus diferencias en el consumo de sustancias. La muestra incluyó 107 (% mujeres = 54.2) adolescentes (M=15.46, DT=1.25) de enseñanza obligatoria en Asturias (España). Se evaluó el consumo de drogas en los últimos 30 días y el último año. El poder reforzante del alcohol se evaluó mediante el Cuestionario de Elección Monetaria. Se identificaron dos subgrupos: Grupo 1 (n = 72) y Grupo 2 (n = 35). El Grupo 2 mostró una demanda e impulsividad más elevada, indicando menor sensibilidad a incrementos en el precio. Comparado con el Grupo 1, el 2 obtuvo una prevalencia más elevada de consumo en el último mes [G1: 26/72 (36.1%) vs. G2: 33/35 (94.3%), p < .001], mayor frecuencia de borracheras (p < .001) y episodios de consumo intensivo de alcohol (p < .001). La PR permite caracterizar e identificar grupos con distintos patrones de consumo de sustancias. La existencia de distintos perfiles debería ser considerada a la hora de desarrollar políticas preventivas.

Palabras clave: Adolescentes; economía conductual; demanda de alcohol; descuento por demora.

The prevalence of alcohol consumption among adolescents in Spain has slightly declined within the last 5 years, with 58.5% reporting regular use. As per the latest estimates (Plan Nacional sobre Drogas, 2020), rates of cannabis use showed an uptrend in 2018 (19.3%), and e-cigarettes displayed the highest growth since 2014 (48.4% vs. 17%). Concerns on rising trends for tobacco use have come to the
forefront recently, in part due to widespread marketing and promotion of e-cigarettes (Bandara et al., 2020; Soneji et al., 2017).

Substance use and particularly drinking alcohol during adolescence are related to devastating consequences, including behavioral (anxiety, impulsivity, and risk-taking) (Spear, 2018), social (accidents, family problems, truancy) (Donoghue et al., 2017; White & Hingson, 2014), and neurological changes (memory, verbal learning, attention, hyperactivity) (Spear, 2018). In addition, early alcohol use is a potential risk factor for subsequent alcohol dependence and the onset and escalation of illicit drugs (Keyes et al., 2020; Rial et al., 2020; Spear, 2018).

In recent years, behavioral economics (BE) has been used increasingly within the addictions field to better understand substance use onset, maintenance, and relapse (Bickel et al., 2014; Cassidy et al., 2020; Mackillop, 2016; Sheffer et al., 2014). BE integrates concepts and methods from economics to understand irrational decision making (e.g., substance use) from a psychological perspective (Reed et al., 2013). Rooted in this framework, reinforcer pathology (RP) conceptualizes addiction as the result of two processes: high reinforcement value of a substance (i.e., high demand) and excessive sensitivity to small immediate rewards despite long-term consequences (i.e., high discounting rates) (Bickel et al., 2011; González-Roz et al., 2020).

Drug demand provides an index of subjective reward from substance use and it is assessed experimentally through hypothetical purchase tasks (HPTs) (Roma et al., 2017; Zvorsky et al., 2019). The assessment of drug demand becomes relevant in prevention research because it is considered a marker of substance use quantity and frequency as well as level of substance use severity (Martínez-Loredo et al., 2020). Both state (i.e., right now) and trait (i.e., in a typical situation) demand can be captured by HPTs in which participants report the amount of substance that they would purchase at different escalating prices. There exist HPTs for assessing both legal (i.e., tobacco and alcohol) and illegal drugs (i.e., cocaine, opioids) (González-Roz et al., 2019; Strickland et al., 2019; Zvorsky et al., 2019).

Specifically, the alcohol purchase task (APT) provides a multidimensional (i.e., cost, effort, and persistence invested in drugs) measure of the reinforcing value of alcohol (Kiselica et al., 2016; Murphy & MacKillop, 2006). BE research in college students shows alcohol demand is related to alcohol-related consequences (Joyner et al., 2019; Lemley et al., 2016; Merrill & Aston, 2020) and treatment outcomes (Cassidy et al., 2019; Murphy et al., 2015). Because the APT provides a high-resolution economic analysis of demand, it is widely used to inform tax policy. As an example, compared to only alcohol drinkers, co-users of alcohol-tobacco (Amlung et al., 2017; Yuresak et al., 2013), and alcohol-marijuana (Morris et al., 2018; Ramirez et al., 2020) informed of increased alcohol demand in an APT, which suggests increased alcohol pricing should be adopted to significantly impact consumption.

Another RP constituent is delay discounting (DD), a behavioral measure of impulsive choice that refers to the preference of small immediate rewards (e.g., alcohol consumption) over larger delayed ones (e.g., non-drug activities) (Reynolds, 2006). DD has been associated with alcohol-related problems (Dougherty et al., 2014), early onset of drug use (Richardson & Edalati, 2016), and typical alcohol intervention outcomes (Fernie et al., 2013). Of note is that DD has been a target of several interventions (Rung & Madden, 2018; Scholten et al., 2019), since it is potentially a predictor of unhealthy behaviors (e.g., low exercise frequency, poor diet habits, wearing a helmet while riding a bike or using sunscreen while being outdoors) and particularly drug use escalation and relapse in adolescents and young adults (Daugherty & Brase, 2010; Krishnan-Sarin et al., 2007; Lemley et al., 2016; Martínez-Loredo et al., 2018a).

Traditionally, RP research has examined the contribution of demand and discounting as separate processes involved in addiction, but it has put less focus on their joint effects (see e.g., Acuff et al., 2020; Phung et al., 2019). In addition, most of the prior studies have mainly comprised college samples (see e.g., Kiselica et al., 2016), and this population is qualitatively different from adolescents, in part due to their higher prevalence of binge episodes (Plan Nacional sobre Drogas, 2020). More recently, several studies have been conducted to profile clusters of DD and demand in individuals who use alcohol (Buscemi et al., 2021; Minhas et al., 2020). These previous efforts have concluded that DD and demand synergistically interact to account for hazardous drinking levels. Despite being valuable, they have included samples of adults and whether these two BE markers are informative to identify empirically discrete clusters in the adolescent population has yet to be elucidated.

With the aim of filling this gap in the research, the present study sought to characterize adolescents within the RP framework. Specifically, it had the following aims: 1) to examine whether DD and alcohol demand can yield empirically-driven subgroups of substance users, and 2) to assess differences in substance use involvement across them. It was hypothesized that discrete clusters of adolescents characterized by different levels of RP would emerge, and that participants showing higher DD and demand would evidence more hazardous levels of substance use. Looking beyond substance use in this age cohort has the potential to inform on preventive and treatment targets. The obtained results are expected to be clinically informative and set the line for future research on mechanisms of change.

**Method**

**Participants and procedure**

The study sample initially comprised 300 adolescents undergoing high school education from Asturias, Spain. Inclusion criteria were as follows: 1) being aged under 18 years, 2) being in secondary school, and 3) having no cognitive or intellectual disabilities. All participants were surveyed in 2019 in a single session and were supervised by trained assistants. The battery of questions took approximately 40 minutes.

A total of 180/300 adolescents did not provide the signed parental informed consent, thus leaving a sample of 120 adolescents that were surveyed in their own classrooms during class hours. After excluding 13 participants (9 because of incomplete data and another 4 due to random response), the final sample was comprised of 107 adolescents aged 14-19 (M = 15.46, SD = 1.25). The sample was 54.2% female and mean age of alcohol onset was 10.04 (SD = 6.42). A percentage of 55.1 (59/107) reported past-month substance use. Among past-month substance users, alcohol (100%), tobacco (27.1%), and cannabis (11.9%) were the most frequently consumed substances.

**Measures**

Data on sociodemographic and drug use were assessed using an ad-hoc survey adapted from the National Survey on Drug use in Secondary Education in Spain (ESTUDES; Plan Nacional sobre Drogas, 2020). The following variables were collected: 1) sociodemographic data (i.e., sex, age, weekly allowance, academic performance from 0 to 10), 2) number of substances used in the past month and year, 3) prevalence and frequency of substance use in the past month and year, 4) age of alcohol onset, 5) number of past-month drunkenness episodes (DE), and 6) frequency of binge drinking occasions (i.e., number of
Delayed reward discounting was assessed using the 21-item Monetary Choice Questionnaire (MCQ; Kaplan et al., 2016). The MCQ is a self-reported valid measure of discounting in which individuals make 21 choices in a yes/no dichotomic response system between smaller immediate and larger rewards (e.g., US$29 [€26] now versus US$82 [€74] in 14 days). As small, medium, and large levels of hyperbolic discounting are included, participants' temporal discounting (i.e., \( k \)) can be grouped at three different levels of magnitude. The smallest magnitude items corresponded with the amounts of US$29 (€26) and US$34 (€14), whereas the largest magnitude items pertained to US$65.39 (€59) and US$82 (€74).

An Alcohol Purchase Task, adapted from Murphy and MacKillop (2006), containing 20 escalating items was used to assess trait alcohol demand. All participants were asked how many standard units of alcohol they would purchase and consume across a range of prices from US$0.22 (€0.20). Data from the APT allow us to generate a demand curve and inform on the relative reinforcing efficacy of alcohol in a multidimensional fashion. The following four demand indicators were provided: 1) intensity (i.e., the overall level of consumption when no effort is made), 2) \( \text{omax} \) (i.e., the maximum quantity of purchased alcohol), 3) breakpoint (i.e., the price at which consumption ceases), and 4) elasticity (i.e., sensitivity of demand to alcohol pricing). As some cases (i.e., 29) presented zero demand, and given the cumulating recommendations against the use of pmax (González-Roz et al., 2019), this index was not included in the statistical analyses.

Statistical analyses

First, a descriptive analysis on sociodemographic (e.g., age, sex, academic performance) and substance use characteristics (e.g., patterns of substance use) was performed. Then, a data cleaning procedure was conducted to identify non-systematic responses from the MCQ and APT. The algorithm by Stein et al. (2015) resulted in no trends (i.e., <0.05 log-unit reduction in consumption per log-unit range in price) or bounces (i.e., demand increases >10% of price increments) in the APT responses. No evidence of non-systematic responses in the MCQ was obtained either. Discounting subscales within the current sample evinced adequate internal consistency (i.e., \( r \)'s between .58-.75).

APR raw data were individually examined for the presence of outliers and calculated following prior guidelines (Tabanich & Fidell, 2000). A total of 16 outliers (\( Z > 4 \)) were identified and accordingly replaced by one unit less than the maximum value. Three observed demand indices (breakpoint, \( \text{omax} \), and intensity) and one derived indicator (i.e., elasticity) from the Koffarnus et al. (2015) formula were used: \( Q = Q_0 \times 10^{(-a \cdot \text{log}(x - b))} \).

The HPCLUS procedure implemented in SAS software for k-means clustering and least squares estimations was used to identify clusters based on the following RP variables: alcohol demand (breakpoint, \( \text{omax} \), intensity) and impulsive choice. This method is appropriate as it identifies clusters of individuals based on quantitative variables (SAS Institute Inc., 2016). Given that 35 participants did not report on sufficient demand levels to adjust to the exponentiated equation, elasticity of demand was not included in the cluster analysis. To facilitate the interpretation and correct for abnormal kurtosis and skewness, all tested predictors were standardized. To identify an optimal baseline model for the entire sample size, three different classes were set without any grouping or co-variable. The final number of classes was selected based on the theoretical interpretability of each class and the aligned box criterion (ABC).

Finally, to examine the external validity of clusters, a set of chi-square and t-tests were carried out to examine differences in substance use involvement (i.e., past-month substance use, age of alcohol onset, and number of both DE and binge drinking occasions) and RP characteristics (i.e., impulsive choice and alcohol demand). To facilitate the interpretation, all the standardized variables were back-transformed. All analyses were carried out using SAS 9.4.

Results

Clusters of adolescents based on reinforcement pathology (RP) variables

As suggested by the highest ABC value (ABC = 5.37), a two-class solution was identified as the best fitting one. The first class comprised 72 participants (67.29% of the sample), whereas class two consisted of 35 adolescents (32.71%). Comparisons across clusters are displayed in Table 1. Participants in C2 evinced significantly higher overall discounting \( [t(105) = -2.82, p = .006] \), as well as discounting of large magnitude reinforcers \([t(105) = -2.37, p = .02]\), breakpoint \([t(40) = -7.00, p < .001]\), \( \text{omax} \) \([t(43.13) = -10.07, p < .001]\), and intensity of demand \([t(43.24) = -7.48, p < .001]\).

Differences between clusters in sociodemographic and substance use involvement

Comparisons in sociodemographic and substance use involvement characteristics are displayed in Table 2. As compared to participants in C1, those grouped into C2 showed a higher age of alcohol onset \((p < .001)\), higher substance use involvement within the past year \([C1 = 56.9\% \text{ vs. } C2 = 100\%, \chi^2 = 28.45, p < .001]\) and month \([C1 = 36.1\% \text{ vs. } C2 = 94.3\%, \chi^2 = 32.22, p < .001]\). The most used substances within these time frames were alcohol (past year: 71%; past month: 55.1%), followed by tobacco (past year: 23.4; past month: 15), and cannabis (past year: 12.1; past month: 6.5).

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1 One unit of alcohol in Spain (UBE in Spanish) is the equivalent of 10g of alcohol.
Table 2. Cluster differences in sociodemographic and substance use involvement characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cluster 1 (n = 72)</th>
<th>Cluster 2 (n = 35)</th>
<th>p</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% females)</td>
<td>48.60</td>
<td>65.70</td>
<td>.09</td>
<td>.16</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>15.71</td>
<td>15.33</td>
<td>.14</td>
<td>.30</td>
</tr>
<tr>
<td></td>
<td>(1.36)</td>
<td>(1.18)</td>
<td></td>
<td></td>
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<tr>
<td>Weekly allowance*</td>
<td>15.26</td>
<td>17.34</td>
<td>.31</td>
<td>.21</td>
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<tr>
<td></td>
<td>(9.66)</td>
<td>(10.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic performance*</td>
<td>7.19 (1.38)</td>
<td>7.18</td>
<td>&lt;.001</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>(1.44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of alcohol onset*</td>
<td>8.15 (7.91)</td>
<td>13.91</td>
<td>&lt;.001</td>
<td>-.49</td>
</tr>
<tr>
<td></td>
<td>(1.58)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Number of substances used in the past year*</td>
<td>1 (0, 4)</td>
<td>1 (1, 4)</td>
<td>&lt;.001</td>
<td>-.59</td>
</tr>
<tr>
<td>Number of substances used in the past month*</td>
<td>0 (0, 2)</td>
<td>1 (0, 3)</td>
<td>&lt;.001</td>
<td>-.59</td>
</tr>
<tr>
<td>Past year substance use n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>41a (56.9)</td>
<td>35b (100)</td>
<td>&lt;.001</td>
<td>.45</td>
</tr>
<tr>
<td>Tobacco</td>
<td>9a (36)</td>
<td>16b (45.7)</td>
<td>&lt;.001</td>
<td>.37</td>
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<tr>
<td>Cannabis</td>
<td>4a (30.8)</td>
<td>9b (69.2)</td>
<td>.003</td>
<td>.29</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1a (1.4)</td>
<td>0a (0)</td>
<td>.48</td>
<td>.07</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>0a (0)</td>
<td>3b (8.6)</td>
<td>.01</td>
<td>.24</td>
</tr>
<tr>
<td>Past month substance use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>26a (36.1)</td>
<td>33b (94.3)</td>
<td>&lt;.001</td>
<td>.55</td>
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<tr>
<td>Tobacco</td>
<td>3a (4.2)</td>
<td>13b (37.1)</td>
<td>&lt;.001</td>
<td>.43</td>
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<tr>
<td>Cannabis</td>
<td>1a (1.4)</td>
<td>6b (17.1)</td>
<td>.002</td>
<td>.30</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ecstasy</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Past-month binge drinking episodes (%)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>.57</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>13b (37.1)</td>
<td></td>
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</tr>
<tr>
<td>1-3</td>
<td>4a (5.6)</td>
<td>12b (34.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-9</td>
<td>3a (4.2)</td>
<td>8b (22.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19</td>
<td>0a (0)</td>
<td>2b (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0a (0)</td>
<td>0a (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past-month drunkenness episodes (%)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>.52</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>15b (42.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>6a (8.3)</td>
<td>17b (48.6)</td>
<td></td>
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</tr>
<tr>
<td>4-9</td>
<td>1a (1.4)</td>
<td>2a (5.7)</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>0a (0)</td>
<td>1a (2.9)</td>
<td></td>
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</table>

Note. Subscripts indicate statistically significant differences across groups. 
*Mean (standard deviation) is displayed. **Median (range) is indicated.

Discussion

The present study is the first to identify clusters of adolescents based on behavioral measures of RP (alcohol demand and DD) and to assess substance use involvement in a Spanish-speaking culture based on the RP framework. The following results are highlighted: (a) two distinct subgroups of adolescents were found based on RP levels, C1 (characterized by shallow discounting and low alcohol demand) and C2 (characterized by steeper discounting and high alcohol demand) and (b) adolescents grouped in Cluster 2 showed higher substance use involvement and a higher frequency of past-month DE and binge drinking episodes.

In the present study, adolescents falling into Cluster 2 showed higher levels of RP than those in Cluster 1 as evidenced by greater demand (i.e., breakpoint, omax, and intensity) and discounting (i.e., overall and large k). This leads them to be interpreted as groups with 'high' and 'low' RP severity, respectively. A similar classification has been recently reported in adult cigarette smokers (González-Roz et al., 2019; Nighbor et al., 2019), and parallels are found with studies showing DD as a predictor of latent class membership in adolescent substance users (Khurana et al., 2015; Martínez-Loredo et al., 2018b).

Adolescents grouped in cluster 2 presented greater substance use involvement (i.e., alcohol, tobacco, and cannabis) and higher frequency of past-month drunkenness and binge drinking occasions. Whether DD or demand precede or follow substance use is still a matter of debate (Snider et al., 2019; Verdejo-García et al., 2008). Although Audrain-McGovern et al. (2009) showed DD predicts cigarette use onset in the adolescent population, no longitudinal studies have been conducted so far to explore the etiological role of demand on substance use. Whatever the nature of the directionality, both impulsive choice and demand suggest synergistic effects on substance use frequency (Sofis et al., 2020) and severity (Weidberg et al., 2019), with DD being one of the impulsivity facets that confers the highest risk for escalating substance use (Martínez-Loredo et al., 2018a).

In this scenario both alcohol demand and DD have relevant implications from a preventive and clinical standpoint. Demand levels observed in C2 were indicative of excessively high alcohol use valuation. Of note is that breakpoint values in C2 were around 13.5€, suggesting that actual drink prices in the participants’ community (i.e., 5-10€ per drink) would need to be raised to impact alcohol demand. It is also worth mentioning that in both clusters some non-drug users (32/107; 30%) informed of high alcohol demand and delay discounting of large magnitudes, signifying a high risk of substance use over time.

Overall, higher levels of both RP processes correlate with higher engagement in drug-related reinforcement (Acuff et al., 2018; Strickland et al., 2019). Of note is that even when substance-free activities prevail over delayed substance use opportunities, the latter alternative is preferred in the end by those with steep discounting (Kirby & Herrnstein, 1995). This suggests that preventive and treatment strategies should specifically address RP processes more intensively than merely increasing the number of pleasant non-drug activities adolescents engage in. Although clinical research has not shown conclusive evidence on any psychological intervention for this population (Martínez-Loredo & Fernández-Hermida, 2019), experimental manipulations of DD hold promise for addressing RP. In particular, framing manipulations to reduce DD yielded the largest effect sizes in two recent review and meta-analytic works (Rung & Madden, 2018; Scholten et al., 2019). Nonetheless, and despite these promising results, any recommendation on its effectiveness for the adolescent population should necessarily be treated with caution due to the absence of randomized trials conducted with adolescents.

These findings should be interpreted in the context of several limitations. First, the study sample reported low levels of substance use. However, it has the benefit of characterizing different subgroups of adolescents (including non-drug using populations) and informing on the risks for substance use onset. Also, because this study is cross-sectional in nature, it cannot elucidate on temporal or causal relationships between RP processes and substance use. Another limitation is that we did not account for substance use severity or psychopathology, so our results may not entirely generalize to the adolescent population. Lastly, given the relatively low sample size, the representation is that we did not account for substance use severity or psychological factors.

Despite these limitations, the results herein underscore the relevance of further research on RP to characterize adolescents’ substance use. Given the link observed among demand, DD, and substance use, interventions should be targeted to reduce the utility (benefit/
cost ratio) of substance use and enhance the value of competing substance-free activities (Field et al., 2020). In the adult population, RP processes seem to be malleable to behavioral interventions (Murphy et al., 2015; Weidberg et al., 2018; Weidberg et al., 2015), but no prior assessments have been conducted among adolescents. Given the relevance of BE measures for predicting substance use involvement, further assessments of RP as ancillary outcomes of prevention and treatment interventions merit consideration.

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**Conflicts of interest**

The authors declare no conflicts of interest

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**References**


