The positive link between executive function and lifetime cannabis use in schizophrenia is not explained by current levels of superior social cognition

Siri Helle, Else-Marie Løberg, Rolf Gjestad, Ashley M. Schnakenberg Martin, Paul H. Lysaker

Division of Psychiatry, Haukeland University Hospital, Bergen, Norway
Department of Biological and Medical Psychology, University of Bergen, Norway
Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway
Department of Clinical Psychology, University of Bergen, Norway
Roudebush Veteran Affairs Medical Center, Indianapolis, IN, USA
Indiana University – Bloomington, Bloomington, IN, USA
Indiana University School of Medicine, Indianapolis, IN, USA

*Corresponding author. Paul H. Lysaker Roudebush VA Medical Center, Day Hospital
116H 1481 West 10th Street, Indianapolis, IN, 46202, USA. plysaker@iupui.edu

Abstract:

There has been a growing link between a history of cannabis use and neurocognitive performance in patients with schizophrenia. Fewer neurocognitive deficits may be a marker of the superior social cognition needed to obtain illicit substances, or cannabis use may indicate a distinct path to schizophrenia with less neurocognitive vulnerability. This study sought to determine whether the relationship of cannabis use and executive function exists independently of social cognition. Eighty-seven patients with schizophrenia were administered measures of social cognition and executive function. Social cognition was assessed using the Bell-Lysaker Emotion Recognition Test to measure affect recognition, and the Eyes and Hinting Tests to measure theory of mind. Executive function was assessed by the Mental Flexibility component of the Delis-Kaplan Executive Functioning Scale. The relations between the variables were examined with structural equation modeling. Cannabis use positively related to executive function, negatively related to affect recognition, and had
no relationship with theory of mind. There were no indirect effects of other illicit substances on amount of regular cannabis use. Alcohol use was related to worse affect recognition. The relationship between cannabis use and better executive function was supported and was not explained by superior social cognition

**Keywords:** Schizophrenia, Cognition, Cannabis, Theory of Mind, Executive Function, Emotional Intelligence

1.0 INTRODUCTION

To date, both the presence and duration of cannabis use has been linked to better neurocognitive functioning in patients with schizophrenia, especially in the domain of executive functioning (Potvin et al., 2008; Løberg and Hugdahl, 2009; Schnell et al., 2009; Rabin et al., 2011; Yucel et al., 2012). Recent research has also suggested a potential dose-response, finding that moderate use, as compared to little to no use or heavy use, was associated with less cognitive impairment as measured by neurocognitive and metacognitive capacity (Schnakenberg Martin et al., 2016). Of note, some studies have failed to replicate the finding of less severe cognitive impairment in individuals with schizophrenia and a history of cannabis use (Coulston et al., 2007; Mata et al., 2008; Bahorik et al., 2013), possibly due to variations in the definition of cannabis use (e.g. focus on a current or past history of use). In trying to understand why cannabis use may be related to better cognition, most authors have rejected the possibility that cannabis use directly increases cognitive functioning (Solowij and Michie, 2007; Løberg et al., 2014; Power et al., 2015). It has been suggested that better executive functioning or overall better neurocognition is a marker of a lesser degree of basic
biological vulnerability for developing the disorder (Løberg et al., 2014). Cannabis users may have developed psychosis through an alternative pathway with less cognitive vulnerability and at an earlier age (Myles et al., 2016; Schnakenberg Martin et al., 2016).

An alternative explanation is that the cannabis-neurocognition relationship is merely a reflection of better overall social cognition. It is possible that the ability to obtain and maintain illicit substances is facilitated by greater capacities for social cognition and social interaction (Solowij and Michie, 2007; Potvin et al., 2008). In this model, the cannabis–neurocognition relationship is considered to be attributed to the conceptual similarity (Penn et al., 1997; Harvey and Penn, 2010), supported by moderate correlations between these functional domains in several studies (Allen et al., 2007; Ventura et al., 2013). In such a model, social cognition could be considered a mediator of the relationship between neurocognition and general functioning (Schmidt et al., 2011).

While social cognition may influence overall neurocognition, these two facets of cognition are considered independent of one another (Lysaker et al., 2014). Neurocognition assesses more generalized abilities of an individual, while social cognition involves noticing the intentions of others, as well as understanding and responding to these intentions (Green et al., 2005). It has been suggested that social cognition includes at least three core domains: affect recognition (emotion processing), theory of mind (ToM), and attributional style/bias (Pinkham et al., 2014). ToM can be defined as the ability to infer the intentions, dispositions, and beliefs of others (Green and Horan, 2010), while affect recognition includes ratings of affects that are displayed in faces or voices. Meta-analyses and reviews report that individuals with schizophrenia show deficits in affect recognition, social perception, and ToM (Bora et al., 2009; Green and Horan, 2010; Kohler et al., 2010; Savla et al., 2013; Green et al., 2015).

If the cannabis–neurocognition relationship is attributed to better social cognition, cannabis using patients would be expected to have higher capacities for social cognition.
However, for social cognition the findings are inconclusive and scarce. Meijer et al. (2012) reported that lifetime cannabis use was associated with better performance on acquired knowledge, facial affect recognition, and facial identity recognition in schizophrenia patients (Meijer et al., 2012). Social cognition was also found to be higher in schizophrenia patients with a history of cannabis use, compared those with little or no use patients (Schnakenberg Martin et al., 2016). A negative effect of cannabis use on performance in a social cognition task that involved managing emotions in patients with schizophrenia spectrum disorders has also been reported (Sanchez-Torres et al., 2013). Potvin and colleagues (2007) performed an fMRI study suggesting that social emotional processing may be less impaired in substance using patients (alcohol and/or cannabis) with schizophrenia who demonstrated activation in more neural regions associated with social cognition, compared to patients with schizophrenia without substance use (Potvin et al., 2007).

The present study sought to test whether variance in social cognition can explain the relationship between one form neurocognition, namely executive function, and cannabis use. We chose to look at executive function given it represents the ability to perform the kinds complex and demanding cognitive processes required for complex social exchanges. To increase the validity of the assessment of social cognition measures of both ToM and affect recognition were included, and stabilized patients were recruited since executive function and social cognition may fluctuate in the acute phase of psychosis (Balogh et al., 2014; Helle et al., 2014). ToM and affect recognition were included as these factors are most closely related to successful interaction with other people. Amount of lifetime regular cannabis use was included to test the notion that social cognition may explain better executive function in cannabis using patients due to the ability to maintain substance use. To examine the interrelationship between executive function, social cognition, and cannabis, in addition to the effects of potential confounders such as other illicit drug use, structural equation modeling
was used. It was hypothesized that executive function would be positively associated with performance on the two measures of Theory of Mind as well as affect recognition. Further, we hypothesized that executive function and social cognition would be positively associated with amount of lifetime cannabis use and that social cognition would mediate the relationship of executive function and cannabis use.

2. METHODS

2.1 Design

This study had a cross-sectional design. Amount of lifetime cannabis use was the dependent variable. Executive functioning, age, and other illicit substance use were the independent variables and social cognition measures were the mediating variables.

2.2 Participants

The participants consisted of 87 patients with a schizophrenia diagnosis which was confirmed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). All patients were recruited from a VA Medical Center (n = 72, 82.8 %) and a Community Mental Health Center (n = 15, 17.2 %). Inclusion criteria were a schizophrenia diagnosis and stabilized symptoms defined as no changes in the use of antipsychotics, hospitalization or housing within the last 30 days. Exclusion criteria included current substance dependence (including cannabis and excluding nicotine) or a chart diagnosis of mental retardation. All patients gave informed consent, and received $30 for participating in the study. The study was approved by the Institutional Review Board of Indiana University-Purdue University Indianapolis.

2.3 Assessments
The clinical instruments and tests were administered by clinically trained research staff, possessing, at minimum, a Bachelor degree in psychology. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to rate psychotic symptoms. The PANSS five-component model of schizophrenia (Bell et al., 1994) was used, and scores for the negative, positive, cognitive, excitement and depression components were reported. Reliability was checked every second month, by blind ratings of taped PANSS interviews. The intraclass correlation coefficients ranged from .80 to .92 for PANSS components.

Substance use was recorded using items from the Addiction Severity Index (ASI) (McLellan et al., 1980; McLellan et al., 1985). The ASI asks participants to report the number of months of lifetime use in which they used a substance at least three times a week, and does not involve psychological testing or assessment. Substances reported included cannabis, alcohol, heroin, methadone, other opiates/analgesics, barbiturates, other sedatives/hypnotics/tranquilizers, cocaine, amphetamines, hallucinogens, and inhalants. The psychometric properties of the ASI have been assessed and validated for use with individuals with serious mental illness (Hodgins and El-Guebaly, 1992; Zanis et al., 1997).

2.4 Measures of executive function and social cognition

Executive functioning was examined by use of the Delis Kaplan Executive Function System (D-KEFS) which is comprised of nine tests designed to assess higher level cognitive functioning (Delis et al., 2001). The test battery includes Trail Making, Verbal Fluency, Design Fluency, Color-Word Interference, Sorting Test, Twenty Questions, Wording Context, Tower Test, and Proverb Test. In an exploratory factor analysis Clark et al. (2010) identified two separate components of executive functioning: inhibition/set shifting and mental flexibility by using D-KEFS in patients with schizophrenia (Clark et al., 2010). In the present study, the mental (cognitive) flexibility component was used as a measure of executive
function and more specifically, was considered to reflect one’s capacity to form ideas of how stimuli relate to one another (Lysaker et al., 2008). This factor is based on a synthesis of more complex executive functioning processes such as concept formation, abstraction, planning and initiation of problem-solving behavior (Clark et al., 2010). The following tests loaded on the cognitive flexibility factor: Word Context Test (total consecutively correct scaled score), Sorting Test Condition 1 (confirmed correct sorts scaled score), Twenty Questions Test (total weighted achievement scaled score), and Proverb Test Condition 1 (total achievement free inquiry scaled score).

ToM was examined by using the Eyes Test and Hinting Test. The Eyes Test consists of 36 photographs of pairs of men’s and women’s eyes (Baron-Cohen et al., 2001). Each photograph was presented one at a time to the participant whose task was to choose between four adjectives that could describe the affective or cognitive mental state of the person on the photograph. One point was given for each correct answer and it was possible to achieve a total score of 36 points. It has been suggested that the Eyes Test measures the ability to infer the mental state without drawing inferences about the content (Bora et al., 2009). The Hinting Test (Corcoran et al., 1995) consist of 10 short vignettes where two people are interacting. The scenarios are read out loud by the examiner, and each is ended by one of the characters giving a hint. The participants were required to report the real intended meaning. Each correct answer received 2 points. If not answered correctly, the examiner gave a prompt. Participants received a score of one when answering correctly after the additional information. It was possible to obtain a total score of 20. The test that was used in the present study was a version containing items rewritten in American English (Greig et al., 2004). Both the Eyes and Hinting Tests have been administered in stabilized outpatients with schizophrenia (Bora et al., 2006) and have been shown to distinguish between a non-clinical control group and a group of individuals with schizophrenia (Scherzer et al., 2012). However, it is useful to use two
different ToM tests when aiming to target different content and contexts related to ToM (Scherzer et al., 2012).

Affect recognition was measured by the Bell-Lysaker Emotion Recognition Task (BLERT) (Bell et al., 1997; Bryson et al., 1997). The BLERT is an audio-visual affect recognition task, designed to evaluate a person’s ability to discriminate between seven affect states, based on facial, voice-tonal and upper-body movement cues that are presented on video. The participant was seated three feet in front of a 21-inch monitor and shown 21 vignettes, that each lasted 10 seconds. The emotions that demonstrated by the same actor in the vignettes included: happiness, sadness, fear, disgust, surprise, anger, and no emotion. Each of the affect states were paired with three monologues, resulting in 21 combinations. After each presentation of the vignettes the tape was paused and the participant selected a response from the list of seven affects options. It has been demonstrated that the BLERT Total score has high categorical stability (weighed k = 0.94) and strong test-retest reliability (r = 0.76) in a sample of patients with schizophrenia (Bryson et al., 1997) and the BLERT has demonstrated discriminant validity (Bell et al., 1997). For the purpose of this study, we used the number of correct responses.

2.5 Statistical analyses

SPSS version 22 was used for the descriptive analyses (CORP, 2013). Categorical variables were presented by number and percentage and continuous variables were presented by mean and standard deviations. The analysis of the data was conducted in two phases. First, a Pearson correlation (Pearson r; one-tailed) was used to assess bivariate associations between the measures of executive function, social cognition (ToM and affect recognition), and substance use (cannabis, illicit substance use and alcohol). An illicit substance use variable was created that included heroin, methadone, other opiates/analgesics, barbiturates, other
sedatives/hypnotics/tranquilizers, cocaine, amphetamines, and hallucinogens. In addition, skewness was analyzed in order to check for normality in the outcome variable, cannabis use, before conducting structural equation modeling (SEM). The structural model of the direct and indirect relations between predictor variables and the cannabis outcome variable was estimated with Mplus 7.3 (Muthén and Muthén, 2008). Cognitive flexibility together with covariate variables, such as alcohol and illicit substance use, were specified as exogenous variables and the social cognition variables measuring ToM (Hinting and Eyes tests) and affective recognition were specified as intermediate variables. In this way, the model consisted of both direct and indirect effects. The Maximum Likelihood Robust (MLR) estimation was used to account and correct the model for non-normality in the outcome variable. Model fit was evaluated according to established guidelines (Kline, 2010; Wang and Wang, 2012). First, a tentative model with all parameters set free was estimated, including variables such as age and gender. Then, the model was re-estimated after removing relations and variables that did not contribute to the model (Jöreskog, 1993). SEM was used to evaluate whether social cognition mediated the relationship between executive function and cannabis use.

3. RESULTS

3.1 Sample characteristic

The sample mean years of age and education were 49.47 (SD = 8.34) and 12.86 (SD = 1.72), respectively. Seventy-five (86.2%) of the participants were male. The substances that were reported with the longest period of use were alcohol, followed by cannabis, cocaine, hallucinogens, amphetamine, heroin, opiates, methadone, sedatives and barbiturates. There were no reported uses of inhalants. See Table 1 for a total overview of sociodemographic, clinical, and cognitive characteristic of the sample.
3.2 Bivariate correlations

See Table 2 for a presentation of correlations among measures of executive function (mental flexibility), social cognition (theory of mind and affect recognition), cannabis use, illicit substance use, and alcohol use. Overall, cognitive flexibility demonstrated small to moderate significant correlations with ToM tasks, affect recognition and cannabis use (p < .05), and cannabis use showed small to moderate correlations with ToM tasks, illicit substance use and alcohol use (p < .05).

3.3 Structural equation model with both direct and indirect relations

First, a tentative model with all parameters set free was estimated. A final model was estimated after removing age and gender which did not contribute to the first tentative model. The final structural model received a satisfactory fit with data ($\chi^2 = 4.11$, df = 3, p = .25, CFI = 0.99, TLI = 0.94, RMSEA = .065, $\text{RMSEA}_{CI} = .000$-.203, RMSEA Close fit p < .05 = .34) (Figure 1).

The results showed that cannabis use was significantly positively related to cognitive flexibility and negatively related to affect recognition. Figure 1 illustrates that cognitive flexibility was also related indirectly with cannabis use via affect recognition. Additionally, Figure 1 illustrates a significant relationship between measures of social cognition, finding a significant direct effect between the hinting test and affect recognition, as well as between the eyes test and affect recognition. Illicit substance use was not related to any of the variables in the model, and alcohol negatively related to affect recognition.

4. DISCUSSION
In this study, we sought to determine whether a relationship exists between cannabis use and better executive functioning independent of social cognition. As predicted, we found that persons with greater capacities to form and shift between ideas reported more months of cannabis use across their lifetime. Elevated executive function and increased cannabis use was not entirely explained, however, by capacities for social cognition, but may be partially explained by affect recognition. To the contrary, a higher cognitive flexibility score was associated with increased affect recognition and decreased cannabis use, and thus affect recognition appeared to partially mediate the relationship between cognitive flexibility and cannabis use. As expected, executive functioning was significantly related to the social cognition measures. There were no indirect effects of other illicit substances on amount of cannabis use. Also, increased alcohol use was significantly related to a lower score on the affect recognition task.

Results thus replicate previous findings (Coulston et al., 2007; Schnell et al., 2009; Sanchez-Torres et al., 2013; Wobrock et al., 2013). They are consistent with a meta-analysis, that found patients with non-affective psychosis who had better executive functioning reported more cannabis use (Yucel et al., 2012). Previous findings also suggested that enhanced social cognition predicted recency and frequency of cannabis use (Arnold et al., 2015). While our findings did not assess recency or frequency of use, our findings fail to support the connection between social cognition and cannabis use, except for in relation to affect recognition, which was associated with a decrease in cannabis use.

One explanation for the present findings is that the results are inconsistent with the idea that the cannabis- neurocognition relationship is driven by enhanced social cognition used to obtain illicit substances. Findings, however, did support the notion that patients with the greatest amount of regular cannabis use may have a lower basic biological vulnerability for psychosis as evidenced by lesser neurocognitive deficits (see e.g. Løberg et al., 2014 for
details on this model). It is also possible that increased executive functioning acts as a protective factor for those with highest levels of cannabis use.

Alternatively, it is also possible that individuals with schizophrenia and a history of cannabis use may initially have had higher levels of social cognition which was responsible for the initiation of cannabis use, but that these abilities decreased with the development of psychosis and/or continued cannabis use. This hypothesis cannot be ruled out with the current analysis. Further, this hypothesis is supported by the literature which has shown that individuals with lifetime cannabis dependence have difficulty determining and discriminating facial emotions (Bayrakçı et al., 2015), as well as neural activation patterns during ToM tasks that are similar to those at risk for psychosis (Roser et al., 2012).

Interestingly, our results and this alternative hypothesis also align with recent findings that suggest a dose-response relationship in which moderate cannabis use is associated with fewer cognitive deficits, as opposed to high and little to no use (Schnakenberg Martin et al., 2016). While we did not compare groups categorically in regards to their cannabis use, our model indicated that when accounting for affect recognition, a domain of social cognition, decreased executive function is associated with increased cannabis use through indirect effects of affect recognition. Thus, our findings show support for why heavy cannabis use in schizophrenia was observed to be associated with more severe cognitive deficits compared to moderate cannabis use.

Use of other types of illicit substances did not influence the results. Increased alcohol use was related to a lower score on the affect recognition test. This is in line with the finding that chronic alcohol use may have adverse effects on the ability to recognize affect for substance users without psychosis (Kornreich et al., 2003). There could be several explanations for this finding that a higher use of alcohol, and also cannabis, are related to worse performance on the affect recognition test in the present study. For example, these
deficits could have been present before the initiation of substance use or may have been a result of extensive use of alcohol and cannabis. Generally, it has been reported that females have better social functioning than men (Ochoa et al., 2012). Also, male gender and younger age is often associated to substance use (Large et al., 2014); however, in the present sample, the majority were men in their late forties and gender and age were not significantly related to cannabis use or the social cognition measures.

In the present study, the BLERT and not the Hinting or Eyes test, was observed to have indirect effects on the relationship between executive function and cannabis use. This may be reflective of differences between the tasks, rather than the domains being measured. For example, the BLERT taps into a more sophisticated system that is relevant to the variables at hand. While the BLERT requires judgements be made about the integration of language, facial recognition and prosody, the eyes test requires judgements only on visual elements and the hinting test only on language. Conceptually, it is also possible that affect recognition, as opposed to ToM, is involved in the relationship between executive function and cannabis use in that cannabis use may uniquely interfere with one’s ability to integrate information as opposed to more automatic processes. This notion is supported by the literature in that deficits in emotion processing have been observed in regular cannabis users without schizophrenia compared to non-using peers (Gruber et al., 2009; Platt et al., 2010), although this pattern of findings has not been consistently observed in schizophrenia (Meijer et al., 2012). Previous research also failed to detect differences between heavy cannabis users without schizophrenia and controls in the Eyes Task but did find that cannabis users required additional processing time to correctly identify happy, sad and angry facial expressions (Platt et al., 2010). Thus, it is possible that insufficient time was permitted in the standardized testing environment to facilitate optimal performance on the BLERT in heavy cannabis users. For example, as cannabis use increases, increased or more intense processing time might be
required for integration of information and successful emotional expression recognition, which is more essential for affect recognition than ToM. Future research is needed to discern if there are more sensitive measures of social cognition more relevant to this unique relationship.

There are limitations. The variance explained by the final model is modest and could indicate that additional constructs may be involved. Also, the sample composition limits the generalization of the findings. Most of the patients were males in their late forties. Recording of amount of substance use were done retrospectively, however, studies have shown that self-report is able to garner accurate information regarding illicit substance use among adults with schizophrenia (Van Dorn et al., 2012). It is also important to acknowledge that individuals meeting diagnostic criteria, as per the DSM-IV, for current substance dependence were not included. Therefore, it is possible that the study findings do not reflect those with active substance dependence. Current/recent cannabis and tobacco use were not systematically assessed and could both potentially influence neurocognitive performance. Thus, future research should consider the roles of these substances as well as the effects of medication, education level, years of hospitalization and negative symptoms. Additionally, this study evaluated the relationship of executive function to cannabis use and social cognition, and thus future work is needed to discern the relationships with other forms of neurocognition, such as verbal memory and attention, and other forms of social cognition such as social perception and attributional style/bias. Age of cannabis initiation was also unknown in this study, which may be important to consider as current literature suggests that cannabis use during adolescence may be particularly relevant both to the risk of development of a psychotic illness (Moore et al., 2007; Bossong and Niesink, 2010), as well as to the potential degree of detriment to executive function (Jockers-Scherübl et al., 2007; Yucel et al., 2012).
In summary, results failed to suggest social cognition has an impact on the positive relationship between executive function and cannabis use in patients with schizophrenia. Affect recognition was observed to partially mediate this relationship, such that elevated executive function was associated with increased affect recognition and decreased cannabis use. However, the link between amount of lifetime cannabis use and executive functioning could have been explained by other factors such as medication use, education and negative symptoms. With replication this work could have clinical implications. For one this relationship could indicate better functional prognosis for the cannabis using patients, provided they cease using illicit substances (Mullin et al., 2012). These findings may also emphasize the importance of developing interventions that target affect recognition, as improving affect recognition may have subsequent effects of decreasing cannabis use.

CONFLICT OF INTEREST
Authors declare that there are no conflicts of interest.

ACKNOWLEDGEMENTS
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Figure 1: Structural model with beta weights describing the magnitudes between executive function, alcohol use, social cognition, and cannabis use.

Note: Illicit substance use was not included in the figure because it was not related to any other variable in the model. Cogn: Flex = Cognitive flexibility component of the Delis Kaplan Executive
Function System; Soc. Cogn: Hinting = ToM (theory of mind) measured with the Hinting Test; Soc. Cogn: Eyes = ToM measured with the Eyes Test; Soc. Cogn: Aff. Recogn = Affect recognition measured with the Bell-Lysaker Emotion Recognition Task; e = error; Cannabis Use, and Alcohol Use are based on lifetime months of regular substance use.

Table 1: Sociodemographic, clinical and cognitive data (N = 87)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Percent (%)</th>
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<tbody>
<tr>
<td>Gender</td>
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<td>Injectable typical antipsychotic</td>
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<th>Standard</th>
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<td>Age</td>
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<td>Life hospitalizations (years)</td>
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<tr>
<td>Depressive</td>
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<td>Total</td>
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<tr>
<td>ToM: Hinting Test</td>
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<td>4.22</td>
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<tr>
<td>ToM: Eyes Test</td>
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<td>Affect Recognition</td>
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<td>Lifetime Substance Use (months)</td>
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<td>Alcohol</td>
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<td>Cannabis</td>
<td>62.09</td>
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<td>Hallucinogens</td>
<td>8.29</td>
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Table 2 Bivariate (one-tailed) correlations between measures of executive functioning, social cognition and substance use

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<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<td>0.424**</td>
<td>0.379**</td>
<td>0.578**</td>
<td>0.220*</td>
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<td>2. Hinting Test</td>
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<td>0.384**</td>
<td>0.190*</td>
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<td>0.193*</td>
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<td>4. Affect Recognition</td>
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<td>-0.069</td>
<td>-0.168</td>
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<td>0.372**</td>
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<td>7. Alcohol Use</td>
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Note: *p < .05; **p < .001.

Highlights

- Association between higher executive function and cannabis use was supported.
- Cannabis use negatively related to affect recognition.
- Association between executive function and cannabis is independent of current social cognition.
- Other illicit substance use was not related to social cognition or cannabis use.