Cannabis use in patients with schizophrenia: motivation for use and relation to clinical variables
Dekker, N.

Citation for published version (APA):
CHAPTER 1.2

Implicit and explicit affective associations toward cannabis use in patients with recent-onset schizophrenia and healthy controls


Abstract

**Background.** Cannabis use is common in patients with recent-onset schizophrenia, and this is associated with poor disease outcome. More insight in the cognitive-motivational processes related to cannabis use in schizophrenia may inform treatment strategies. The present study is the first known to compare implicit and explicit cannabis associations in individuals with and without psychotic disorder.

**Methods.** Participants consisted of 70 patients with recent-onset psychotic disorder and 61 healthy controls with various levels of cannabis use. Three Single-Category Implicit Association Tests (SC-IAT) were used to assess ‘relaxed’, ‘active’ and ‘negative’ implicit associations toward cannabis use. Explicit expectancies of cannabis use were assessed with a questionnaire using the same words as the SC-IAT.

**Results.** There were no differences in implicit associations between patients and controls, however patients scored significantly higher on explicit negative affect expectancies than controls. Both groups demonstrated strong negative implicit associations toward cannabis use. Explicit relaxed expectancies were the strongest predictors of cannabis use and craving. There was a trend for implicit active associations to predict craving.

**Conclusions.** The findings indicate that patients suffering from schizophrenia have associations toward cannabis similar to controls, but they have stronger negative explicit cannabis associations. The strong negative implicit associations toward cannabis could imply that users of cannabis engage in a behaviour they do not implicitly like. Explicit relaxing expectancies of cannabis might be an important mediator in the continuation of cannabis use in patients and controls.
Chapter 1.2  - Implicit and explicit affective associations toward cannabis

Introduction


Further, these studies find that patients not only report positive effects, but also negative effects of cannabis use, like cognitive impairment. All of the above mentioned studies relied on self-report from the patient. Self-report measures, however, have been criticized because of their susceptibility to self presentation biases (e.g. Holtgraves 2004) and the possibility that cognitive processes mediating substance abuse are not accessible through introspection (McCusker 2001, Stacy 1997). For these reasons, Greenwald and Banaji (1995) proposed the use of more implicit (indirect) measures in addition to the use of explicit measures, which may tap different underlying cognitive-motivational processes (Stacy 1997, Wilson et al 2000). Moreover, several studies have found that implicit and explicit alcohol- and cannabis related cognitions predict unique variance in alcohol and cannabis use (Stacy 1997, Wiers et al 2002, Wiers et al 2005, Ames et al 2007).

Implicit measures are intended to assess relatively automatic associations that are difficult to gauge with explicit self-report measures. In general, these measures intend to make a participant react fast and spontaneous without self-reflection or introspection. Explicit measures assess cognitions that are related to slower deliberate processes that may inhibit more automatic, impulsive thinking and behaviour (Greenwald and Banaji 1995, Kahneman 2003). A test often used to assess alcohol or drug-related memory associations is the Implicit Association Test (IAT; Greenwald et al 1998). The IAT assesses the relative strength of associations indirectly, without asking people to reflect and report motivations for their behaviour. It is a computerized categorization task based on the principle that people find it easier to categorize stimuli together if those stimuli are strongly associated rather than if the stimuli are not associated. During the past decade, varieties of the IAT have been applied in the field of addiction research (e.g. Wiers et al 2002, Wiers et al 2005, De Houwer et al 2004, Wiers et al 2007a, Wiers et al 2007b). To date, two studies have used a cannabis-IAT to assess implicit associations toward cannabis. Field et al (2004) found more negative associations for marijuana related words in non-users compared to users, which could be interpreted as indicating that non-users associated unpleasant words more strongly with cannabis compared to users. No significant differences were found between non-users and users for positive marijuana associations. Ames et al (2007) reported that implicit excitement associations toward cannabis predicted cannabis use when
controlled for explicit cognition measures. Determining the predictive value of implicit measures after controlling for explicit measures is often used to determine the unique predictive power of implicit measures beyond commonly used explicit questionnaires. Implicit associations toward cannabis have not been investigated in patients with schizophrenia or related disorders. Also, few studies have been reported on craving for cannabis in psychotic disorder, although craving is regarded as a central phenomenon in drug dependence (Robinson and Berridge 1993, Franken et al 2003).

In the current study, one of our questions was whether patients with recent-onset schizophrenia and healthy controls differ on implicit and explicit cannabis-related cognitions. Secondly, we were interested in the extent to which explicit and implicit cannabis-related cognitions predict craving and cannabis use. We included participants with varying levels of cannabis exposure in order to determine whether the differences between patients and controls would depend on their cannabis use status, and secondly for a proper variance in cannabis use patterns and craving levels in the prediction model. Our study may contribute to more insight in the underlying processes in addictive behaviour in cannabis using patients suffering from schizophrenia.

**Methods**

**Participants**
We included male in- and outpatients from the Adolescent Clinic of the Psychiatric Department of the Academic Medical Centre in Amsterdam. This clinic is specialized in the treatment of young patients with schizophrenia spectrum disorders. In general, two third of patients are admitted for psychosis for the first or second time (Dekker et al 2008), and most of the patients use antipsychotic medication (De Haan et al 2003). Patients were included in the study if they had a diagnosis of schizophrenia or related disorder (schizoaffective disorder, schizophreniform disorder, or psychosis not otherwise specified), according to the Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association 1994) and were between 16 and 30 years old. Other inclusion criteria were that patients should be able and willing to give written informed consent, and be able to understand, speak and read Dutch. Exclusion criteria were diagnosis of a primary alcohol- or drug-related psychosis, a demonstrable brain or neurological or endocrine disease, or mental retardation. Male healthy controls were recruited from the community, and matched with respect to age and level of education. In a first recruitment phase, a larger proportion of controls had never used cannabis compared to patients. To ensure comparable levels of cannabis use in both participant groups, we later recruited controls more strictly on the basis of their level of cannabis use. Only males were included. Males generally have an earlier age at onset of psychosis, more often need intensive psychiatric care and more often use cannabis compared to females. Therefore males are overrepresented at our clinic. Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree family member with a history of psychotic disorder. After complete description of the study, written informed consent was obtained from all participants. The study was approved by the human subject review board of our institution.

**Materials and measures**

**Drug use**
Drug use was assessed with the Composite International Diagnostic Interview (CIDI, WHO 1994) section L. Participants with lifetime cannabis use of 5 times or less were considered to be ‘non users’.
Participants who had used cannabis more than 5 times lifetime were subdivided in ‘past users’ (those who had used cannabis more than 12 months ago) and ‘recent users’ (those who had used cannabis in the recent 12 months). Recent use was further subdivided into ‘infrequent use’ (less than weekly use in the past year) and ‘frequent use’ (daily or weekly use in the past year). In ‘recent users’, we estimated total amount of cannabis joints used in the past year by multiplying total weeks of cannabis use in the past year by average amount of cannabis joints used per week in the period that cannabis was used. Although there is a variety in percentage of delta-9-tetrahydrocannabinol ($\Delta^9$THC) and cannabidiol (CBD) in different cannabis products (Niesink et al 2007), one cannabis joint was considered to contain 1/2 gram of cannabis product (e.g. hash, weed etc.).

**Craving for cannabis**

The Obsessive Compulsive Drug Use Scale (OCDUS; Franken et al 2002) was used in past and recent cannabis users to measure craving for cannabis in the past 7 days. It is a self-rating scale consisting of 12 items with a 5-point, Likert-type rating that measures drug craving in the past 7 days. The 12 items were summed to create a total craving score (Cronbach’s alpha = 0.85).

**Implicit association test**

Implicit affective associations toward cannabis were assessed with three unipolar Single Category Implicit Association Tests (SC-IATs; Karpinski and Steinman 2006). Each SC-IAT measured a different affective association toward the use of cannabis; ‘active’ for positive arousal, ‘negative’ for negative affect, and ‘relaxed’ for positive sedation. Other IAT studies in addiction research have also used these subscales (e.g. Ames et al 2007, Wiers et al 2007b), because they represent the three main types of expectancies (Goldman and Darkes 2004, Wiers 2008a). Each affective category was compared with a neutral category labelled ‘neutral’. In the SC-IAT, participants have to categorize words as quickly as possible into different categories by pressing a left or right response-button. Each SC-IAT consisted of four phases that came in a fixed order (see table 1). For someone who has a very strong association between cannabis and one of the affective categories (e.g. active), the combination block where cannabis and active are on the same side will be significantly easier (and thus faster) to perform than the reversed combination block where cannabis and active are on different sides. Each combination phase consisted of 40 words. The three SC-IATs were presented in a fixed order. The IAT-tasks were programmed in Inquisit 2.0 (by Millisecond Software). Stimulus words were presented in blue font (34-point) in the middle of the screen. The affective label words were always presented at the top of the screen, appropriately positioned on the left or the right side of the screen, depending on the required response (as in Greenwald et al 1998). Feedback appeared in green letters (34-point) below the stimuli words: in case of a wrong response the words ‘try again’ appeared on the screen. The words used (see Appendix) were matched on number of letters, syllables, familiarity, and on valence and arousal values. The valence and arousal values of stimulus words were matched on group level (positive-arousal, positive sedation, negative and neutral words) by using student word ratings. As main outcome measure for the IAT, we chose one of the recently recommended new "D-algorithms" as main reaction time measure (D2SD, Greenwald et al 2003). In this algorithm all trials (including the practise phases) are included, an error-penalty to the reaction times on erroneous responses is given, and the outcome is divided by a personalized standard deviation of the combination phases (so the measure is not influenced by differences in response speed between participants, which is optimal for comparison between clinical and non-clinical groups).
Table 1. Schematic overview of the block sequence in the Active, Relaxed and Negative Single Category- Implicit Association Tests.

<table>
<thead>
<tr>
<th>Block 1</th>
<th>Block 2</th>
<th>Block 3</th>
<th>Block 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practise phase</td>
<td>Combination phase</td>
<td>Reversed practise phase</td>
<td>Reversed combination phase</td>
</tr>
<tr>
<td><strong>Active SC-IAT</strong></td>
<td>active</td>
<td>neutral</td>
<td>active</td>
</tr>
<tr>
<td></td>
<td>cannabis</td>
<td>cannabis</td>
<td>cannabis</td>
</tr>
<tr>
<td><strong>Relaxed SC-IAT</strong></td>
<td>relaxed</td>
<td>neutral</td>
<td>relaxed</td>
</tr>
<tr>
<td></td>
<td>cannabis</td>
<td>cannabis</td>
<td>cannabis</td>
</tr>
<tr>
<td><strong>Negative SC-IAT</strong></td>
<td>neutral</td>
<td>neutral</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>cannabis</td>
<td>cannabis</td>
<td>cannabis</td>
</tr>
</tbody>
</table>

Note: The following explanation is for the Active SC-IAT (for an explanation of the Relaxed SC-IAT, replace active with relaxed; for an explanation of the Negative SC-IAT, replace active with negative). During the practise phase (block 1), participants press the left key when the stimulus word that comes up in the middle of the screen is an active word (e.g. energetic), and press the right key when the stimulus word is neutral (e.g. standard). In the Combination task (block 2), participants press the left key when the stimulus word is an active or a cannabis word (e.g. hash), and press the right key when the stimulus word is neutral. During the Reversed practise phase (block 3), participants press the left key when the stimulus word is neutral, and press the right key when the target word is an active word. During the Reversed combination task, participants press the left key when the stimulus word is a neutral or a cannabis word, and press the right key when the stimulus word is an active word. Note that during the Combination phase and the Reversed Combination phase, cannabis is paired with one of the affective categories (e.g. active) or the neutral category respectively. The difference score between the reaction times of these two combined blocks is the so-called IAT-effect and gives an indication of strength of the association between the target (e.g. cannabis) and the affective category (e.g. active) (Greenwald et al 1998).

**Expectancy questionnaire**

The explicit cannabis expectancy measure was a questionnaire with 18 unipolar items, each consisting of a statement on using cannabis and an affective outcome (for example: ‘Smoking cannabis makes me relaxed’). Participants indicated the extent to which they agreed or disagreed with each item on an unmarked Visual Analogue Scale (VAS). The questionnaire consisted of an active (positive-arousal) scale, a negative outcome scale, and a relaxed (positive-sedation) scale, with the same affective words as used in the implicit test. Internal consistencies were as follows: VAS-active 0.81; VAS-relaxed 0.86; and VAS-negative 0.82.

**Procedure**

After signing the informed-consent form, drug use was assessed with the CIDI. Next, participants performed the cannabis SC-IATs on a computer, and subsequently the explicit expectancy questionnaire and craving questionnaire were filled out.

**Data screening**

IAT effects were calculated in such a way that higher IAT scores reflected a stronger association between cannabis and the affective dimension. The total amount of cannabis joints used in the past year scores and total craving scores were positively skewed, and log_{10} transformations addressed this problem satisfactorily. Of two participants, the score of total cannabis joints used in the past year were missing.

**Statistical analysis**

For comparisons between patients and controls on explicit and implicit measures, we used multivariate analysis of variance (MANOVA) with the three explicit variables and three implicit variables as dependent variables. In order to assess the relative contribution to multivariate differences, a discriminant analysis was performed that focused on the structure coefficients.
In the comparisons between patients and controls we first took all participants into account, second only past and recent cannabis users, third only recent infrequent and frequent users, and last only recent frequent cannabis users. We used multiple hierarchical regression analysis to evaluate the predictive utility of the explicit and implicit measures for craving and cannabis use (total cannabis joints used in past year). In the regression models we entered participant group into step 1, and highest achieved level of education into step 2 of the regression equation as background variables. In step 3, we added measures of explicit expectancies, and finally in step 4 we added measures of implicit associations. The implicit measures were entered last to evaluate their predictive value added, above and beyond that of the other (explicit) variables. The alpha level was set at .05 for all analysis to ensure an optimal trade-off between completeness (not leaving out possible interesting effects) and correctness (restricting Type-II error) given the exploratory nature of the data.

Results
Sample characteristics
Table 2 gives the sample characteristics. The patient group and the control group did not significantly differ in age, level of education, cannabis use (i.e. non use, past use only, recent infrequent use, and recent frequent use), total cannabis joints used in the past year, craving, and cannabis use disorder in the past year.

Table 2. Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>$\chi^2$</th>
<th>df</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (sd)</td>
<td>23.0 (3.6)</td>
<td>22.6 (3.7)</td>
<td>F=0.25</td>
<td>129</td>
<td>0.79</td>
</tr>
<tr>
<td>range</td>
<td>17.2-30.4</td>
<td>16.2-31.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>70 (100)</td>
<td>63 (100)</td>
<td></td>
<td></td>
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<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Schizophrenia, n (%)</td>
<td>50 (71.4)</td>
<td></td>
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<tr>
<td>Schizoaffective disorder, n (%)</td>
<td>12 (17.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophreniform disorder, n (%)</td>
<td>4 (5.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis NOS, n (%)</td>
<td>4 (5.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education: highest achieved level (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38 (54.3)</td>
<td>28 (45.9)</td>
<td>0.92</td>
<td>1</td>
<td>0.34</td>
</tr>
<tr>
<td>2</td>
<td>16 (22.9)</td>
<td>14 (23.0)</td>
<td>0.00</td>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>3</td>
<td>16 (22.9)</td>
<td>19 (31.1)</td>
<td>1.14</td>
<td>1</td>
<td>0.29</td>
</tr>
<tr>
<td>Age at onset of cannabis use, mean (sd)</td>
<td>15.4 (2.6)</td>
<td>15.0 (1.4)</td>
<td>Z= -0.17</td>
<td>1</td>
<td>0.87</td>
</tr>
<tr>
<td>range</td>
<td>11-23</td>
<td>12-20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non use</td>
<td>9 (12.9)</td>
<td>15 (24.6)</td>
<td>3.00</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>Past use only*</td>
<td>15 (21.4)</td>
<td>6 (9.8)</td>
<td>3.25</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>Recent infrequent use*</td>
<td>10 (14.3)</td>
<td>13 (21.3)</td>
<td>1.11</td>
<td>1</td>
<td>0.29</td>
</tr>
<tr>
<td>Recent frequent use*</td>
<td>36 (51.4)</td>
<td>27 (44.2)</td>
<td>0.67</td>
<td>1</td>
<td>0.41</td>
</tr>
<tr>
<td>Total cannabis joints in past year, mean (sd), range</td>
<td>461.9 (611)</td>
<td>339.9 (518)</td>
<td>Z = -1.06</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Total craving for cannabis score, mean (sd), range</td>
<td>20.8 (8.0)</td>
<td>20.5 (6.5)</td>
<td>Z = -0.29</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Cannabis use disorder in past year, n (%)</td>
<td>33 (47.1)</td>
<td>28 (45.9)</td>
<td>0.021</td>
<td>1</td>
<td>0.89</td>
</tr>
</tbody>
</table>

$^*$ 1 = Lower secondary prof. education/ intermediate vocational education, 2 = Higher general secondary education/ higher vocational education, 3 = Pre-university education/ university
$^*$ *cannabis use more than 12 months ago
$^*$ weekly or daily use in past 12 months
$^*$ in recent (past 12 months) cannabis users
$^*$ in past and recent cannabis users
$^*$ less than weekly use in past 12 months
Figure 1. Means on the explicit (a) and implicit (b) measures in all past and recent cannabis users by participant group. 

a) Means on the explicit (Visual Analogue Scale) measures (61 patients and 46 controls). b) Mean IAT effects (D-2SD, milliseconds) separately for each SC-IAT in all past and recent cannabis users by participant group (56 patients and 44 controls).

Comparison between patients and controls on explicit cannabis-related cognitions

MANOVA performed in all patients (n = 70) and controls (n = 61) indicated that patients differed significantly on their explicit cannabis use expectancies from healthy controls, $F(3, 127) = 5.58, p = 0.001$, Wilks’ Lambda = 0.88, partial eta squared 0.12. Relative contributions to this multivariate difference were (in descending order, with structure coefficients in parentheses): negative (0.87), active (0.10 ), relaxed (0.04 ). An inspection of the mean scores indicated that patients had higher scores on the negative scale ($M = 4.74, SD = 2.35$) than controls ($M = 3.35, SD = 2.07$).
MANOVA performed in all past and recent users of cannabis (61 patients and 46 controls) also indicated that patients and controls scored significantly different on the explicit scale, $F(3, 103) = 4.81$, $p = 0.004$. Wilks’ Lambda = 0.88, partial eta squared = 0.12, with relative contributions: negative (0.85), active (0.15), relaxed (-0.03). See figure 1a for mean scores on the explicit expectancy measure for all past and recent users of cannabis. MANOVA performed in the group of recent users (46 patients, 40 controls) and recent frequent users (36 patients, 27 controls) also indicated that patients and controls scored significantly different on the explicit scales (resp. $F(3, 82) = 3.39$, $p = 0.02$, Wilks’ lambda 0.89, partial eta squared = 0.11, and $F(3, 59) = 3.17$, $p = 0.03$, Wilks’ lambda 0.86, partial eta squared = 0.14), with highest relative contributions for this multivariate difference on the negative scale. Relative contributions in all recent users: negative (0.83), active (0.25), relaxed (-0.13). Relative contributions in recent frequent users: negative (0.89), relaxed (-0.19), active (0.14).

Comparison between patients and controls on implicit cannabis-related cognitions
Prior to conducting analysis on the SC-IAT, we detected outliers and excluded them from the dataset: five participants (4 patients, 1 control) were excluded from further analysis because they had an percentage of response errors on the SC-IAT that was more than three standard deviations from the mean, and two participants (1 patient, and 1 control) were excluded because more than 10% of their reaction times were faster than 300 ms on the SC-IAT (see Greenwald et al 2003). MANOVA performed in all patients (n=65) and controls (n=59) indicated that patients did not differ significantly from healthy controls on their implicit cannabis use associations, $F(3,120) = 1.16$, $p = 0.327$, Wilks’ Lambda = 0.97, partial eta squared 0.03. Additionally, no significant differences emerged between patients and controls when all past and recent users (56 patients, 44 controls), $p = 0.25$, when only recent users (42 patients, 38 controls), $p > 0.30$, or when recent frequent users (33 patients, 25 controls), $p > 0.80$, were taken into account. See figure 1b for mean scores on the SC-IATs for all past and recent users of cannabis.

Factors predicting craving and cannabis use
Prior to conducting regression analysis, we determined that no participant exceeded Cook’s distance >1. The regression models were evaluated on the basis of the results of bivariate analyses (see table 3); only the explicit and implicit variables that were significantly correlated with craving or cannabis use were included in the multiple regression models.

<table>
<thead>
<tr>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Expl Active</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. Expl Negative</td>
<td>-0.31**</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3. Expl Relaxed</td>
<td>0.39**</td>
<td>-0.43**</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4. SC-IAT Active</td>
<td>0.13</td>
<td>-0.01</td>
<td>0.09</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5. SC-IAT Negative</td>
<td>-0.03</td>
<td>0.12</td>
<td>-0.10*</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6. SC-IAT Relaxed</td>
<td>-0.19*</td>
<td>-0.11</td>
<td>0.08</td>
<td>0.02</td>
<td>0.11</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7. Craving</td>
<td>0.26**</td>
<td>0.11</td>
<td>0.36**</td>
<td>0.20*</td>
<td>-0.22*</td>
<td>-0.04</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8. Cannabis use</td>
<td>0.03</td>
<td>-0.12</td>
<td>0.47**</td>
<td>0.06</td>
<td>-0.11</td>
<td>0.31</td>
<td>0.57**</td>
<td>-</td>
</tr>
</tbody>
</table>

Note. Expl. Active = Explicit Positive-Arousal cannabis use expectancies; Expl Negative = explicit Negative cannabis use expectancies; Expl Relaxed = Explicit Positive-Sedation cannabis use expectancies; SC-IAT = Single Category Implicit Association Test; SC-IAT Active = D (standardized difference score)- 2SD score for the positive-arousal SC-IAT; SC-IAT negative = D - 2SD score for the negative SC-IAT; SC-IAT relaxed = D - 2SD score for the positive-sedation SC-IAT; Craving = total OCDUS score; Cannabis use = total cannabis joints used in past year in participants that have used cannabis in the past year. * p ≤ 0.10. ** p < 0.05. *** p < 0.01.
Craving as dependent variable

Craving was best predicted by the explicit relaxed measure ($\beta = 0.25$, $p = 0.017$), adjusted for the other predictors (see table 4). The implicit measures (as a group) showed a trend toward significance in the prediction of craving ($\Delta R^2 = 0.05$, $p = 0.06$) above and beyond the background variables and explicit measures. Overall, the full model explained 20.9% of the variance in the total craving score, $R^2$ adjusted $= 0.15$, $F (7, 92) = 3.47$, $p < 0.005$. In subsequent analysis we evaluated a trimmed regression model for craving, which included all (borderline) significant ($p < 0.10$) predictor variables (see table 5). This overall trimmed regression model was statistically significant, $F (3, 96) = 6.97$, $p < 0.0005$ explaining 18% of the variance in craving, $R^2$ adjusted $= 0.15$. Again, craving was best predicted by the explicit relaxed measure ($\beta = 0.31$, $p = 0.001$), adjusted for the other implicit predictors. The implicit measure of active associations predicted craving borderline significantly ($\beta = 0.17$, $p = 0.068$).

Cannabis use as dependent variable

Explicit relaxed expectancies significantly predicted cannabis use ($\Delta R^2 = 0.21$, $p < 0.0001$) above and beyond the background variables (see table 4). Overall, the full model explained 24.6% of the variance in total cannabis joints used in the past year, $R^2$ adjusted $= 0.21$, $F (4, 73) = 5.96$, $p < 0.0005$.

Table 4. Summary of hierarchical multivariate regression analysis for variables predicting craving and cannabis use (cross-sectional)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cumulative</th>
<th>Simultaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$\Delta R^2$</td>
</tr>
<tr>
<td>Craving n=100</td>
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<td></td>
</tr>
<tr>
<td>Participant group</td>
<td>0.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Education 1</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Education 2</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Expl. Relaxed</td>
<td>0.16</td>
<td>0.14**</td>
</tr>
<tr>
<td>SC-IAT Active</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>SC-IAT Negative</td>
<td>0.21</td>
<td>0.05*</td>
</tr>
<tr>
<td>Cannabis use n=78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant group</td>
<td>0.01</td>
<td>-0.23</td>
</tr>
<tr>
<td>Education 1</td>
<td>0.14</td>
<td>0.25</td>
</tr>
<tr>
<td>Education 2</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Expl. Relaxed</td>
<td>0.25</td>
<td>0.21***</td>
</tr>
</tbody>
</table>

Note. Craving = total OCDUS score; Education 1 = Lower secondary prof. education/intermediate vocational education; Education 2 = higher general secondary education/higher vocational education; Expl. Active = explicit positive-arousal cannabis use expectancies; Expl. Relaxed = explicit positive-sedation cannabis use expectancies; SC-IAT = Single Target Implicit Association Test; SC-IAT Active = D (standardized difference score) - 2SD score for the Positive-Arousal SC-IAT; SC-IAT Negative = D - 2SD score for the negative SC-IAT; Cannabis use = total cannabis joints used in past year (in participants that have used cannabis in the past year); $\# p \leq 0.10$; * $p < 0.05$; ** $p < 0.01$

Table 5. Trimmed regression model for craving

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cumulative</th>
<th>Simultaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$\Delta R^2$</td>
</tr>
<tr>
<td>Craving n=100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expl. Relaxed</td>
<td>0.13**</td>
<td>0.02</td>
</tr>
<tr>
<td>SC-IAT Active</td>
<td>0.16</td>
<td>0.03$^2$</td>
</tr>
<tr>
<td>SC-IAT Negative</td>
<td>0.18</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Note. Craving = total OCDUS score; Education 1 = Lower secondary prof. education/intermediate vocational education; Education 2 = higher general secondary education/higher vocational education; Expl. Relaxed = explicit positive-arousal cannabis use expectancies; SC-IAT = Single Target Implicit Association Test; SC-IAT Active = D (standardized difference score) - 2SD score for the Positive-Arousal SC-IAT; SC-IAT Negative = D - 2SD score for the negative SC-IAT; Cannabis use = total cannabis joints used in past year (in participants that have used cannabis in the past year); $\# p \leq 0.10$; * $p < 0.05$; ** $p < 0.01$
Discussion

In this study we found that patients with recent-onset psychotic disorder and controls did not differ in implicit affective cannabis associations. In contrast, patients scored significantly higher on explicit negative cannabis expectancies than healthy controls, irrespective of their level of cannabis use. An explanation for this finding could be that all patients received education in our clinic about how cannabis use can deteriorate symptoms and course of the disease. Additionally, patients might have experienced more severe negative effects of smoking cannabis. Some evidence for this comes from Green et al (2004), who found that a larger proportion of individuals with psychosis reported psychotic symptoms as negative effect of cannabis, compared to healthy controls. Peters et al (2009) found that patients with schizophrenia reported more often than controls to have felt depressed, anxious, suspicious and to have experienced more psychotic symptoms during cannabis intoxication. Additionally, an experimental study showed that patients with schizophrenia, compared to healthy controls, were more sensitive to the cognitive effects of ∆9THC on learning and recall (D’Souza et al 2004, D’Souza et al 2005). However, Henquet et al (2006) did not replicate this finding, but found that differential ∆9THC sensitivity was restricted to subjects homozygous for the catechol-O-methyltransferase (COMT Val158Met) Valine (Val) allele and that this was in part conditional on psychometric psychosis liability.

Both patients and controls had strong explicit relaxed outcome expectancies of cannabis use. Relaxation is a consistently reported effect of cannabis in both people with and without psychosis (Green et al 2003, Pencer and Addington 2008, Dekker et al 2009). Relaxation might be an important motivator for use of cannabis in both participant groups. Our regression analysis showed that the explicit relaxed subscale was the strongest predictor for craving and level of cannabis use. Ames et al (2007) also found that explicit relaxed expectancies strongly predicted cannabis use in a high school population. Possibly, people that experience relaxing effects may eventually smoke more cannabis, and consequently develop more craving for cannabis.

Another notable association among patients and controls was the strong implicit negative association toward cannabis. This finding is in line with previous research on implicit associations toward alcohol use (Wiers et al 2002, De Houwer et al 2004, Wiers et al 2005) and toward smoking (Swanson et al 2001). However, another cannabis IAT study (Field et al 2004) found that negative associations were present in non-users of cannabis, but not in users of cannabis. Usage of a different IAT may explain differences between their and our findings: Field et al (2004) used a bipolar IAT, were positive associations were measured relative to negative associations.

There are some plausible explanations for the strong implicit negative cannabis associations. It might be that users of cannabis engage in a behaviour they do not implicitly like, and go along with their cannabis use behaviour more on the explicit rather than on the implicit level. Other explanations have to do with concerns about the validity of the IAT effect. One concern is that strong negative implicit associations may partly reflect general associations that are present in a culture instead of someone’s personal associations (Karpinski and Hilton 2001). Houben and Wiers (2007a, 2007b) examined this by using personalized alcohol-IATs (where the labels ‘positive’ and ‘negative’ were replaced by the labels ‘I like’ or ‘I dislike’). They found implicit positive associations toward alcohol and weaker negative attitudes toward alcohol, which is in line with the hypothesis that the standard alcohol-IAT may to some extent reflect negative general associations with alcohol. However, in one of their studies (2007b), the personalized IAT did not show evidence for implicit positive attitudes toward alcohol.
Another concern is that the IAT measures associations at the level of the category, and not at the level of the individual words from this category (De Houwer, 2001). People might associate ‘cannabis’ (the category label in our study) with negative consequences because of usage of this word in the media and associate words like ‘weed’ or ‘stoned’ with more pleasant effects. Houben and Wiers (2006a) found that this ‘label effect’ indeed may play a role in the IAT, however in all IAT versions they found strong negative alcohol associations, suggesting they reflect something ‘real’ in memory rather than an IAT artefact. Lastly, it has been argued that IAT effects could reflect non-associative factors based on salience, rather than on implicit associations (Rothermund and Wentura, 2004). Salience could facilitate IAT performance: when two salient categories have to be categorised under the same key, this will be easier than categorising under two different keys. A previous alcohol-IAT study showed that this salience asymmetry could only partly explain the results found for the negative associations, and not at all for the positive and arousal associations (Houben and Wiers 2006b). Additionally, many studies (e.g. Thush et al 2007a, Thush et al 2007b, Ames et al 2007) show that the IAT predicts behaviour and it correlates with explicit measures on less controversial themes (Hofmann et al. 2005), implying that the IAT encompasses personal associations, at least in part. Also, in our study implicit associations correlated significantly with craving, so extrapersonal contamination is not likely to completely account for the effects with the cannabis SC-IAT. In the present study there was a trend for implicit active associations to predict craving. Wiers et al (2002) hypothesized that their finding of implicit arousal associations in heavy drinkers is in line with the incentive-sensitization theory (Robinson and Berridge 1993) according to which addictive behaviours are related more to ‘wanting’ (sensitized arousal), than to liking of substances. This sensitized arousal or intensively wanting of substances may be transformed in craving (Robinson and Berridge 1993), and thereby explain our finding.

As opposed to craving, cannabis use was unrelated to implicit associations. This is in contrast with another cannabis IAT study (Ames et al 2007) who revealed that implicit excited associations predicted cannabis use. Differences between the present study and previous findings of Ames et al (2007) might be contributed to differences in the study population, outcome variables and differences in the IATs used. In summary, there is reason to doubt the validity of the strong negative substance-associations found here and in many other studies (extrapersonal associations, saliency effects), but the active and relaxation associations appear to be more valid and related to meaningful other constructs including craving.

Limitations and strengths
A limitation of this study is that the percentages of THC en CBD in cannabis products used by the participants was unknown. THC is thought to give psychotomimetic effects (D’Souza et al 2004) and CBD has anxiolytic and antipsychotic properties (Zuardi et al 2006, Leweke et al 2000). Although it is likely that the variation of cannabis ingredients was equally distributed among patients and controls, we do not know the different contributions of THC and CBD to explicit and implicit cannabis associations. Another limitation is that we did not have self-reports on cannabis intoxication at the time of testing and we did not use urinary screens to confirm that subjects were not intoxicated at the time of testing. To control for possible slower reaction times and response errors due to cannabis intoxication, we resp. used the D2SD reaction time measure (Greenwald et al 2003) which is not influenced by differences in response speed between participants, and we excluded IAT data of five participants who had a percentage of response errors on the SC-IAT that were more than three standard deviations from the mean. Lastly, our study had a cross-sectional nature and many of the...
observed relationships were relatively weak. A prospective study examining relations between cannabis associations and cannabis use variables might overcome these limitations. However, this study does provide additional information for the role of cannabis-related cognitions in patients with recent-onset schizophrenia spectrum disorders. Strengths of this study were that we had a relatively large sample of recent-onset schizophrenia patients, and a matched control group. To our knowledge, this is the first study that assessed implicit cannabis associations in both patients with psychosis and controls.

**Conclusions and practical implications**

Our findings indicate that patients suffering from schizophrenia have associations toward cannabis similar to controls, but they have stronger negative explicit cannabis associations. The finding of strong negative implicit associations toward cannabis in both patients and controls could imply that they engage in a behavior they do not implicitly like. Explicit relaxed associations toward cannabis were the strongest predictor of cannabis use and craving, which might imply that the perceived relaxing effects of cannabis is an important mediator in the continuation of cannabis use. Therefore, intervention and prevention strategies aimed at reducing cannabis use should target the explicit cognitions related to the relaxing effects of cannabis that may be due to the CBD compound in cannabis. Further, because implicit positive arousal cognitions were associated with craving, an important intervention would be to challenge these cognitions in order to prevent relapse into cannabis use. Although researchers have begun to study whether it is possible to change implicit alcohol associations (Wiers et al. 2008b), future research is needed to indicate how automatic cannabis associations could be changed, and if so, how this effects the use of cannabis.

**Appendix**

### IAT word stimuli (translated from Dutch)

<table>
<thead>
<tr>
<th>Positive arousal stimuli (active words)</th>
<th>Neutral stimuli (neutral words)</th>
</tr>
</thead>
<tbody>
<tr>
<td>creative</td>
<td>indefinite</td>
</tr>
<tr>
<td>energetic</td>
<td>general</td>
</tr>
<tr>
<td>cheerful</td>
<td>usual</td>
</tr>
<tr>
<td>motivated</td>
<td>standard</td>
</tr>
<tr>
<td>talkative</td>
<td>impartial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive sedation stimuli (relaxed words)</th>
<th>Neutral stimuli (neutral words)</th>
</tr>
</thead>
<tbody>
<tr>
<td>relaxed</td>
<td>accompanying</td>
</tr>
<tr>
<td>calming</td>
<td>preceding</td>
</tr>
<tr>
<td>contented</td>
<td>supplementary</td>
</tr>
<tr>
<td>comforting</td>
<td>frequent</td>
</tr>
<tr>
<td>reassuring</td>
<td>additional</td>
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</table>

<table>
<thead>
<tr>
<th>Negative stimuli (negative words)</th>
<th>Neutral stimuli (neutral words)</th>
</tr>
</thead>
<tbody>
<tr>
<td>miserable</td>
<td>central</td>
</tr>
<tr>
<td>suspicious</td>
<td>daily</td>
</tr>
<tr>
<td>listless</td>
<td>middle</td>
</tr>
<tr>
<td>anxious</td>
<td>common</td>
</tr>
<tr>
<td>confused</td>
<td>customary</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Target (cannabis words)</th>
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</tr>
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<tbody>
<tr>
<td>weed</td>
<td></td>
</tr>
<tr>
<td>hash</td>
<td></td>
</tr>
<tr>
<td>cannabis</td>
<td></td>
</tr>
<tr>
<td>stoned</td>
<td></td>
</tr>
<tr>
<td>blow</td>
<td></td>
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</tbody>
</table>
References


Chapter 1.2 - Implicit and explicit affective associations toward cannabis


Wiers RW: Alcohol and drug expectancies as anticipated changes in affect: negative reinforcement is not sedation. Substance Use & Misuse 2008a; 43, 429-444


Zuardi AW, Crippa JAS, Hallak JEC, Moreira FA, Guimarães FS. Cannabidiol, a cannabis sativa constituent, as an antipsychotic drug. Brazilian journal of medical and biological research 2006; 39, 421-429.