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

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CHAPTER 1.3

Craving for cannabis in patients with psychotic disorder, their non-affected siblings and healthy controls: psychometric analysis of the Obsessive Compulsive Drug Use Scale

Abstract

Cannabis use is more common in individuals with non-affective psychotic disorder and their siblings compared to healthy controls. As cannabis use is associated with a greater risk to develop psychotic disorder and an adverse outcome in those who already developed psychosis, it is important to know the role of craving in continued cannabis use and relapse in these vulnerable subjects. Therefore, we examined the validity of the Obsessive Compulsive Drug Use Scale for cannabis (OCDUS-CAN) in patients with non-affective psychotic disorder, their siblings, and healthy controls who all used cannabis in the past year. Simultaneous component analysis (SCA) was used to determine component weights that optimally explained the (co)variance of the OCDUS-CAN variables in these different populations simultaneously. A three-component SCA solution explained 74.2% of the total variance, and consisted of well-interpretable subscales that could be best described as craving/urge, resistance, and impact. Reliability of the subscales was good. The three subscales significantly discriminated between frequent and infrequent cannabis users. Patients scored higher on the craving/urge and impact scale than siblings and controls, which could be related to primary and secondary symptoms of their disorder. The OCDUS-CAN is well suitable for people with or without vulnerability for psychotic disorder.
Introduction

Cannabis is one of the most frequently used substances in patients with schizophrenia (Hambrecht and Häßner 1996, Cantwell et al 1999, Barnes et al 2006) and cannabis use is more common in people with psychosis than in the general population (Regier et al 1990, Hall and Degenhardt 2000). Moreover, cannabis use in patients with a psychotic illness is associated with increased relapse and rehospitalisation and with decreased treatment adherence (Linszen et al 1994, Zammit et al 2008). Non-psychotic siblings of individuals with schizophrenia also have higher rates of cannabis use than healthy controls (Smith et al 2008), which is an important finding since cannabis abuse is associated with a greater risk of developing psychosis (Moore et al 2008), and siblings of individuals with schizophrenia have a greater genetic vulnerability to develop schizophrenia like disorders (Gottesman 1991, GROUP 2010, Van Winkel et al 2010). Little is known about underlying mechanisms that lead to continued cannabis use in high risk subjects and patients with psychiatric disorder, and about the role of craving in continuous use and relapse after initial abstinence. Craving is regarded as a central phenomenon of drug dependence (Robinson and Berridge 1993, Franken 2003). The WHO defines craving as a very strong desire for a psychoactive substance or for the intoxicating effects of that substance, and further states that craving develops as a result of conditioned associations that evoke conditioned withdrawal responses, and that it may also be induced by the provocation of any physiological arousal state resembling an alcohol or drug withdrawal syndrome (WHO 2008).

Measuring craving for cannabis in individuals with a vulnerability for psychotic illness and in patients with a psychotic disorder is important both from a clinical and scientific point of view. A valid measure of craving for cannabis could help health care providers and scientists understand the different elements that compose craving. Also, a valid cannabis craving measure could be used for monitoring urges for cannabis use, which is important, because craving predicts relapse into drug use (Doherty et al 1995, Anton et al 1996, Robbins and Ehrman 1998, Roberts et al 1999, Hartz et al 2001). In addition, monitoring craving for cannabis before, during and after pharmacological or psychological treatment may improve our understanding of how treatment affects craving. Only a few studies on craving for cannabis in patients with psychotic disorder are available (Potvin et al 2006, Akerele and Levin 2007, Van Nimwegen et al 2008, Dekker et al 2009a). These studies focused on the relation between craving and the effects of antipsychotic treatment and underlying associations towards the use of cannabis, and used self-report questionnaires for cannabis craving, like a modified version of the Penn Alcohol Craving Scale (PACS; Potvin et al 2006), the Marijuana Craving Report (Akerele and Levin 2007), and the Obsessive Compulsive Drug Use Scale for cannabis use (OCDUS-CAN; Van Nimwegen et al 2008, Dekker et al 2009a). To our knowledge, there are no reports about the validity of these measurement specifically for cannabis craving, nor in patients with psychotic disorder. In addition, no studies of cannabis craving in siblings of individuals with psychotic disorder have been reported. We are aware of one validated self-report questionnaire measuring subjective craving for cannabis, namely the Marijuana Craving Questionnaire (MCQ; Heishman et al 2001, Singleton et al 2002), but the MCQ has not been validated in a population with psychotic disorder.

The first aim of our study was to assess whether the Obsessive Compulsive Drug Use Scale (Franken et al 2002) for cannabis use (OCDUS-CAN) is a valid cannabis-craving scale that can be used for both research and clinical purposes. More specifically, we assessed 1) whether a common factor structure of the OCDUS-CAN can be found in patients with psychotic disorder, their non-affected siblings and
healthy controls; 2) whether this common factor structure is dependent on frequency of cannabis use; and 3) whether the OCDUS-CAN subscales are internally consistent. The second aim of the study was to assess whether the OCDUS-CAN subscale scores differentiate between patients, siblings and controls and between low and high frequent cannabis users.

Methods

Participants
Participants took part in the Genetic Risk and Outcome of Psychosis (GROUP) study, a multi site longitudinal cohort study in The Netherlands that focuses on vulnerability and resilience factors for variation in expression and course of non-affective psychotic disorders (for details, see Korver and Quee et al submitted). Inclusion criteria for patients were the following: (1) age range 16 to 50 years, (2) diagnosis of non-affective psychotic disorder according to DSM-IV (APA, 1994) and (3) good command of Dutch language. Inclusion criteria for siblings and controls were age 16-50 years, and good command of Dutch language. Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree family member with a history of psychotic disorder. Patients were recruited from mental health centres covering more than 75% of the mental health institutes in the Netherlands, including both inpatient and outpatient clinics. Participating siblings with a lifetime or current diagnosis of non-affective psychotic disorder were considered as patients. Healthy controls were recruited by advertisements and by mailings in the local area. All participants gave written informed consent after complete description of the study. The study was approved by the human subject review boards of all four Academic Centres. To increase the size of the control group, research data of 36 healthy male controls were added from another observational study in which the OCDUS-CAN was used as well (described in Dekker et al 2009a). This study applied the same inclusion and exclusion criteria for healthy controls as the GROUP study, and - as in the current study- used the Composite International Diagnostic Interview (CIDI; WHO 1994) to measure substance use patterns.

Measures
Diagnosis
To establish DSM-IV (APA, 1994) diagnosis of psychotic disorder, three sites of the GROUP study used the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al 1992) and one site used the SCAN Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1; Wing et al 1990). Age at first occurrence of positive symptoms was taken as age of onset of the illness. The Positive and Negative Syndrome Scale (PANSS; Kay et al 1987) was used to assess symptoms in patients.

Substance use
Substance use was assessed with a short version of the CIDI (WHO 1994) sections B (tobacco use), J (alcohol use) and L (drug use). It contains items on the quantity of tobacco use and alcohol use in the past year, and items on the quantity and severity of use of drugs like cannabis and cocaine in the past year and lifetime. Frequency of drug use is categorised in daily, weekly, or less than weekly use. Current cannabis use was defined as cannabis use in the last month. Nicotine use was defined as daily use of cigarettes for at least one month in the past 12 months. Alcohol use in the past year was defined as having consumed more than 12 alcoholic drinks in the past 12 months. One alcoholic drink was considered to be equal to approximately 10 grams of ethanol. Illicit substance use (other than...
cannabis) in the past year was defined as having used any hard drug (using terms like stimulants, speed, amphetamines, hallucinogens, opiates, cocaine or ecstasy) in the past year. In order to have biological validation concerning about recent use of cannabis, urinalysis for the presence of tetrahydrocannabinol (THC) was carried out using immunoassays with a cut off of 50ng/ml. Cannabis urine screening has a detection window up to 30 days, but the detection time has been documented in literature to be even longer (up to three months), depending on intensity of cannabis use (Musshoff and Madea 2006). Given the relatively high cut-off level of 50ng/ml, a conservative detection window of one month can be inferred. Urinalysis was not available for the 36 healthy controls from the observational study (see above, Dekker et al 2009a).

**Craving for cannabis**

Cannabis craving was measured with the OCDUS-CAN (see appendix), which is a cannabis-specific version of the original OCDUS (Franken et al 2002). It is a self-rating scale with a 5-point, Likert-type rating that measures drug craving in the past 7 days. Higher scores indicate higher craving for cannabis. The original OCDUS is based on the Obsessive Compulsive Drinking Scale (OCDS: Anton et al 1996), which has been translated into Dutch by Schippers et al (1997). Franken et al (2002) reported good reliability and validity for the original OCDUS in 102 heroin dependent patients. In this study, three underlying factors were found using exploratory Principal Component Analysis (PCA) and Varimax rotation: ‘thoughts and interference’, ‘desire and control’, and ‘resistance to thoughts and intention’. The first two factors showed substantial correlations with a measure of instant (now) craving. As suggested by the authors (Franken et al 2002) one item about becoming anxious or upset if one was prevented from using, was deleted because of the low factor loading of this item on the first factor, resulting in an OCDUS-CAN with 12 items.

**Statistical analysis**

Participants were divided into 6 groups according to subject type (patient, non-affected sibling or control) and frequency of consumption (frequent = at least weekly cannabis use in the past year, infrequent = less than weekly cannabis use in the past year). To compare the three subjects groups (patients, non-affected siblings, controls) and the two frequency groups (frequent use, infrequent use) on demographics and substance use characteristics, chi-square tests were used for categorical variables and one-way between-groups analyses of variance were conducted for continuous variables. To assess whether the OCDUS-CAN has a common factor structure in all three subject groups and in the two frequency groups Simultaneous Component Analysis (SCA) was used. To ensure sufficient variance in levels of cannabis use and craving, the SCA was restricted to those participants that had used cannabis in the preceding 12 months. Only data from subjects who had fully completed the OCDUS-CAN were included in the analyses. Components are linear combinations of the OCDUS-CAN items. Separate principal component analysis (PCA) in each population leads to component weights that, by definition, explain the maximum amount of variance of the OCDUS items. These component weights, however, generally result in a different component structure in each population. SCA on the other hand tries to find component weights that optimally explain the variance of the variables in different populations simultaneously (Millsap and Meredith 1988). The variance accounted for by SCA can be compared with the variance accounted for by the optimum solution in explained variance terms (i.e. separate PCA). If the explained variance of the OCDUS-CAN items by the subpopulation specific PCA components is comparable to that of the SCA components it can be concluded that the common
component solution adequately describes the (co)variance of the OCDUS-CAN items in the different populations. In other words, it can then be stated that the component structure is invariant over these populations. However, when a common component structure is found, this does not automatically mean that these components have the same meaning in the different populations. This can be assessed by comparing the factor loadings of components in the different populations.

In this study, the component weights resulting from a PCA solution of the mean correlation matrix (i.e. the correlation matrix based on the pooled populations) were used as a starting point. Since a three factor solution was reported in the original OCDUS study (Franken et al 2002), we started our analysis with a three-component solution. The resulting SCA weight matrix was transformed into a more simple structure by Varimax rotation. This weight matrix was further transformed into a simple weight matrix using only 1 and 0 as weights. The latter transformation is based on the values of the component weights in the Varimax rotated weight matrix. This caused only minimal loss of variance explained and greatly increased interpretability of the resulting components. Since we used only 1 and 0 as weights (i.e. binary weights) subscale scores could be calculated by simple adding the scores of the items of a subscale. All analysis were performed with the SCA computer program (Kiers 1990).

To assess whether the OCDUS-CAN subscales are internally consistent, Cronbach’s alphas of the subscales were determined. Correlations between the subscales were expressed as Pearson PM correlation coefficients.

To assess whether the OCDUS-CAN subscale scores were able to differentiate between the subject groups and frequency groups, we used linear regression analysis. For each of the subscale scores, we used a regression model with the component score as the dependent variable, and subject group, frequency group, and the interaction between subject and frequency groups as independent variables. To control for age, gender, nicotine use in the past year, alcohol use in the past year and hard drug use in the past year, these variables were included in the regression model as covariates. To take intra-family correlation into account (data from patients and siblings are not independent), we used a mixed model regression analysis with family as a random factor and a compound symmetry covariance matrix.

**Results**

**Sample characteristics**

OCDUS-CAN and CIDI data were available for 621 subjects: 346 patients, 165 non affected siblings and 110 controls. Of the patients, 232 (67.1%) were diagnosed with schizophrenia, 29 (8.4 %) with schizoaffective disorder, 39 (5.5 %) with schizophreniform disorder, 39 (11.3 %) with psychotic disorder NOS, and 27 (7.8 %) with another psychotic disorder. Means of PANSS subscales in patients were as follows: positive syndrome scale 2.0 (SD 0.8), negative syndrome scale 2.1 (SD 0.9), and general psychopathology scale 1.8 (SD 0.5). Mean duration of illness in patients was 3.7 (SD 3.8) years. Of all 346 patients, 284 (82.1 %) were currently using antipsychotic medication.
<table>
<thead>
<tr>
<th></th>
<th>Patients-frequent users</th>
<th>Patients-infrequent users</th>
<th>Siblings-frequent users</th>
<th>Siblings-infrequent users</th>
<th>Controls-frequent users</th>
<th>Controls-infrequent users</th>
<th>All groups</th>
<th>&quot;χ&quot; or &quot;F&quot;</th>
<th>df</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Gender, male (%)</td>
<td>92.7 (n=239)</td>
<td>86.2 (n=87)</td>
<td>76.0 (n=96)</td>
<td>87.1 (n=9)</td>
<td>75.0 (n=62)</td>
<td>83.4 (n=48)</td>
<td>55.6 (n=621)</td>
<td>5</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>25.5 (6.2)</td>
<td>25.4 (6.0)</td>
<td>23.9 (6.2)</td>
<td>23.4 (4.8)</td>
<td>24.4 (6.3)</td>
<td>22.0 (5.5)</td>
<td>24.6 (6.1)</td>
<td>4</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Education a</td>
<td>1 (%)</td>
<td>55.7 (n=239)</td>
<td>47.6 (n=87)</td>
<td>40.5 (n=96)</td>
<td>39.4 (n=9)</td>
<td>48.4 (n=62)</td>
<td>48.2 (n=48)</td>
<td>5.5 (n=621)</td>
<td></td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>2 (%)</td>
<td>22.8 (n=239)</td>
<td>31.7 (n=87)</td>
<td>26.9 (n=96)</td>
<td>34.8 (n=9)</td>
<td>33.9 (n=62)</td>
<td>32.6 (n=48)</td>
<td>7</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (%)</td>
<td>21.5 (n=239)</td>
<td>20.7 (n=87)</td>
<td>23.7 (n=96)</td>
<td>25.8 (n=9)</td>
<td>17.7 (n=62)</td>
<td>47.8 (n=48)</td>
<td>6.3 (n=621)</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Ethnicity, Caucasian (%)</td>
<td>72.5 (n=239)</td>
<td>82.4 (n=87)</td>
<td>83.3 (n=96)</td>
<td>87.0 (n=9)</td>
<td>85.5 (n=62)</td>
<td>91.3 (n=48)</td>
<td>91.3 (n=48)</td>
<td>4.3 (n=621)</td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>Nicotine use in past year, yes (%)</td>
<td>96.5 (n=239)</td>
<td>90.8 (n=87)</td>
<td>77.1 (n=96)</td>
<td>61.8 (n=9)</td>
<td>79.0 (n=62)</td>
<td>50.0 (n=48)</td>
<td>83.7 (n=621)</td>
<td>94.5 (n=48)</td>
<td>6.3 (n=621)</td>
<td></td>
</tr>
<tr>
<td>Alcohol use past year, yes (%)</td>
<td>88.9 (n=239)</td>
<td>92.0 (n=87)</td>
<td>90.7 (n=96)</td>
<td>95.7 (n=9)</td>
<td>93.5 (n=62)</td>
<td>95.8 (n=48)</td>
<td>89.0 (n=621)</td>
<td>95.5 (n=48)</td>
<td>6.3 (n=621)</td>
<td></td>
</tr>
<tr>
<td>Alcoholic drinks per week, mean (SD)</td>
<td>9.8 (14.4)</td>
<td>10.8 (9.0)</td>
<td>9.0 (9.4)</td>
<td>12.4 (14.4)</td>
<td>11.0 (10.9)</td>
<td>10.0 (7.2)</td>
<td>10.3 (12.3)</td>
<td>10.7 (8.3)</td>
<td>6.3 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Current cannabis use, yes (%)</td>
<td>55.4 (n=239)</td>
<td>25.0 (n=87)</td>
<td>83.7 (n=96)</td>
<td>59.1 (n=9)</td>
<td>86.9 (n=62)</td>
<td>76.1 (n=48)</td>
<td>61.7 (n=621)</td>
<td>79.5 (n=48)</td>
<td>6.3 (n=621)</td>
<td></td>
</tr>
<tr>
<td>Urine test for THC, positive (%)</td>
<td>49.8 (n=239)</td>
<td>13.3 (n=87)</td>
<td>65.9 (n=96)</td>
<td>10.8 (n=9)</td>
<td>54.3 (n=62)</td>
<td>8.6 (n=48)</td>
<td>40 (n=621)</td>
<td>96.4 (n=48)</td>
<td>6.3 (n=621)</td>
<td></td>
</tr>
<tr>
<td>Other illicit substance use in past year b, yes (%)</td>
<td>34.0 (n=239)</td>
<td>32.2 (n=87)</td>
<td>32.3 (n=96)</td>
<td>18.8 (n=9)</td>
<td>40.3 (n=62)</td>
<td>22.9 (n=48)</td>
<td>31.6 (n=621)</td>
<td>9.6 (n=48)</td>
<td>6.3 (n=621)</td>
<td></td>
</tr>
</tbody>
</table>

*1 = Lower secondary professional education/intermediate vocational education
*2 = Higher general secondary education/higher vocational education
*3 = Pre-university education/university
*Other illicit substances = stimulants (speed, amphetamines), hallucinogens, opiates, cocaine, ecstasy

Figures in bold have adjusted standardised residuals > 3.0; figures underlined have adjusted standardised residuals < -3.0.
Table 1 shows the similarities and differences in sociodemographic and substance use variables between the six groups. Mean age of all subjects was 24.6 (SD 6.1) years, with a statistically significant difference in age between the subgroups ($P = 0.001$), but post-hoc comparisons between subgroups did not survive Bonferroni correction. The sample was predominantly male (83.4%), with frequent cannabis using males even stronger overrepresented (92.7%), and infrequent cannabis using male siblings being under-represented (58.0%).

In the subgroup of patients with frequent cannabis use in the past year there was an under-representation of Caucasians and users of alcohol and an over-representation of nicotine users. Finally, in the group of infrequent cannabis using controls, subjects with a relatively low education and nicotine users were underrepresented.

Urine tests for THC were available in 525 (84.5%) of all 621 subjects, with highest proportion of available urine tests results in frequent cannabis using patients (96.2%), and lowest proportion of available urine tests in frequent cannabis using controls (56.4%). Frequent cannabis using siblings had highest proportion of positive THC urine test results (65.9%). According to the CIDI, frequent cannabis using siblings and controls had the highest proportion of currents cannabis users (83.7% resp. 86.9%).

**Underlying factor structure of the OCDUS-CAN**

Table 2 shows that a three-component SCA solution using binary component weights explained a mean of 74.2 % of the total variance in the three subject groups (patients: 73.6%, siblings: 69.6%, controls: 79.3%) compared to a mean of 74.7 % when using separate PCA’s (patients: 74.4%, siblings 70.0%, controls 79.5%). In addition, table 3 shows that a three-component SCA solution using binary component weights explained a mean of 72.1% of the total variance in the two groups defined by frequency of cannabis use (frequent 70.5%, infrequent 73.7%) compared to a mean of 72.7% when using separate PCA’s (frequent 71.2%, infrequent 74.2%). The small differences between the SCA and PCA solutions indicate the existence of a common component structure that adequately describes the covariance between the OCDUS-CAN items. Furthermore, there were no substantial differences in the factor loading of components in the three subject groups or the two frequency groups.

The first component can be labelled ‘craving/ urge’ and includes items related to time spend on thoughts/urges and frequency of thoughts/urges related to cannabis use, and intensity of the experienced urge. The second component can be labelled ‘resistance’ and comprises two items related to how much an effort is made to resist thoughts and use of cannabis. The third component can be labelled ‘impact’ and includes items that relate to interference of thoughts and urge related to cannabis use on social and work functioning, the distress these thoughts cause, and how much control people have to stop thoughts or to not use cannabis.
### Table 2. Simultaneous component analysis factor loadings (three-factor solution) and variance explained of the OCDUS stratified on subject type.

<table>
<thead>
<tr>
<th>OCDUS item</th>
<th>Patients</th>
<th>Siblings</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How much of your time—when you are not using—is occupied by ideas, thoughts, impulses, or images related to cannabis use?</td>
<td>0.85</td>
<td>0.37</td>
<td>0.67</td>
</tr>
<tr>
<td>2. When you do not use, how often do you feel the urge or drive to use cannabis?</td>
<td>0.88</td>
<td>0.36</td>
<td>0.67</td>
</tr>
<tr>
<td>3. When you do not use, how much time of the day do you feel the urge or drive to use cannabis?</td>
<td>0.91</td>
<td>0.44</td>
<td>0.71</td>
</tr>
<tr>
<td>4. How much effort do you make to resist these thoughts related to cannabis or try to disregard or turn your attention away from these thoughts?</td>
<td>0.90</td>
<td>0.42</td>
<td>0.71</td>
</tr>
<tr>
<td>5. How much of an effort do you make to resist the use of cannabis?</td>
<td>0.88</td>
<td>0.41</td>
<td>0.72</td>
</tr>
<tr>
<td>6. How much does the urge to use cannabis interfere with your social or work functioning?</td>
<td>0.91</td>
<td>0.44</td>
<td>0.71</td>
</tr>
<tr>
<td>7. How much do these thoughts related to cannabis interfere with your social or work functioning?</td>
<td>0.91</td>
<td>0.44</td>
<td>0.71</td>
</tr>
<tr>
<td>8. How much distress or disturbance do these thoughts related to cannabis cause?</td>
<td>0.91</td>
<td>0.44</td>
<td>0.71</td>
</tr>
<tr>
<td>9. How successful are you in stopping or diverting these thoughts related to cannabis?</td>
<td>0.91</td>
<td>0.44</td>
<td>0.71</td>
</tr>
<tr>
<td>10. How much control did you have over your cannabis use in the past week?</td>
<td>0.91</td>
<td>0.44</td>
<td>0.71</td>
</tr>
<tr>
<td>Subscale's internal consistency</td>
<td>0.91</td>
<td>0.86</td>
<td>0.91</td>
</tr>
<tr>
<td>SCA Total variance explained by the three components based on SCA with binary weights</td>
<td>73.6%</td>
<td>69.6%</td>
<td>79.3%</td>
</tr>
<tr>
<td>Total Variance explained by the three components based on subject type specific PCA's</td>
<td>74.4%</td>
<td>70.0%</td>
<td>79.9%</td>
</tr>
</tbody>
</table>
Table 3. Simultaneous component analysis factor loadings (three-factor solution) and variance explained of the OCDUS stratified on frequency type

<table>
<thead>
<tr>
<th>OCDUS item</th>
<th>Frequent users</th>
<th>Infrequent users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How much of your time—when you are not using— is occupied by ideas, thoughts, impulses, or images related to cannabis use?</td>
<td>0.84 0.26 0.64</td>
<td>0.88 0.24 0.71</td>
</tr>
<tr>
<td>2. How frequently do these thoughts related to cannabis occur?</td>
<td>0.87 0.27 0.64</td>
<td>0.69 0.24 0.65</td>
</tr>
<tr>
<td>7. When you do not use, how much time of the day do you feel the urge or drive to use cannabis?</td>
<td>0.89 0.31 0.66</td>
<td>0.87 0.24 0.68</td>
</tr>
<tr>
<td>8. When you do not use, how often do you feel the urge or drive to use cannabis?</td>
<td>0.88 0.32 0.67</td>
<td>0.89 0.21 0.64</td>
</tr>
<tr>
<td>11. How strong was the drive to use cannabis in the past week?</td>
<td>0.85 0.33 0.68</td>
<td>0.84 0.28 0.66</td>
</tr>
<tr>
<td>5. How much of an effort do you make to resist these thoughts related to cannabis or try to disregard or turn your attention away from these thought?</td>
<td>0.27 0.86 0.22</td>
<td>0.24 0.91 0.26</td>
</tr>
<tr>
<td>10. How much an effort do you make to resist the use of cannabis?</td>
<td>0.33 0.86 0.22</td>
<td>0.26 0.91 0.25</td>
</tr>
<tr>
<td>3. How much do these thoughts related to cannabis interfere with your social or work functioning?</td>
<td>0.62 0.14 0.84</td>
<td>0.70 0.21 0.89</td>
</tr>
<tr>
<td>4. How much distress or disturbance do these thoughts related to cannabis cause?</td>
<td>0.61 0.11 0.82</td>
<td>0.71 0.17 0.87</td>
</tr>
<tr>
<td>6. How successful are you in stopping or diverting these thoughts related to cannabis?</td>
<td>0.60 0.13 0.77</td>
<td>0.55 0.29 0.72</td>
</tr>
<tr>
<td>9. How much does the urge to use cannabis interfere with your social or work functioning?</td>
<td>0.65 0.14 0.84</td>
<td>0.70 0.22 0.87</td>
</tr>
<tr>
<td>12. How much control did you have over your cannabis use in the past week?</td>
<td>0.53 0.30 0.72</td>
<td>0.43 0.24 0.69</td>
</tr>
<tr>
<td>Subscale’s internal consistency</td>
<td>.91 .64 .84 .92 .79 .84</td>
<td></td>
</tr>
<tr>
<td>SCA Total variance explained by the three components based on SCA with binary weights</td>
<td>70.5% 73.7%</td>
<td></td>
</tr>
<tr>
<td>Total Variance explained by the three components based on frequency of use type (specific PCA’s)</td>
<td>71.2% 74.2%</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Subscale correlation matrix for the OCDUS for the total pooled population with Cronbach’s alpha on diagonal (n = 621)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OCDUS Total score</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Craving/Urge</td>
<td>0.92**</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Resistance</td>
<td>0.62**</td>
<td>0.36**</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>3. Impact</td>
<td>0.87**</td>
<td>0.78**</td>
<td>0.29**</td>
<td>0.85</td>
</tr>
</tbody>
</table>

** Correlation is significant at 0.01 level (2-tailed)

Table 4 shows that for the pooled population of patients, siblings and controls (N=621), Cronbach’s α of the subscales were as follows: 0.93 for the component ‘craving/urge’, 0.69 for the subscale ‘resistance’, and 0.85 for the subscale ‘impact’. Cronbach’s α of the subscales in the different subject and frequency groups are displayed in tables 2 and 3. Table 4 also shows the subscale correlation matrix for the pooled population, indicating moderate positive correlations between the second subscale and first and third subscale (r=.36 and r=.29 respectively), and a strong positive correlation between the first and third subscale (r=.78). These overall correlations are very similar to the subscale correlations in the various subgroups (patients, siblings, controls; frequent users, infrequent users) (data not presented). Given the relatively low internal consistency and the small number of items in the second subscale (‘resistance’), we also examined a two-component SCA solution. However, this two-component SCA solution did not solve the problem. It resulted in the same ‘resistance’ component with the same two items and another component with all other items. In addition, the two component solutions explained less variance than the three factor solution: 67.7% vs. 74.7%.

Differences in OCDUS-CAN scale scores between subgroups

As the interaction effect between subject type and frequency type was not statistically significant in predicting each of the component scores, we present the results of the regression analysis with only the main effects of subject group and frequency of cannabis use group (table 5). After controlling for frequency of cannabis use, age, gender, nicotine use in the past year, alcohol use in the past year, hard drug use in the past year, and intra-family correlation, mean OCDUS-CAN subscale scores were significantly different between the subject group, in all three subscales (see table 5 for details). Patients scored significantly higher on the subscale ‘craving/urge’ than siblings (β= -0.16, SE B= 0.07, t=-2.2, P=0.028) and controls (β= -0.19, SE B= 0.08, t=-2.3, P=0.021). Patients also scored significantly higher on the subscale ‘resistance’ than siblings (β= -0.19, SE B= 0.06, t=-3.0, P=0.003) and controls (β= -0.25, SE 0.06, t=-3.6, P<0.001). Using the same control variables, siblings and controls scored higher on the subscale ‘resistance’ than patients (β= 0.31, SE B=0.13, t=3.4, P=0.002, resp. β=0.5, SE B=0.15, t=3.5, P=0.001). When controls were used as reference category, there were no significant differences in subscale scores between siblings and controls. Frequent users had significantly higher scores on all three subscales (‘craving/urge’ subscale β=0.71, SE B= 0.06, t=11.0, P <0.001: ‘resistance’ subscale β=0.72, SE B=0.12, t=6.3, P <0.001, ‘impact’ subscale β=0.42, SE B= 0.54, t= 7.8, P < 0.001) compared to infrequent cannabis users even after controlling for subject type, age,
gender, nicotine use in the past year, alcohol use in the past year, hard drug use in the past year, and intra-family correlation.

Table 5. Subscale means (SD), stratified to subject type and frequency of cannabis use in the past 12 months

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Patients (n=346)</th>
<th>Siblings (n=165)</th>
<th>Controls (n=110)</th>
<th>F value</th>
<th>P value</th>
<th>Frequent users (n=417)</th>
<th>Infrequent users (n=204)</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Craving/Urge</td>
<td>1.95 (0.90)</td>
<td>1.61 (0.68)</td>
<td>1.59 (0.58)</td>
<td>3.7</td>
<td>0.024</td>
<td>2.06 (0.85)</td>
<td>1.27 (0.38)</td>
<td>121.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2: Resistance</td>
<td>2.30 (1.26)</td>
<td>2.36 (1.16)</td>
<td>2.58 (1.32)</td>
<td>6.4</td>
<td>0.002</td>
<td>2.60 (1.27)</td>
<td>1.88 (1.34)</td>
<td>39.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3: Impact</td>
<td>1.62 (0.73)</td>
<td>1.32 (0.51)</td>
<td>1.25 (0.42)</td>
<td>8.1</td>
<td>&lt;0.001</td>
<td>1.64 (0.71)</td>
<td>1.14 (0.32)</td>
<td>60.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Discussion

In this study we found a three component structure of the OCDUS-CAN that was both invariant over subject type (patients with non affective psychotic disorder, unaffected siblings, and healthy controls) and over cannabis frequency type (frequent, infrequent cannabis user). The three components were interpreted as ‘craving/urge’, ‘resistance’ and ‘impact’. This means that these OCDUS-CAN subscales can be applied and can be easily interpreted in patients with non-affective psychotic disorder, their siblings, and healthy controls who used cannabis recently (in the past year) in various amounts.

The first (‘craving/urge’) and third (‘impact’) subscale had good internal consistency, with an overall Cronbach’s α of 0.93 and 0.85 respectively. The second subscale (‘resistance’) consisted of only two items and consequently had a somewhat lower but still acceptable internal consistency with an overall Cronbach’s α of 0.69. This three-factor solution also corresponds very well with the factor solution of the original OCDUS in heroin dependent patients (Franken et al 2002). Our component ‘resistance’ was the same as their factor ‘resistance to thoughts and intention’. In addition, our component ‘urge/craving’ was similar to their factor ‘desire and control’ with an overlap of three of the five items. Finally, our ‘impact’ component is very similar to their ‘thoughts and interference’ scale with an overlap of four of the five items. Differences in the assignment of specific items to components/factors were found in only three items: two items about time spend on thoughts and frequency of thoughts related to cannabis use and one item about control on use. These differences may be accounted for by differences in the type of drug for which craving was measured, and differences in subject types. Furthermore, differences may be attributable to methodological differences in the two studies; Franken et al (2002) used PCA, and the present study used SCA.

As mentioned in the introduction, the the 47-item MCQ (Heishman et al 2001, Singleton et al 2002) is another validated self-report questionnaire measuring subjective craving for cannabis. The MCQ contains items that were drawn from theoretical conceptualizations of craving with four aspects: compulsivity (inability to control cannabis use), emotionality (cannabis use in anticipation of relief from withdrawal or negative mood), expectancy (cannabis use in anticipation of positive outcomes)
and purposefulness (intention and planning to use cannabis for positive outcomes). It is difficult to compare the OCDUS with the MCQ on the content of their scales, because the MCQ has a different approach to the measurement of craving than the OCDUS. This is understandable, because craving is a broad concept of which there is no agreement on how it should be defined and measured (e.g. Sayette et al 2000). It would be interesting to assess the concurrent validity of the OCDUS-CAN and the MCQ or the short 12-item version of the MCQ (Heishman et al 2009). To obtain more information about construct validity of the OCDUS-CAN, subscale scores of the OCDUS-CAN could be correlated to other underlying constructs of addiction, such as attentional bias for cannabis or implicit (automatic) associations toward cannabis. The OCDUS-CAN has not been related to attentional bias, but in heroin and cocaine research the OCDUS showed high correlations with attentional bias for cocaine and heroin cues and with a single-item for craving (Franken et al 2000a) (Franken et al 2000b). Finally, a recent study in patients with psychotic disorder and healthy controls found a trend for the relationship between (implicit) positive arousal associations toward cannabis use and craving for cannabis measured with the OCDUS-CAN (Dekker et al 2009a). These studies provide some early evidence for construct validity of the OCDUS.

In the present study, we found that patients scored significantly higher on the ‘craving/ urge’ and ‘impact’ scale than siblings and controls after controlling for frequency of use and other potential confounders. This means patients experience higher craving levels compared to siblings and controls and that it causes more distress, independent of their level of cannabis use. One may speculate that this higher craving in patients could be related to symptoms of their disease. Perhaps positive and negative symptoms or secondary dysphoria associated with the psychotic disorder is related to more severe craving for cannabis in patients. Although longitudinal studies generally do not show evidence for self medication effects (Arsenault et al 2002, Stefanus et al 2004, Fergusson et al 2005, Henquet et al 2005, Van Os et al 2002) except Ferdinand et al (2005), and self-medication as reason to use cannabis is reported only in a minority of patients (Dekker et al 2009b), no study has examined these specific disease related motivations for cannabis use in relation to craving. Another explanation of higher craving in patients could be the use of antipsychotic medication. However, the exact effect of antipsychotic medication on craving is not known. Although some efficacy studies of antipsychotics in patients with schizophrenia and comorbid substance use disorder suggest that conventional antipsychotics may induce or worsen substance use disorders, some atypical antipsychotics have shown a role in alleviating comorbid substance abuse (Green 2005, Van Nimwegen et al 2008).

Further, studies concerning self-reported reasons for cannabis use in patients with psychotic illness have shown that cannabis use to relieve side effects of medication is indeed reported by patients, but only in 15 to 38% (Dekker et al 2009b). The finding that patients with a non-affective psychosis experience more craving may (partly) explain the increased rates of cannabis use in people with psychotic illness (Hall and Degenhardt 2000, Regier et al 1990). However, the exact mechanism to the development of more craving in these patients, i.e. how it relates to use of antipsychotic medication and to primary and secondary symptoms of psychotic disorders, is still unknown and needs further investigation. It is important to note that siblings did not report higher craving levels on the OCDUS-CAN scales than controls, suggesting that higher craving levels are not related to the underlying vulnerability for psychosis but rather to the presence of psychosis-related symptoms or the use of antipsychotic medication. Although we found that patients reported higher craving levels than siblings and controls, a much larger effect was found for the difference in OCDUS-CAN scores between frequent and infrequent cannabis users; frequent cannabis users had significantly higher scores on all OCDUS-CAN subscales than infrequent cannabis users. This is in line with the findings of
another study (Dekker et al 2009a) reporting a positive correlation between scores on the OCDUS-CAN and the level of cannabis use. However, more precise information on dose-response relationships could be provided by comparing craving levels among more refined categories of frequency of cannabis use than the ones used in the current study.

A limitation of the current study is that we have no information on test-retest reliability of the OCDUS-CAN. However, Franken et al (2002) reported that the original OCDUS had good test-retest reliability in heroin dependent patients with interclass correlations coefficients (ICCs) for the three subscales ranging from 0.72 to 0.79 over a period of 48 hours. Another limitation is that we have no data on the predictive validity of the OCDUS-CAN. This needs further investigation. Lastly, this study population was predominantly male. Although gender was used as covariate in the regression analysis, we did not investigate whether the OCDUS-CAN scales differentiate between males and females. Although males are more prone to use cannabis than females in psychosis samples (e.g. Gonzales-Pinto et al 2008, Foti et al 2010) as well as in normal population samples (Cotto et al 2010), reports about effects of gender on cannabis craving are needed.

Strengths of the present study are (1) the use of the same craving instrument (OCDUS-CAN) in a large sample of patients, their unaffected siblings and normal controls, (2) the use of simultaneous component analysis (SCA) to study the underlying structure of the OCDUS-CAN, and (3) the correction of the relationship between group status and craving levels for a large number of potential confounders.

The key focus of the current study was the search for a common factor or component structure of the OCDUS-CAN in different groups of psychosis vulnerability and different levels of cannabis use. This is the first study providing evidence that the OCDUS-CAN is a valid instrument to assess craving for cannabis in clinical and research samples of patients with psychotic disorder, but also in siblings and individuals without a (family) history of psychotic illness. The three subscales score can be easily estimated using a summated scoring approach, and thus, scoring the OCDUS in terms of these three subscales is simple. The resulting subscales have good internal consistency and clearly discriminate between frequent and infrequent cannabis users, independent of their psychosis vulnerability status. We recommend that the second subscale ‘resistance’ is expanded with newly generated items to establish an even better internal consistency. More research is needed on the underlying mechanisms related to the different aspects of craving, and the effectiveness of substance use disorder treatments in cannabis using individuals who are vulnerable for psychotic disorder. In these studies, the OCDUS-CAN can be recommended as a valid indicator for one of the most crucial predictors and outcome parameters.
Appendix

OCDUS-CAN (translated)

Directions: The questions below ask you about your cannabis use and your attempts to control your cannabis use. The questions refer to the past week. If you have never used cannabis, and/or if you never considered using it, you do not have to fill in this instrument. Could you then mark the following box:

□ Never used cannabis and never considered cannabis use

Note: The following questions are about thoughts (images, ideas, impulses) related to cannabis in the past week.

1. How much of your time—when you are not using—is occupied by ideas, thoughts, impulses, or images related to cannabis use?
   1. None
   2. Less than 1 hour a day
   3. 1-3 hours a day
   4. 4-8 hours a day
   5. Greater than 8 hours a day

2. How frequently do these thoughts related to cannabis occur?
   1. Never: I have not had these thoughts related to cannabis in the past week
   2. Seldom: No more than 8 times a day
   3. Sometimes: More than 8 times a day, but most hours of the day are free of those thoughts
   4. Often: More than 8 times a day and during most hours of the day
   5. Always: An hour rarely passes without several such thoughts occurring

3. How much do these thoughts related to cannabis interfere with your daily functioning (e.g. work, contact with family and friends)?
   1. Not at all: Thoughts related to cannabis never interfere—I can function normally
   2. Mild: Thoughts related to cannabis slightly interfere with my social or occupational activities, but my overall performance is not impaired
   3. Moderate: Thoughts related to cannabis definitely interfere with my social or occupational performance, but I can manage
   4. Severe: Thoughts related to cannabis cause substantial impairment in my social or occupational performance
   5. Extreme: Thoughts related to cannabis interfere completely with my social or work performance

4. How much distress or disturbance do these thoughts related to cannabis cause?
   1. Not at all: These thoughts do not cause distress
   2. Mild: Thoughts related to cannabis are not too disturbing
   3. Moderate: Thoughts are disturbing, but still manageable
   4. Severe: Thoughts are very disturbing
   5. Extreme: Thoughts cause nearly constant disabling distress

5. How much of an effort do you make to resist these thoughts related to cannabis or try to disregard or turn your attention away from these thoughts? (Rate your effort made to resist these thoughts, not your success or failure in actually controlling them)
   1. Always: My thoughts are so minimal, I don’t need to actively resist, or, if I have these thoughts, I make an effort to always resist
   2. Most of the time: I try to resist most of the time
   3. Sometimes: I make some effort to resist
   4. Seldom: I give in to such thoughts without attempting to control them, but I do so with some reluctance
   5. Never: I complete and willingly give in to all such thoughts

6. How successful are you in stopping or diverting these thoughts related to cannabis?
   1. Always: I am completely successful in stopping or diverting such thoughts
   2. Most of the time: I am usually able to stop or divert such thoughts with some effort and concentration
   3. Sometimes: I am sometimes able to stop or divert such thoughts
   4. Seldom: I am rarely successful in stopping such thoughts and can only divert such thoughts with difficulty
   5. Never: I am rarely able to divert such thoughts even momentarily
Note: the following questions are not about thoughts related to cannabis, but about the urge or drive to use cannabis in the past week.

7. If you do not use cannabis, how much time of the day do you feel the urge or drive to use cannabis?
   1. Not at all
   2. Less than 1 hour a day
   3. 1-3 hours a day
   4. 4-8 hours a day
   5. Greater than 8 hours a day

8. When you do not use, how often do you feel the urge or drive to use cannabis?
   1. Never: I have not had the urge or drive to use cannabis in the past week
   2. Seldom: Less than 8 times a day
   3. Sometimes: More than 8 times a day, but most hours of the day are free of those urges or drives
   4. Often: More than 8 times a day and during most hours of the day
   5. Always: An hour rarely passes without such urges or drives occurring

9. How much does the urge to use cannabis interfere with your daily functioning (e.g. work, contact with family and friends)?
   1. Not at all: This urge does not cause no distress
   2. Mild: This urge is not too disturbing
   3. Moderate: This urge is disturbing, but I can still manage
   4. Severe: This urge is very disturbing
   5. Extreme: This urge causes extreme, nearly constant disabling distress

10. How much of an effort do you make to resist the use of cannabis? (Only rate the your effort to resist, not your success or failure in actually controlling the drinking)
    1. Always: I use so little (or no) cannabis, I don’t need to actively resist, or, I always try to resist the use of cannabis
    2. Most of the time: I try to resist the use of cannabis most of the time
    3. Sometimes: I make some effort to resist the use of cannabis
    4. Seldom: I give in to the use of cannabis without attempting to control it, but I do so with some reluctance
    5. Never: I complete and willingly give in to cannabis use

11. How strong was the drive to use cannabis in the past week?
    1. Not at all: I have not felt the drive to use cannabis
    2. Mild: I have felt a mild drive to use cannabis
    3. Moderate: I have felt a moderate drive to use cannabis
    4. Severe: I have felt a strong drive to use cannabis
    5. Extreme: The drive to use cannabis is completely involuntary and overpowering

12. How much control did you have over use of cannabis in the past week?
    1. Very much: I have complete control over my cannabis use
    2. Reasonably much: I am usually able to exercise voluntary control over my cannabis use
    3. Moderate: I can control my cannabis use only with difficulty
    4. Hardly: I must use cannabis and can only delay using cannabis with difficulty
    5. None: I am rarely able to delay using cannabis even momentarily
Chapter 1.3 - Craving for cannabis

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Chapter 1.3  - Craving for cannabis


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