Cannabis use in patients with schizophrenia: motivation for use and relation to clinical variables
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CHAPTER 2.3

*Cannabis and cognitive performance in psychosis: a cross-sectional study in patients with non-affective psychotic illness and their unaffected siblings*


Submitted for publication.
Abstract

Background. The relationship between cannabis use and cognitive functioning in patients with psychosis has yielded contradictory findings. In individuals at genetic high risk for psychosis, information is sparse. The aim of this study was to assess the association between recency and frequency of cannabis use and cognitive functioning in patients with psychosis and their unaffected siblings.

Method. Cross-sectional study in 956 patients with non-affective psychosis, 953 unaffected siblings, and 554 control subjects. Participants completed a cognitive test battery including assessments of verbal learning, set shifting, sustained attention, processing speed, working memory, acquired knowledge, reasoning and problem solving and social cognition. Cannabis use was assessed by urinalysis and by the Composite International Diagnostic Interview. Using mixed-model analyses, the main effects of Cannabis (recency and frequency) and the interaction with Status (patient, sibling, control) on cognitive functioning were assessed.

Results. Current cannabis use was associated with poorer performance on immediate verbal learning, processing speed and working memory (Cohen’s d -0.20 to -0.33; p<0.005). Lifetime cannabis use was associated with better performance on acquired knowledge, facial affect recognition and face identity recognition (Cohen’s d +0.17 to +0.33; p<0.005). There was no significant interaction between Cannabis and Status on cognitive functioning.

Conclusion. Lifetime cannabis using individuals might constitute a subgroup with a higher cognitive potential. The residual effects of cannabis may impair short term memory and processing speed.
Introduction

Cognitive impairment is recognized as a core feature of schizophrenia (Green 1996, Palmer et al 2009). Mild cognitive alterations are also observed in unaffected relatives of patients who are at increased risk to develop a psychotic disorder (Snitz et al 2006). In both patients with psychosis and their unaffected siblings, cannabis use is more prevalent than in the general population (Barnes et al 2006, Smith et al 2008). In patients with psychosis, cannabis use has been associated with worse disease outcome (Linszen et al 1994). In unaffected siblings the psychotomimetic effect of cannabis is increased compared to control subjects, suggesting that familial liability to psychosis is associated with sensitivity to cannabis (van Winkel 2011, Genetic Risk and Outcome of Psychosis (GROUP) Investigators 2011). Whether cannabis use is also associated with cognitive alterations in patients with psychosis and their unaffected relatives is however still a matter of debate.

Acute administration of the major psychoactive component in cannabis ($\Delta^8$-tetrahydrocannabinol; THC) has been shown to cause impaired attention and memory in schizophrenia patients and their unaffected siblings (D’Souza et al 2005, Henquet et al 2006). These impairments in patients and siblings were larger compared to those in healthy controls, suggesting an increased sensitivity to the adverse cognitive effects of acute cannabinoid administration. On the contrary, better cognitive functioning has also been reported in cannabis using patients in contrast to non-using patients with a psychotic disorder on tasks of planning and reasoning, visual memory, processing speed, global cognition and working memory (Coulston et al 2007a, Potvin et al 2008, Loberg and Hugdahl 2009, Yucel et al 2010). This superior cognitive functioning in cannabis using patients seems counterintuitive given the deleterious acute and long-term effects that have been reported in cannabis using subjects without psychotic illness (Solowij and Michie 2007, Morrison et al 2009). Two hypotheses attempt to explain these results. First, it has been suggested that cannabis improves cognition, either by counteracting a putative neurotoxic process related to schizophrenia, or by stimulating prefrontal neurotransmission (Verrico et al 2003, Jockers-Scherubl et al 2007, Coulston et al 2007a, Coulston et al 2007b, Potvin et al 2008, Cohen et al 2008). Secondly, it has been suggested that causality is the other way around. In this view, patients with psychotic disorder and lifetime cannabis use may form a subgroup with a relatively lower genetic vulnerability for psychosis and better premorbid functioning compared to patients who have never used cannabis (Schnell et al 2009, de la Serna et al 2010, Yucel et al 2010).

Elucidating the association between cannabis use and cognitive functioning in patients and individuals at genetic high risk for psychosis is of both theoretical and clinical relevance (Loberg and Hugdahl 2009). Whilst spared cognitive functioning through cannabis use would be relevant for the development of cognitive enhancing medication, a further cognitive decline associated with cannabis use should stimulate development of interventions aiming at a reduction of cannabis use. It is essential to account for the recency of cannabis use in studies on the association between cannabis and cognition, since contradictory findings between acute administration and lifetime cannabis use have been found (D’Souza et al 2005, Henquet et al 2006, Coulston et al 2007a, Potvin et al 2008, Loberg and Hugdahl 2009, Yucel et al 2010). In addition, the frequency of cannabis use should be taken into account in order to investigate dose-response relationships (Coulston et al 2007a). Thus, the aim of the present study was to investigate if cognitive performance differs between cannabis users and non-users depending, on the recency and frequency of use. The second aim was to investigate whether these associations are different in patients with non-affective psychosis, their unaffected siblings, and control subjects.
Methods

Study design and population
Data were derived from the first assessment in the Genetic Risk and Outcome of Psychosis (GROUP) study. The GROUP study is a population based cohort study with a six year follow-up of patients with non-affective psychotic disorders, their unaffected siblings and parents, and control subjects. Data were gathered by four academic schizophrenia research centres and their affiliated mental health care institutions in the Netherlands and Belgium. The main objective of the GROUP study is to investigate the dynamic interaction between genetic and environmental factors that contribute to the expression and course of psychosis over time. The procedure of recruitment, criteria of inclusion and exclusion, informed consent, assessments, and population characteristics have been described previously (Körver et al submitted). For the current study we included subjects from the GROUP study that had performed cognitive testing and from whom both self-report on cannabis use and a drug urine screening were available, leading to a study sample of 2463 subjects (956 patients, 953 non-affected siblings, 554 controls).

Substance use and clinical symptoms
Substance use was assessed with a short version of the Composite International Diagnostic Interview (CIDI; World Health Organization, 1990) sections B (tobacco use), J (alcohol use), and L (substance use), and with urinalysis. Urine was screened for the presence of THC with a cut off of 50ng/ml, in order to infer a detection window of one month. Cannabis Recency was categorized as current (urinalysis positive for THC), lifetime (urinalysis negative AND cannabis use ≥ 5 times lifetime based on the CIDI), and never (urinalysis negative and cannabis use < 5 times lifetime based on the CIDI). Although this latter group may have included subjects who had limited experience with cannabis, for simplicity this group is referred to as ‘never-users’. Cannabis Frequency was categorized as daily, weekly, or less than weekly, based on the CIDI. Severity of positive and negative symptoms in patients was rated with the Positive and Negative Syndrome Scale (PANSS) with total scores for positive, negative and general symptoms (Kay et al 1987).

Cognitive assessment
Subjects were administered 10 cognitive tasks that yielded 13 outcome parameters which were used as dependent variables in the analyses. The cognitive assessment took 90 to 120 minutes and included the Word Learning Task (WLT; assessing verbal learning with outcome parameters of Immediate Recall and Retention Rate after 20 minutes), the Response Shifting Task (RST; assessing set shifting ability with outcome parameters of Reaction Time and Accuracy), the Continuous Performance Task-HQ (CPT-HQ; assessing sustained visual attention with outcome parameters of Reaction Time and Accuracy), WAIS-III Digit-symbol Coding (processing speed), WAIS-III Arithmetic (working memory), WAIS-III Information (acquired knowledge), WAIS-III Block Design (reasoning and problem solving), the Degraded Facial Affect Recognition Task (DFAR; assessing recognition of neutral, happy, fearful and angry emotions), the Benton Face Recognition Task (BFRT; assessing visuospatial discrimination of unfamiliar faces), and the Hinting Task (assessing theory of mind). For a further description of the abovementioned tasks we refer to the baseline description of cognitive functioning in GROUP (Meijer et al submitted).
Chapter 2.3 - Cannabis use and cognitive performance in psychosis

Statistical analysis
Statistical analyses were performed using SPSS 17.0 for Windows. Differences in demographic and substance use characteristics among patients, siblings, and controls were assessed using one way analysis of variance (ANOVA) and χ² tests. Demographic and clinical characteristics in current and lifetime cannabis using patients were compared to those in never using patients using independent t-tests and χ² tests. Tests were two-tailed with a significance level of 0.05.

In the entire study sample (n=2463), separate linear mixed-model regression analyses for each of the 13 outcome parameters were conducted to assess the main effects of Status (patient, sibling, control), Cannabis Recency (current, lifetime and never) and Status x Cannabis Recency. For subjects with cannabis use during the year prior to inclusion of the study (n=612), the same analysis was conducted, with the variable Cannabis Frequency (daily, weekly, less) instead of Cannabis Recency. Although not a primary aim of this study, the main effects of Status are presented in the results section to facilitate interpretation. Cannabis effects have been assessed in regression analyses together with the main effect of Status. Any effects of Cannabis should thus be interpreted in addition to existing cognitive differences between the Status groups.

To control for intra-family correlation, family was used as a random factor with a random intercept regression model. Potential confounders that have been mentioned previously (Coulston et al. 2007b; Potvin et al. 2008) were entered separately into the regression model as covariates. If a potential confounder changed the effect estimates by 10% or more it was kept as covariate in the final model. The following covariates were entered: age, gender, heavy alcohol use (>14 units weekly for women and >20 units weekly for men), a history of illicit substance use other than cannabis over the past year (cocaine, amphetamines, XTC, opiates, inhalants, hallucinogens), and highest parental educational degree. Since the Dutch educational system already differentiates after primary school, a coding system was used that goes from lowest (1=primary school) up to highest (8=university). In the analyses for the Degraded Facial Affect Recognition task, scores on the Benton Face Recognition Task were used as an extra covariate to adjust for non-emotional facial processing skills. If the interaction term was not statistically significant, it was removed from the model and the analysis was repeated with the main effects and relevant confounders. To correct for multiple comparisons, alpha was set to 0.005. Due to the increased power caused by the large n, effect sizes (Cohen’s d) were calculated to facilitate the interpretation of the statistical significant effects.

Normality of the cognitive parameters was checked visually with histograms and box plots and confirmed if the test-statistic W in the Shapiro Wilk test exceeded 0.90. Parameters for CPT accuracy and the Hinting Task were not normally distributed due to ceiling effects. Data transformations did however not substantially improve normality. Therefore these two tasks were analyzed by differing methods. Besides conducting mixed-model regression analyses, a second analysis was performed by splitting subjects into two similar sized groups of ‘affected’ and ‘unaffected’ individuals. “Affected” for the CPT accuracy (range 0-100%) was defined as <100% accurate responses (=51.6% of total sample) and for the hinting task (range 0-20) as a score <20 (=57.8% of total sample). This dichotomous outcome was analyzed using a generalized estimating equations (GEE) approach (Hanley et al 2003). The regression model and procedures were the same as in the mixed-model regression analyses. To minimize the risk of type I errors, the analyses yielding the most conservative results were selected for the discussion.
Results

Characteristics of the study sample
As presented in table 1, control subjects were older (30.2 years) than patients (27.3 years) and siblings (27.9 years). Males were overrepresented in the patient group (76.4%) compared to siblings (45.4%) and controls (45.5%). Parental educational degree and subject educational degree was lowest in patients. Of all subjects, 38.3% (n=943) had used cannabis lifetime, and 10.5% (n=258) were current cannabis users. Patients and siblings were more likely to be current or lifetime cannabis users compared to controls. Regarding the frequency of cannabis use over the past year, patients and siblings were more likely to be daily users compared to controls. Patients were more likely to be nicotine users (66.4%) or users of illicit substances (20.4%) compared to siblings (37.5% and 7.8% respectively) and controls (25.5% and 6.0%, respectively). Groups did not differ in the proportion of heavy alcohol users.

Table 1. Demographic variables in patients, siblings and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Siblings</th>
<th>Controls</th>
<th>F (df)</th>
<th>χ² (df)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>27.3 (7.4)</td>
<td>27.9 (8.3)</td>
<td>30.2 (10.5)</td>
<td>21.6 (2, 2459)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Gender, % male</td>
<td>76.4</td>
<td>45.4</td>
<td>45.5</td>
<td>229.0 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Education, % lowest (% highest)</td>
<td>12.3 (4.3)</td>
<td>7.1 (12.0)</td>
<td>2.2 (9.4)</td>
<td>244.5 (16)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Parental education, % lowest (% highest)</td>
<td>6.7 (18.3)</td>
<td>5.1 (18.8)</td>
<td>4.3 (16.1)</td>
<td>35.22 (16)</td>
<td>&lt; 0.004</td>
<td></td>
</tr>
<tr>
<td>Nicotine use, %</td>
<td>66.4</td>
<td>37.5</td>
<td>25.5</td>
<td>282.4 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Heavy alcohol use, %</td>
<td>10.9</td>
<td>9.0</td>
<td>7.7</td>
<td>4.6 (2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Other substance use, %</td>
<td>20.4</td>
<td>7.8</td>
<td>6.0</td>
<td>97.09 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Cannabis Recency (n=2463)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current, %</td>
<td>16.3</td>
<td>7.9</td>
<td>4.9</td>
<td>60.16 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Lifetime, %</td>
<td>49.8</td>
<td>33.4</td>
<td>26.9</td>
<td>93.82 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Never, %</td>
<td>33.9</td>
<td>58.7</td>
<td>68.2</td>
<td>200.49 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Cannabis Frequency past year (n=612)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily, %</td>
<td>48.3</td>
<td>25.6</td>
<td>19.5</td>
<td>38.71 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Weekly, %</td>
<td>26.6</td>
<td>28.3</td>
<td>30.5</td>
<td>0.57 (2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Less, %</td>
<td>25.1</td>
<td>46.1</td>
<td>50.0</td>
<td>32.12 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

*test statistic: F for continuous data, χ² for categorical variables, NS=not significant

Table 2 shows that patients with current or lifetime cannabis use were 2.3 years younger than never users and more often male (86.1% vs. 57.4%). Current or lifetime cannabis using patients had lower functioning on the GAF disability scale (52.9 vs. 58.3), higher PANSS positive symptoms (14.6 vs. 12.4), but similar PANSS negative symptoms compared to patients who had never used cannabis. In both groups around 85% of patients received treatment with antipsychotics.
Table 2. Demographic and clinical variables of patients with and without a lifetime history of cannabis (CB) use

<table>
<thead>
<tr>
<th>Demographic and clinical variables</th>
<th>Lifetime CB use</th>
<th>Never CB use</th>
<th>( t ) or ( \chi^2 ) (df)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>26.5 (6.4)</td>
<td>28.9 (8.7)</td>
<td>4.9 (954)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>86.1</td>
<td>57.4</td>
<td>97.5 (1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Education, %lowest (%highest)</td>
<td>15.2 (3.0)</td>
<td>6.8 (6.8)</td>
<td>34.1 (8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Parental education, %lowest (%highest)</td>
<td>7.1 (19.0)</td>
<td>5.9 (17.0)</td>
<td>11.9 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>GAF - disability, mean (SD)</td>
<td>52.9 (16.0)</td>
<td>58.3 (15.5)</td>
<td>4.8 (919)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PANSS Positive Scale, mean (SD)</td>
<td>14.6 (6.7)</td>
<td>12.4 (5.7)</td>
<td>-4.9 (930)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PANSS Negative Scale, mean (SD)</td>
<td>15.2 (6.6)</td>
<td>14.7 (6.4)</td>
<td>-1.2 (930)</td>
<td>NS</td>
</tr>
<tr>
<td>Antipsychotic treatment, % yes</td>
<td>86.3</td>
<td>84.9</td>
<td>2.0 (2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Current and lifetime cannabis using patients combined.
* Test statistic: \( t \) for continuous data, \( \chi^2 \) for categorical variables, NS=not significant.

Cannabis Recency

For none of the cognitive outcome variables the interaction Status (patients, sibling, control) x Cannabis Recency (current, lifetime, never) was statistically significant and therefore the interaction term was removed from the regression models. Figure 1a demonstrates that patients performed worse than controls on all cognitive parameters except RST reaction time, while siblings performed intermediate to patients and controls on selected tasks. In the model including Status, Cannabis Recency and relevant confounders, current - but not lifetime- cannabis users performed significantly worse compared to never users on immediate verbal learning (d=−0.20), WAIS-III Digit Symbol Coding (d=−0.22) and WAIS-III Arithmetic (d=−0.20) (Figure 1b). Lifetime cannabis users performed better than never users on WAIS-III Information (d=+0.17), Degraded Facial Affect Recognition task (d=+0.33), and Benton Face Recognition Task (d=0.21). In addition, current cannabis users performed significantly better than never users on the WAIS-III Information task (d=+0.19). GEE analyses confirmed the mixed-model regression results for the not normally distributed data. For CPT-accuracy, the proportion of ‘affected’ individuals was not significantly different within current (58.8%), lifetime (53.1%), and never users (49.0%), Wald \( \chi^2(2)=0.98, p=0.61 \). Also for the Hinting task, the proportion of ‘affected’ individuals was not significantly different within current (64.0%), lifetime (60.0%), and never users (54.8%), Wald \( \chi^2(2)=0.35, p=0.84 \).

Cannabis Frequency

For none of the cognitive outcome variables the interaction term Status x Cannabis Frequency was statistically significant. In the resulting model, including Status, Cannabis Frequency, and relevant confounders, there was no significant effect of Cannabis Frequency on any of the cognitive parameters (Figure 1c). GEE analyses confirmed the mixed-model regression results for the not normally distributed data. For CPT-accuracy, the proportion of ‘affected’ individuals was not significantly different within daily (57.1%), weekly (59.6%), and less frequent users (52.6%), Wald \( \chi^2(2)=1.87, p=0.39 \). For the Hinting task, the proportion of ‘affected’ individuals was not significantly different within daily (70.7%), weekly (60.5%), and less frequent users (60.9%), Wald \( \chi^2(2)=1.74, p=0.42 \).
Figure 1. Main effects of Status (Figure 1a), Cannabis Recency (Figure 1b, see following page), and Cannabis Frequency (Figure 1c, see following page) on cognitive functioning.

WLT IR: Word Learning Task Immediate Recall; WLT RR: Word Learning Task Retention Rate; RST RT: Response Shifting Task Reaction Time; RST Acc: Response Shifting Task Accuracy; CPT RT: Continuous Performance Task-HQ Reaction Time; CPT Acc: CPT-HQ Accuracy; DS Coding: WAIS-III Digit-symbol Coding; Arithmetic: WAIS-III Arithmetic; Information: WAIS-III Information; Block: WAIS-III Block Design; Affect Rec: Degraded Facial Affect Recognition total score; Face Rec: Benton Face Recognition; Hinting: Hinting Task; F: Test statistic from mixed model regression analyses; df: degrees of freedom. Effects that remained significant after correction for multiple comparisons (p<0.005) in current/lifetime users compared to never users are circled in Figure 1b.
Figure 1b)

<table>
<thead>
<tr>
<th></th>
<th>CB Recency</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0.12</td>
</tr>
<tr>
<td>T2</td>
<td>0.10</td>
</tr>
<tr>
<td>T3</td>
<td>0.08</td>
</tr>
<tr>
<td>T4</td>
<td>0.06</td>
</tr>
<tr>
<td>T5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

WLT IR: Word Learning Task Immediate Recall; WLT RR: Word Learning task Retention Rate; RST RT: Response Shifting task Reaction Time; RST Acc: Response Shifting Task Accuracy; CPT RT: Continuous Performance Task-HQ Reaction Time; CPT Acc: CPT-HQ Accuracy; DS Coding: WAIS-III Digit-symbol Coding; Arithmetic: WAIS-III Arithmetic; Information: WAIS-III Information; Block: WAIS-III Block Design; Affect Rec: Degraded Facial Affect Recognition total score; Face Rec: Benton Face Recognition; Hinting: Hinting Task; F: Test statistic from mixed-model regression analyses; df: degrees of freedom. Effects that remained significant after correction for multiple comparisons (p<0.005) in current/lifetime users compared to never users are circled in Figure 1b.
WLT IR: Word Learning Task Immediate Recall; WLT RR: Word Learning Task Retention Rate; RST RT: Response Shifting Task Reaction Time; RST Acc: Response Shifting Task Accuracy; CPT RT: Continuous Performance Task-HQ Reaction Time; CPT Acc: CPT-HQ Accuracy; DS Coding: WAIS-III Digit-symbol Coding; Arithmetic: WAIS-III Arithmetic; Information: WAIS-III Information; Block: WAIS-III Block Design; Affect Rec: Degraded Facial Affect Recognition Total Score; Face Rec: Benton Face Recognition; Hinting Task: F: Test statistic from mixed model regression analysis; df: degrees of freedom. Effects that remained significant after correction for multiple comparisons (p<0.005) in current/lifetime users compared to never users are circled in Figure 1b.

Figure 1c)
Discussion

The aim of this cross-sectional study was to investigate how recency and frequency of cannabis use are associated with cognitive performance in patients with non-affective psychosis, their unaffected siblings, and control subjects. Our findings indicate worse performance on immediate verbal learning, processing speed and working memory in current cannabis users. Furthermore, lifetime cannabis use was associated with better performance on acquired knowledge, affect recognition and face identity recognition. The effect sizes of these associations were in the small range which may explain why previous studies that included smaller sample sizes have found contradictory results (Coulston et al. 2007b). Of those subjects who had used cannabis over the past year, daily or weekly users did not perform significantly different compared to subjects who had used less than weekly. Finally, associations between cannabis use and cognitive functioning were not significantly different in patients, siblings and controls. The interpretation of these findings is discussed here. As the comparison of cognitive performance between patients, siblings and controls (figure 1a) was not the primary aim of this study, we refer to our baseline study on cognitive assessment in GROUP for further interpretation of these results (Meijer et al submitted).

A negative association between cognitive functioning and current- but not lifetime- cannabis use is likely to result from a residue of cannabinoids in the central nervous system. Worse immediate verbal learning in current cannabis users is in agreement with other studies for patients with psychotic illness (Liraud and Verdoux 2002, Pencer and Addington 2003, D'Souza et al 2005, Sevy et al. 2007, Jockers-Scherubl et al. 2007, Coulston et al. 2007a, Yucel et al. 2010). Also in healthy controls, immediate verbal learning is one of the most consistently impaired cognitive functions after acute cannabis administration, and congruent with our results, this effect appears to be transient after a four-week abstinence (Grant et al. 2003, Solowij. and Michie 2007).

In contrast with our finding of worse processing speed in current users, the majority of studies in schizophrenia patients reported either absent, or even positive effects of both current and lifetime cannabis use on visual processing speed (Sevy et al. 2007, Jockers-Scherubl et al. 2007, Coulston et al. 2007a, Schnell et al. 2009, DeRosse et al. 2010). Positive associations in those studies might have been driven by higher premorbid cognitive functioning in cannabis using patients (Fried et al. 2005, Schnell et al. 2009). Worse processing speed performance in current- but not lifetime- cannabis users is in agreement with evidence from studies in control subjects (Ehrenreich et al. 1999, Fried et al. 2005). Similar to our findings, recent cannabis use in schizophrenia patients has been associated with worse working memory (Ringen et al. 2010), but absent or positive associations have also been reported (Sevy et al. 2007, Mata et al. 2008, Scholes and Martin-Iverson 2010). Opposite findings may have resulted from differing sample sizes or the heterogeneity of working memory measures that have been used. WAIS-III Arithmetic may be regarded as a relatively complex measure of working memory, with split loadings on processing speed and verbal comprehension (Tellegen 2003). Our findings are supported by studies in control subjects that reported impaired working memory following intravenous THC administration and cannabis smoking (Ilan et al. 2004, Morrison et al. 2009), while lifetime cannabis use was not associated with working memory impairments (Scholes and Martin-Iverson 2010).

With regard to the effects of Cannabis Frequency, findings that daily and weekly users did not perform significantly different from less frequent users are corroborated by the literature in schizophrenia patients (Rodriguez-Sanchez et al. 2010) and in healthy subjects (Pope Jr. et al. 2002).
Tolerance for the adverse cognitive effects of cannabis in more frequent users might have accounted for the absence of a dose-response relationship on cognition (Ramaekers et al. 2009). We found that lifetime cannabis users performed better than never users on tasks of acquired knowledge, facial affect recognition, and face identity recognition. Research on the association between cannabis use and performance on facial affect and identity processing is sparse in both patients and controls. One study reported that patients who had used cannabis prior to psychosis onset showed a relative sparing of face identity recognition at 10-12 year follow-up, but this difference was lost after co-varying for age at psychosis onset (Stirling et al. 2005). In non-psychotic polysubstance users, cannabis use was not associated with quality of facial affect recognition, but this association might have been confounded by differing effects of other substances (Fernandez-Serrano et al. 2011).

A positive association between lifetime cannabis use and cognitive functioning may seem counterintuitive given the detrimental effects in acute administration studies (D’Souza et al. 2005, Morrison et al. 2009). It has been suggested that substance using patients might need better cognitive and social skills in order to maintain an illicit substance use (Joyal et al. 2003, Potvin et al. 2005), but in the Netherlands cannabis is not illegal and can be purchased with lesser restrictions. In other words, subjects do not need superior social functioning to obtain cannabis. Our findings are however in correspondence with a recent meta-analysis reporting that superior neuropsychological functioning in cannabis using schizophrenia patients was largely driven by studies that included lifetime users rather than current or recent users (Yucel et al. 2010). Our results support the hypothesis that cannabis using patients might constitute a subgroup of patients that is intrinsically less vulnerable for schizophrenia than patients who have never used cannabis (Mueser et al. 1998).

This so-called vulnerability hypothesis postulates that a psychotic illness triggered by an environmental stressor such as cannabis may be less severe than a psychotic illness that is predominantly due to inherent genetic vulnerability. This developmental model has been supported by various studies that investigated the order in which cannabis use and psychosis occur. Three studies found that cognitive functioning was specifically preserved in patients who had started cannabis consumption before disease onset (Stirling et al. 2005, Rodriguez-Sanchez et al. 2010) or before the age of 17 (Jockers-Scherubl et al. 2007). These studies suggest that it is not the cognitive effects of cannabis per se, but the contribution of cannabis to disease onset that explains better cognitive functioning in cannabis using patients. Secondly, evidence from follow-up studies suggests that acutely admitted psychotic patients using cannabis have a higher recovery potential for both cognitive and clinical parameters, especially after cessation of cannabis use (Loberg and Hugdahl 2009, Gonzalez-Pinto et al. 2009).

Thirdly, studies focusing on neurodevelopmental and genetic factors have added credibility to the vulnerability hypothesis. Cannabis use before psychosis onset has been associated with less neurological soft signs after transition to psychosis, which is thought to reflect a lower genetic loading in those patients (Bersani et al. 2002, Stirling et al. 2005, Ruiz-Veguilla et al. 2009). It should however be stressed that lifetime cannabis use in our patients was associated with a lower educational degree. In healthy individuals adolescent cannabis use is known to increase the risk of poor school performance, and in particular early school leaving (Lynskey and Hall 2000). Cannabis use is also known to impact negatively upon later employment in control subjects (Fergusson and Boden 2008), and the impact may be even more severe in a cognitively vulnerable population of psychotic patients.
Other than in patients with psychosis and healthy controls, evidence on the association between cannabis use and cognition in genetic high risk subjects is sparse. In agreement with our results, Henquet et al (2006) found that acute THC administration in unaffected siblings and control subjects was associated with a decline in domains of verbal memory and processing speed. In addition, preliminary evidence suggested that sensitivity to the cognitive effects of THC might be moderated by a functional polymorphism in the catechol-O-methyltransferase (COMT) gene that is also known to moderate the risk to develop psychosis in reaction to cannabis use (Henquet et al 2006). The present study is to our knowledge the first observational study to assess the relationship between daily-life cannabis use and cognitive functioning in genetic high risk subjects.

Finally, patient or sibling status did not moderate the association between recency or frequency of cannabis use and cognitive functioning. Although there have been suggestions of an increased vulnerability to the cognitive adverse effects of acute THC administration in patients and their siblings (D’Souza et al 2005, Henquet et al 2006), we did not replicate this finding. A first explanation might be that such an interaction effect is restricted to the first hours following acute intoxication of cannabis and not applicable to effects resulting from a residue of cannabinoids in the brain. A second difference in study methodologies is the psychoactive substance of use. While previous studies found an interaction effect on cognitive functioning between psychosis vulnerability and THC, we assessed associations with current, daily-life cannabis use. Contrary to cannabis, THC is a synthetic preparation that is devoid of cannabidiol, which is a potential inhibitor of pharmacological effects of CB1 agonists (Pertwee 2008). Further research needs to clarify the association between individual cannabis components and cognitive functioning in individuals with psychosis and their unaffected relatives.

Despite the absence of an interaction effect, our findings do not imply that campaigns to discourage cannabis use are without merit. The adverse effects of cannabis use on psychotic symptomatology are well acknowledged in both patients (Linszen et al 1994, Macleod 2007, Castle, 2008) and individuals at genetic risk for psychosis (Caspi et al 2005, Genetic Risk and Outcome of Psychosis (GROUP) Investigators 2011).

The following limitations should be taken into account. First, the cross-sectional design restricts the drawing of causal inferences between cannabis use and cognitive functioning. Second, we cannot fully exclude the possibility that some of the current users in our study were tested within less than 24 hours after cannabis consumption so that the effects measured were those of acute intoxication. However, instructing frequent users to abstain from cannabis use before testing could cause negative cognitive effects as well, similar to those of acute intoxication (Pope Jr. et al 2002).

The strength of this study is that-due to the comprehensive database of the GROUP study- we were able to address recommendations that have been made in prior studies (Coulston et al 2007b, Yucel et al 2010), such as investigating both recency and frequency of cannabis use, the inclusion of a cannabis-using control group, biological validation of self-report cannabis measures by urine drug screening, the assessment of a broad range of cognitive measures, and controlling for a range of possible confounders. Furthermore, the current study expanded on existing studies by the inclusion of unaffected siblings, so that we were able to draw conclusions on the association between cannabis and cognition in people at genetic high risk for psychosis.

Our findings implicate that cannabis use in patients, siblings, and controls is associated with differences in cognitive performance, depending on the recency of use. Current cannabis users perform worse on task of short-term memory and processing speed which may reflect residual effects. Lifetime cannabis users perform better on social cognition and acquired knowledge, which is more likely to be a result from a lower genetic vulnerability rather than an effect of cannabis itself.
This discrepancy between potential and actual performance is clinically relevant for those patients whose cannabis use might complicate a potentially less severe course of psychosis. Future studies are needed to test the validity of the vulnerability hypothesis. A longitudinal, prospective design may optimally address this issue, as it permits within-patient comparisons of cognitive performance before initiation and after cessation of cannabis use. These studies should also include subjects at genetic high risk, to elucidate if indeed the better functioning individuals only develop psychosis following a late environmental risk factor such as cannabis use.

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