Cannabis use and cognitive functions in at risk mental state and first episode psychosis

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Abstract

Background: Meta-analyses suggest that schizophrenia patients with a history of cannabis use have less impaired cognitive functioning compared to patients without cannabis use.

Aims: To assess the association between recency and frequency of cannabis use and cognitive functioning in at-risk mental state for psychosis (ARMS) and First Episode Psychosis (FEP) individuals.

Methods: 136 participants completed a cognitive test battery and were assessed for current and past cannabis use. Analyses of covariance models where applied to evaluate the main effects of cannabis use and patient group (ARMS vs. FEP) as well as their interactions on cognitive functioning.

Results: No differences were observed in cognitive performance between current, former and never users, and there were no significant interactions between cannabis use and patient group. Furthermore, within the group of current cannabis users, frequency of cannabis use was not significantly associated with cognitive functioning.

Conclusion: The results of the present study do not support the notion that FEP patients and ARMS individuals with a history of cannabis use have less impaired cognitive functioning compared to those without cannabis use.

Keywords: First episode psychosis (FEP), at risk mental state (ARMS), cannabis, cognition, schizophrenic psychosis.

Declaration of interest: None.

1. **Introduction**

While the cognitively impairing effects of cannabis during acute intoxication have been acknowledged for some time, evidence has been accumulating in recent years that cannabis may also cause subtle neuropsychological impairments that persist beyond acute intoxication (Solowij and Pesa 2010). Recent studies have shown that long-term, heavy cannabis use can lead to cognitive deficits in a wide range of domains, including memory, attention, inhibitory control, executive functions, and decision making, and that these deficits are still present after one week (Meier, Caspi et al. 2012) and one month (Bolla, Eldreth et al. 2005; Medina, Hanson et al. 2007) of abstinence. Furthermore, an increasing number of studies indicate that the magnitude and persistence of cognitive impairment is positively associated with the frequency and duration of use and negatively associated with the age of onset of heavy cannabis use (Solowij and Pesa 2010; Meier, Caspi et al. 2012).

It has been suggested that the cognitive impairments observed in healthy cannabis users are similar to those reported in patients suffering from schizophrenic psychoses (Solowij and Michie 2007). Neuropsychological impairment is recognized as core feature of schizophrenia (Palmer, Dawes et al. 2009) and is not only present in patients with schizophrenic psychoses, but already in individuals with an at-risk mental state (ARMS) for psychosis (Brewer, Wood et al. 2006; Pflueger, Gschwandtner et al. 2007; Riecher-Rossler, Pflueger et al. 2009; Giuliano, Li et al. 2012). Furthermore, it has been reported that ARMS individuals with later transition to psychosis perform worse on tests measuring verbal fluency, memory (Fusar-Poli, Deste et al. 2012; Van der Meer 2012) as well as speed of information processing (Brewer, Francey et al. 2005; Riecher-Rossler, Pflueger et al. 2009) than those without transition. Accordingly, it has been demonstrated that prediction of psychosis can be improved by taking neurocognitive performance measures into account (Riecher-Rossler, Pflueger et al. 2009; Koutsouleris, Davatzikos et al. 2012).

Given that cognitive impairments are frequently present in patients with schizophrenia and healthy, heavy cannabis users and given that brain structural changes have been observed in cannabis using schizophrenia patients particularly in cannabinoid receptor rich

regions (Rapp, Bugra et al. 2012), we would expect cannabis using schizophrenia patients to demonstrate particularly severe neurocognitive deficits. Surprisingly, however, the four most recent meta-analyses all demonstrated that schizophrenia patients with a history of cannabis use have less impaired cognitive functioning compared with non-using schizophrenia patients (Potvin, Joyal et al. 2008; Loberg and Hugdahl 2009; Yucel, Bora et al. 2010; Rabin, Zakzanis et al. 2011).

Two main hypotheses have been put forward to explain these unexpected findings. Firstly, it has been proposed that cannabis using schizophrenia patients may belong to a subgroup with better pre-morbid functioning and lower vulnerability to psychosis and that, therefore, many patients in this subgroup only transitioned to psychosis due to early initiation of heavy cannabis use (Schnell, Koethe et al. 2009; Yucel, Bora et al. 2010). This is supported by the fact that cannabis using first episode psychosis (FEP) patients consistently showed fewer neurological soft signs than FEP patients not using cannabis (Ruiz-Veguilla, Callado et al. 2012). The initial neurocognitive performance advantage of this subgroup could be so large that it would not be neutralized by the putatively subtle cognitive decline caused by cannabis. Secondly, it has been suggested that cannabis could improve cognitive functioning by counteracting a putative neurotoxic process related to schizophrenia or by stimulating prefrontal neurotransmission (Coulston, Perdices et al. 2011). Although only adverse consequences of cannabis use have traditionally been considered in schizophrenia research, the latter hypothesis is not as far-fetched as it may seem because a growing body of evidence indicates that cannabinoid drugs have a dual neuroprotective-neurotoxic profile (Sarne, Asaf et al. 2011). Furthermore, there is evidence from small-scale clinical studies that some patients with schizophrenia might benefit from treatment with synthetic Δ-9-tetradhydrocannabinol (Δ-9-THC), the principle psychoactive constituent of cannabis, as well as cannabidiol, which is another constituent of cannabis (Leweke, Koethe et al. 2007; Schwarcz, Karajgi et al. 2009). However, while several lines of evidence point to a beneficial and even antipsychotic effect of cannabidiol (Roser et al. 2010), the evidence for a beneficial

effect of THC is much smaller and more controversial. Moreover, the hypothesis that some patients might experience neuroprotective and/or neurocognitive enhancing effects of cannabis is difficult to reconcile with results from prospective observational studies showing that FEP patients who stopped consuming cannabis have better long-term functional outcome and fewer negative symptoms compared to those continuing to consume (Gonzalez-Pinto et al., 2011).

Although a relatively large number of studies have examined associations between cannabis use and cognitive performance in schizophrenia patients, most of them have serious methodological limitations. For instance, several authors have criticized that many studies have not adjusted for potentially confounding variables, measured only a limited range of cognitive functions, and used only a single index to classify cannabis use and this single index was either not clearly elucidated, was too restricted, and/or tended to be too broad , and/or did not consider recency of cannabis use (Coulston, Perdices et al. 2007; Segev and Lev-Ran 2012). The latter seems to be particularly important because the most recent meta-analysis suggests that the less impaired cognitive performance observed in cannabis using schizophrenia patients is mainly driven by the inclusion of lifetime users, rather than current or recent users (Yucel, Bora et al. 2010). A further limitation of previous studies is that they have not examined whether the associations between cannabis use and neuropsychological functioning are stable across different stages of developing psychoses. Most studies so far have only included FEP or chronic schizophrenia patients and only one study has investigated ARMS patients (Korver, Nieman et al. 2010).

Hence, the present study for the first time analyzed associations between cannabis use and cognitive functioning concomitantly in both ARMS and FEP patients. It also improves on many of the previous studies by assessing cognitive functioning across a wide range of domains, by adjusting for the most important confounders, by including mostly antipsychotic-naïve participants, and by distinguishing between former, current, and never users of cannabis. Based on previous findings (Yucel, Bora et al. 2010; Meijer, Dekker et al.

2012), we hypothesized that less impaired cognitive functioning would only be present in former users of cannabis, but not in current users. In addition, we expected that, within the group of current users, cognitive performance would be worse with increasing frequency of cannabis use.

2. Methods

Setting and recruitment

The neuropsychological data analyzed in this study were collected within the prospective **F**rüh**e**rkennung von **Psy**chosen (***FePsy***) study, which aims to improve the early detection of psychosis. A more detailed description of the overall study design can be found elsewhere (Riecher-Rossler, Gschwandtner et al. 2007; Riecher-Rossler, Pflueger et al. 2009). Participants were recruited into the study via the ***FePsy***-Clinic at the Psychiatric Outpatient Department of the University Hospital Basel, which was set up specifically to identify, assess, and treat individuals in the early stages of psychosis. The study was approved by the ethics committee of the University of Basel and all participants provided written informed consent.

Screening Procedure

Screening was performed with the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rossler, Aston et al. 2008).This instrument allows the rating of individuals regarding the inclusion/exclusion criteria corresponding to the PACE criteria (Yung, Phillips et al. 1998; Yung, McGorry et al. 2007) and has been shown to have a good interrater-reliability (K = .67) for the assessment of the main outcome category “at risk for psychosis” and a high predictive validity (Riecher-Rössler, Aston et al. 2008). Individuals were classified as being in an At-Risk Mental State (ARMS) for psychosis, having a first episode psychosis (FEP), or being not at risk for psychosis (usually other psychiatric disorders). Only ARMS and FEP individuals were included in the present study.

Neuropsychological Assessment

The neuropsychological test battery was mainly based on computer-administered tests. All neuropsychological assessments were conducted by psychologists and well-trained, supervised advanced students of psychology. The test battery covered the domains of general intelligence, executive functions, working memory, attention, verbal learning and memory (Pflueger, Gschwandtner et al. 2007; Riecher-Rossler, Pflueger et al. 2009).

The general intelligence was estimated with the Mehrfachwahl–Wortschatz-Test (MWT-A) (Lehrl 1991) and the Leistungsprüfsystem, scale 3 (LPS) (Horn 1983). Both are well established German intelligence scales for assessing verbal and nonverbal (abstract reasoning) abilities.

Executive functions were assessed with computer-administered Tower of Hanoi (ToH) (Gedika and Schöttke 1994), Wisconsin Card Sorting Test (WCST) (Heaton, Chelune et al. 1993; Drühe-Wienholt and Wienholt 1998) and Go/No-Go subtest of the Tests for Attentional Performance (Zimmermann and Fimm 1993).

The working memory was measured with the subtest “Working Memory” of the TAP (Zimmermann and Fimm 1993), the selective attention with the subtest Go/No-Go and the vigilance with the Continuous Performance Test (CPT-OX) (Rosvold, Mirsky et al. 1956).

Verbal learning and memory was assessed by the California Verbal-Learning Test (CVLT) (Delis, Kramer et al. 1987). To minimize problems associated with multiple comparisons (i.e. Type 1 error inflation), group comparisons on CVLT performance were made on the basis of CVLT composite scores instead of individual measures. The following three composites were used: auditory attention, verbal learning, and inaccurate recall. These composites were derived from a confirmatory factor analysis model that best fitted the data of a relatively large sample of epilepsy patients (model 3 in the study of Banos et al. (Banos, LaGory et al. 2004)).

Psychopathological assessments

The Brief Psychiatric Rating Scale (BPRS) (Lukoff, Nuechterlein et al. 1986; Ventura, Lukoff et al. 1993) was used to assess positive psychotic symptoms (i.e., hallucinations, suspiciousness, unusual thought content and conceptual disorganization) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen 1989) was used to assess negative symptoms.

Cannabis use

Cannabis use was assessed with the Basel Interview for Psychosis (BIP), a semi-structured interview that was specifically developed to obtain medical histories of ARMS and FEP individuals (Riecher-Rössler et al., in preparation). The BIP contains two items assessing the frequency of past and present cannabis use. Both items assess the frequency of cannabis use on a five-point ordinal scale using the following response categories: daily, several times a week, several times a month, less than several times a month, and not at all. Whenever cannabis use was suspected, this was additionally assessed by urine toxicology screens, i.e. in 53 (41%) of the included patients. Urine tests were considered positive when THC-COOH was present in the urine in a concentration of at least 10µg/l, in order to infer a detection window of ≈1 month. Although urine tests were only available in subset of our sample, the agreement between urine tests and the questionnaire item on current use was excellent. That is, all patients with cannabis-positive urine had responded to the questionnaire item measuring current cannabis use with a frequency of at least rarely and all patients with cannabis-negative urine had responded with a frequency less than several times per month. Hence, relying only on information of the BIP in those patients who did not have urine toxicology screens was considered well justified.

Patients were categorized into three groups: Current, former, and never users. Current users were those that had cannabis-positive urine or a current cannabis use frequency of at least several times a month. Former users were required to have cannabis-negative urine (if available), a past cannabis use frequency of at least several times per month and current cannabis use of rarely or never. Never users were required to have cannabis-negative urine (if available) and past and current cannabis use frequencies of never. Patients who could not be assigned to one of these categories (e.g., because they had consumed cannabis neither regularly nor never) were excluded.

Statistical analysis

All data were analyzed by using the R environment for statistical computing (R Development Core Team 2012). Differences in socio-demographic and clinical characteristics between current, former, and never users within each patient group (i.e., ARMS, FEP, and combined group) were tested with one-way Analysis of Variance (ANOVA), Kruskal Wallis, χ^2 or Fisher's exact tests.

To investigate the effects of cannabis use (past, former, and never) and patient group (ARMS and FEP) on neurocognition, the following procedure was applied. First, all of the 17 neurocognitive outcome variables were screened for outliers. Values that were 3 standard deviations above or below the mean were treated as missing if they could be attributed to misunderstanding of instructions and truncated (i.e. replaced by the mean +/- three standard deviations) if no obvious cause for their emergence could be found. Because most of the neurocognitive outcome measures – even after removal of outliers – did not conform to assumptions of normality and/or homogeneity of variance, the Box-Cox transformation (Box and Cox 1964) was applied to each of these variables. The Box-Cox procedure automatically selected and applied exponential transformations that were optimal with regard to normalizing distributions and equalizing variances (see Supplementary Table 1 for the chosen transformation of each variable).

Because some of the outcome measures, as well as control variables, contained considerable proportions of missing data (see Supplementary Table 1), we next performed multiple imputation (MI) using the Multivariate Imputation by Chained Equations (MICE) software (van Buuren and Groothuis-Oudshoorn 2011). MI is considered the method of choice of handling complex incomplete data problems because it yields unbiased parameter estimates and standard errors under a missing at random (MAR) or missing completely at random (MCAR) missing data mechanism and maximizes statistical power by using all available information (Enders 2010). Although the MAR or MCAR assumption is not directly testable (Raykov 2011), it was considered plausible in the present situation because the variables with the highest proportion of missing values, such as those of the CVLT, resulted from changes in the study design over the years and so the probability of being missing was unlikely to be directly dependent on the missing values themselves. Furthermore, even if our data were missing not at random (MNAR), the MI procedure most likely would have led to less biased results than the traditional complete case analysis (cf. Enders 2010, on pages 40, 80, and 344). To estimate the missing values, we used predictive mean matching and sets of predictors restricted to those that correlated with at least 0.1 with the variable to be imputed. To protect against a potential power falloff from a too small number of imputations (Graham, Olchowski et al. 2007), we generated 100 imputations of the missing values such that 100 completed datasets were obtained. The analyses of interest (see below) were then conducted in each completed data set, and parameter estimates were pooled according to Rubin's rules (Little and Rubin 1987).

For each neurocognitive outcome variable, an Analysis of Covariance (ANCOVA) was conducted. Cognitive functioning was the dependent variable and cannabis use, patient group, sex, age, premorbid IQ except for the outcome variable MWT-IQ for which we used years of education instead of premorbid IQ, and the cannabis use × patient group interaction were independent variables. If the cannabis use × patient group interaction was not significant, it was removed from the final models.

To investigate whether neurocognition was associated with the frequency of cannabis use, additional ANCOVAs were fitted for each neurocognitive outcome variables based on the group of current cannabis users only and using the frequency of current cannabis use, patient group, sex, age, premorbid IQ except for the outcome variable MWT-IQ for which we used years of education instead of premorbid IQand cannabis frequency × patient group as independent variables. Again, if the cannabis frequency × patient group interaction was not significant, it was removed from the final models. The analysis was restricted to current cannabis use because it was less likely to be subject to recollection bias than past cannabis use. Furthermore, the effects of cannabis were less likely to be confounded by the time that has elapsed since its last use, which could be up to 10 years in some cases.

3. Results

Sample description

126 ARMS individuals and 98 FEP patients were recruited into *FePsy* study from March 1, 2000 to April1, 2013. Of these, 18 ARMS and 13 FEP patients were excluded because they did not have any cognitive performance measures. In the remaining sample, 3 ARMS and 8 FEP patients were excluded because they had used cocaine, MDMA, opiates, hallucinogens, or amphetamines at least several times per week at some time in their lives. Finally, 31 ARMS and 15 FEP patients were excluded because they had neither consumed cannabis regularly nor never and therefore could not be assigned to one of the three cannabis groups. Analyses were performed on the remaining sample, which consisted of 136 participants (74 ARMS and 62 FEP patients). The 88 individuals that were excluded from this study did not differ from the included individuals with regard to gender, sex, premorbid IQ except for the outcome variable MWT-IQ for which we used years of education instead of premorbid IQ, patient group frequency, and BPRS total and positive symptoms scores. Socio-demographic and clinical characteristics as well as frequencies of cannabis use of the included individuals are presented in Table 1. Within the total group and ARMS groups,

cannabis groups (i.e., current, former, and never users) were significantly different with regard to age. Pairwise comparisons revealed that this was because never users were significantly older than former users within both the total (p=0.022) and ARMS (p=0.033) groups. There were no significant differences between current, former, and never users of cannabis with regard to gender, premorbid IQ except for the outcome variable MWT-IQ for which we used years of education instead of premorbid IQ, age at onset of cannabis use, BPRS positive symptoms, BPRS total score, SANS total score, and use of antipsychotics, tranquilizers, and antidepressives neither within the total group nor within the FEP or ARMS subgroups. Almost all ARMS individuals were antipsychotic naïve; only three ARMS individuals (3/70) had received low doses of second generation antipsychotic medication during no more than three weeks for behavioral control by the referring psychiatrist or general practitioner prior to study inclusion. Also, the majority of the FEP patients (33/56) were antipsychotic-naïve.

Effects of cannabis use and patient group on cognitive functioning

In the ANCOVA models that included recency of cannabis use (current, former and never use) and patient group (ARMS vs. FEP) as between subject factors and sex, age, premorbid IQ except for the outcome variable MWT-IQ for which we used years of education instead of premorbid IQ, and use of antipsychotics as covariates, there were no significant interactions effects between recency of cannabis use and patient group on any cognitive performance measure. The main effect of recency of cannabis use (former, past and never use) was only significant for the dependent variable Go/NoGo omissions. Inspections of the regression coefficients of the two dummy variables formed from the categorical variable recency of cannabis use indicated that this was because both former and current users had fewer omissions than never users. However, these differences were no longer significant when p-values were corrected for multiple testing by the Benjamini-Hochberg method (Benjamini and Hochberg 1995). Figure 1 displays the performance differences of current and former users compared to never users on all analyzed cognitive performance measures

in the total group. Supplementary Table 2 provides effect sizes (Cohen's *d*), confidence intervals, test statistics and *p*-values of the cannabis group differences in the total group. Supplementary Figure 1-2 and Supplementary Table 3-4 report about the same differences separately for ARMS and FEP patients.

As shown in Figure 2, FEP patients tended to have lower cognitive performance than ARMS individuals on most cognitive measures. However, the differences between these two groups were only statistical trends for the number of omissions in the Go/NoGo task (*p*= 0.071) and for the number of omissions in the CPT task (*p*=0.069).

Cannabis frequency and cognitive functioning

In the analyses restricted to current users, the interaction between patient group and cannabis frequency (daily, weekly, and less than weekly use of cannabis) was not statistically significant for any of the cognitive performance measures, as can be seen in Figure 3.. Supplementary Table 5 provides effect sizes (Cohen's *d*), confidence intervals, test statistics and *p*-values of these differences in the total group. Supplementary Figure 3-4 and Supplementary Table 6-7 report about the same differences separately for ARMS and FEP patients.

4. Discussion

In this study, we examined for the first time the effects of cannabis use on neuropsychological performance in a combined sample of FEP and ARMS participants. We hypothesized that - compared to never users of cannabis – less impaired cognitive functioning would only be present in former users, but not in current users of cannabis and that, within the group of current users, high cannabis use frequency would be associated with worse cognitive performance. Both hypotheses were not confirmed in the present study. Except for a small significant difference in the number of omissions during Go/NoGo trials, which did not withstand correction for multiple testing, there were no cognitive performance differences between former, current, and never users of cannabis. Furthermore, we did not

find worse cognitive performance with increased cannabis use frequency within the group of current users.

The rejection of the first hypothesis in the present study stands in contrast to the four most recent meta-analyses (Potvin, Joyal et al. 2008; Loberg and Hugdahl 2009; Yucel, Bora et al. 2010; Rabin, Zakzanis et al. 2011) , which found less impaired cognitive functioning in schizophrenia patients with a history of cannabis use, and to several studies indicating that this difference might be due to the inclusion of former users (Yucel, Bora et al. 2010; Meijer, Dekker et al. 2012). There are multiple possible reasons for these discrepancies: First, while most of the studies defined the group of cannabis users according to diagnostic criteria of cannabis abuse or dependence using Structured Clinical Interview (SCID) for DSM-IV (Coulston, Perdices et al. 2007), we assessed cannabis use with a semi-structured interview and by urine toxicology screens. The use of the SCID criteria might have led to the inclusion of more heavy users than in our study. Furthermore, in other studies, the cannabis-naïve group was often defined by the absence of a DSM-IV cannabis use disorder, which, unlike in our study, might have led to the inclusion of occasional cannabis users or more frequent and heavy users whose functioning is unaffected to the extent in which an substance use disorder diagnosis is made.

Second, the discrepancy between our and other studies might be due to differences in neuropsychological test batteries. For instance, some of the neuropsychological performance measures, such as the number of omissions in the Go/NoGo and working memory task were subject to strong floor effects (i.e., a relatively large number of subjects had zero omissions). Thus, it is possible that these measures did not differentiate enough between groups with different cognitive functioning. On the other hand, we neither found differences in the cognitive measures that were not subject to floor or ceiling effects.

Finally, we might have obtained different results because our participants consumed cannabis with different potency and cannabinoid ratios than in other studies. A growing number of studies suggest that THC and cannabidiol, which are both contained in cannabis

products with varying concentration, have opposite effects on cognition (Bhattacharyya, Morrison et al. 2010). Data suggest diverging trends across Europe in the mean level of THC of cannabis in recent years, with a decrease or stabilisation in some countries and an increase in other countries (King 2008).

The rejection of our second hypothesis is in line with other studies, which also did not find schizophrenia patients who used cannabis daily or weekly performing significantly worse than participants with less frequent use of cannabis (Rodriguez-Sanchez, Ayesa-Arriola et al. 2010; Meijer, Dekker et al. 2012). Although this seems counterintuitive, one explanation might be that daily and weekly users of cannabis to some extent became tolerant to the negative effects of cannabis. Meijer et al. (Meijer, Dekker et al. 2012), who also did not find a dose-response effect, speculated that the classification of frequency in daily, weekly and monthly use might not be sensitive enough to detect cognitive differences.

The following limitations should be taken into account: We did not assess the duration, quantities of cannabis use, concentration of cannabidiol and THC, and maximum frequency of use over the life time. Consequently, we could not control for these influences. Furthermore, the moderate sample size of the present study precluded the detection of small effects. This could be particularly problematic because some studies indicate that cognitive performance differences between cannabis use groups are rather small (Meijer, Dekker et al. 2012). However, we also did not find statistical trends for differences in cognitive functioning in most variables even without correction for multiple testing. Furthermore, the sign of the differences between groups was quite heterogeneous. Moreover, Yücel et al. (2010) found in their meta-analysis that the difference between lifetime/past cannabis users with never users on global cognition has an average effect size of Cohen's $d = 0.55$. If we take this as an estimate of the population effect size and calculate power based on a two sample t-test with group sizes equal to our study, a significance level of 0.05, and a two-tailed hypothesis test, we get an estimated power of 0.7 for testing the main effect of interest in our study. Hence, we consider it rather unlikely that our hypotheses were mainly rejected due to insufficient

statistical power. It should also be noted that, although our sample size was moderate, it was still larger than in most previous studies (cf., Rabin, Zakzanis et al. 2011).

In conclusion, the results of the present study do not support the notion that FEP and ARMS participants with a history of cannabis use have less impaired cognitive functioning. We also found no evidence that the less impaired cognitive functioning in cannabis using FEP patients, which has been reported in some previous studies, is due to the inclusion of former users or that associations between cannabis use and cognitive functioning differ between ARMS and FEP patients.

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