Psychopharmacology (2013) 230:299–308
DOI 10.1007/s00213-013-3157-y

ORIGINAL INVESTIGATION

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

H. Bugra · E. Studerus · C. Rapp · C. Tamagni · J. Aston · S. Borgwardt · A. Riecher-Rössler

Received: 19 December 2012 / Accepted: 18 May 2013 / Published online: 12 June 2013

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 The objective of this study was 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 One hundred thirty-six participants completed a cognitive test battery and were assessed for current and past cannabis use. Analyses of covariance models were 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, the 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

Electronic supplementary material The online version of this article (doi:10.1007/s00213-013-3157-y) contains supplementary material, which is available to authorized users.

H. Bugra · E. Studerus · C. Rapp · C. Tamagni · J. Aston · S. Borgwardt · A. Riecher-Rössler (✉)
Center for Gender Research and Early Detection,
University of Basel Psychiatric Clinics, c/o University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland
e-mail: anita.riecher@upkbs.ch

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 1 week (Meier et al. 2012) and 1 month (Bolla et al. 2005; Medina 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 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 a core feature of schizophrenia (Palmer 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 et al. 2006; Pflueger et al. 2007; Riecher-Rössler et al. 2009; Giuliano 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 et al. 2012; Van der Meer 2012), as well as speed of information processing (Brewer et al. 2005; Riecher-Rössler 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-Rössler et al. 2009; Koutsouleris 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 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 et al. 2008; Loberg and Hugdahl 2009; Yucel et al. 2010; Rabin 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 premorbid 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 et al. 2009; Yucel et al. 2010). This is supported by the fact that cannabis-using first episode psychosis (FEP) patients consistently had fewer neurological soft signs than FEP patients not using cannabis (Ruiz-Veguilla 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 et al. 2011). Although only adverse consequences of cannabis use have traditionally been considered in schizophrenia research, the latter hypothesis is not as farfetched as it may seem because a growing body of evidence indicates that cannabinoid drugs have a dual neuroprotective–neurotoxic profile (Sarne 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 principal psychoactive constituent of cannabis, as well as cannabidiol, which is another constituent of cannabis (Leweke et al. 2007; Schwarcz 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 et al. 2007b; 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 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 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 et al. 2010; Meijer 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.

Methods

Setting and recruitment

The neuropsychological data analyzed in this study were collected within the prospective Früherkennung von Psychosen (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-Rössler et al. 2007, 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 (Riecher-Rössler et al. 2008). This instrument allows the rating of individuals regarding the inclusion/exclusion criteria corresponding to the PACE criteria (Yung et al. 1998, 2007) and has been shown to have a good interrater reliability (K=0.67) for the assessment of the main outcome category "at risk for psychosis" and a high predictive validity (Riecher-Rössler et al. 2008). Individuals were classified as being in an ARMS for psychosis, having an 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 et al. 2007; Riecher-Rössler et al. 2009).

The general intelligence was estimated with the Mehrfachwahl-Wortschatz Test (MWT-A) (Lehrl 1991) and the Leistungsprüfsystem, scale 3 (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 (Gedika and Schöttke 1994), Wisconsin Card Sorting Test (Heaton et al. 1993; Drühe-Wienholt and Wienholt 1998), and Go/No-Go subtest of the Test 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 et al. 1956).

Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT) (Delis 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. (2004)).

Psychopathological assessments

The Brief Psychiatric Rating Scale (BPRS) (Lukoff et al. 1986; Ventura 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 semistructured interview that was specifically developed to obtain medical histories of ARMS and FEP individuals (Ackermann, master thesis, unpublished; 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 10 μg/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 sociodemographic 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, 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 ± 3 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 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, 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 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 IQ, and 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.

Results

Sample description

One hundred twenty-six ARMS individuals and 98 FEP patients were recruited into the FePsy study from March 1, 2000 to April 1, 2013. Of these, 18 ARMS and 13 FEP patients were excluded because they did not have any cognitive performance measures. In the remaining sample, three ARMS and eight 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, years of education, patient group and BPRS total and positive symptoms scores. Sociodemographic and clinical characteristics as well as frequencies of cannabis use of the included individuals are presented in Table 1.

Table 1 Sample description

	Total group					ARMS				FEP			
	Nonusers, *N*=56	Current users, *N*=47	Past users, *N*=33	*p* value	*N*	Nonusers, *N*=32	Current users, *N*=24	Past users, *N*=18	*p* value	Nonusers *N*=24	Current users, *N*=23	Past users, *N*=15	*p* value
Gender				0.263	136				0.231				0.598
Women	24 (42.9 %)	13 (27.7 %)	13 (39.4 %)			15 (46.9 %)	6 (25.0 %)	6 (33.3 %)		9 (37.5 %)	7 (30.4 %)	7 (46.7 %)	
Men	32 (57.1 %)	34 (72.3 %	20 (60.6 %)			17 (53.1 %)	18 (75.0 %)	12 (66.7 %)		15 (62.5 %)	16 (69.6 %)	8 (53.3 %)	
Age	30.7 (9.40)	26.4 (7.56)	25.6 (5.71)	0.005**	136	28.9 (8.87)	24.7 (6.25)	23.2 (4.13)	0.016*	33.2 (9.69)	28.3 (8.48)	28.5 (6.11)	0.098
Years of education	11.9 (3.40)	10.7 (2.42)	11.5 (2.78)	0.098	136	11.8 (3.30)	10.3 (1.88)	12.2 (2.79)	0.052	12.1 (3.60)	11.0 (2.86)	10.5 (2.55)	0.292
Antipsychotics currently				0.129	136				0.453				0.113
No	45 (80.4 %)	40 (85.1 %)	22 (66.7 %)			31 (96.9 %)	23 (95.8 %)	16 (88.9 %)		14 (58.3 %)	17 (73.9 %)	6 (40.0 %)	
Yes	11 (19.6 %)	7 (14.9 %)	11 (33.3 %)			1 (3.12 %)	1 (4.17 %)	2 (11.1 %)		10 (41.7 %)	6 (26.1 %)	9 (60.0 %)	
Chlorpromazine equivalent dose [mg]	130 (127)	223 (139)	197 (107)	0.276	28	150 (.)	200 (.)	225 (106)	0.866	128 (135)	227 (151)	191 (112)	0.350
Antipsychotic compound				0.437	136				0.205				0.451
None	45 (80.4 %)	40 (85.1 %)	22 (66.7 %)			31 (96.9 %)	23 (95.8 %)	16 (88.9 %)		14 (58.3 %)	17 (73.9 %)	6 (40.0 %)	
Aripiprazole	0 (0.00 %)	0 (0.00 %)	1 (3.03 %)			0 (0.00 %)	0 (0.00 %)	0 (0.00 %)		0 (0.00 %)	0 (0.00 %)	1 (6.67 %)	
Risperidone	3 (5.36 %)	3 (6.38 %)	4 (12.1 %)			0 (0.00 %)	1 (4.17 %)	0 (0.00 %)		3 (12.5 %)	2 (8.70 %)	4 (26.7 %)	
Quetiapine	3 (5.36 %)	2 (4.26 %)	1 (3.03 %)			0 (0.00 %)	0 (0.00 %)	0 (0.00 %)		3 (12.5 %)	2 (8.70 %)	1 (6.67 %)	
Olanzapine	5 (8.93 %)	2 (4.26 %)	5 (15.2 %)			1 (3.12 %)	0 (0.00 %)	2 (11.1 %)		4 (16.7 %)	2 (8.70 %)	3 (20.0 %)	
Antidepressants currently				0.816	136				0.996				0.566
No	42 (75.0 %)	37 (78.7 %)	24 (72.7 %)			21 (65.6 %)	16 (66.7 %)	12 (66.7 %)		21 (87.5 %)	21 (91.3 %)	12 (80.0 %)	
Yes	14 (25.0 %)	10 (21.3 %)	9 (27.3 %)			11 (34.4 %)	8 (33.3 %)	6 (33.3 %)		3 (12.5 %)	2 (8.70 %)	3 (20.0 %)	
Tranquilizer currently				0.882	136				1.000				0.640
No	43 (76.8 %)	38 (80.9 %)	26 (78.8 %)			26 (81.2 %)	19 (79.2 %)	14 (77.8 %)		17 (70.8 %)	19 (82.6 %)	12 (80.0 %)	
Yes	13 (23.2 %)	9 (19.1 %)	7 (21.2 %)			6 (18.8 %)	5 (20.8 %)	4 (22.2 %)		7 (29.2 %)	4 (17.4 %)	3 (20.0 %)	
BPRS total score	1.94 (0.51)	1.86 (0.53)	1.82 (0.52)	0.539	120	1.74 (0.43)	1.61 (0.31)	1.72 (0.47)	0.504	2.23 (0.46)	2.11 (0.59)	1.94 (0.57)	0.349
BPRS positive symptoms	2.30 (0.91)	2.10 (0.80)	2.04 (1.00)	0.396	123	1.77 (0.60)	1.53 (0.38)	1.52 (0.48)	0.146	3.07 (0.73)	2.68 (0.69)	2.78 (1.10)	0.283
SANS total score	1.20 (0.88)	1.23 (0.90)	1.58 (0.96)	0.211	122	1.22 (0.98)	1.22 (0.87)	1.80 (0.99)	0.147	1.17 (0.74)	1.24 (0.95)	1.31 (0.90)	0.894
Current cannabis use				<0.001***	136				<0.001***				<0.001***
None	56 (100 %)	0 (0.00 %)	25 (75.8 %)			32 (100 %)	0 (0.00 %)	15 (83.3 %)		24 (100 %)	0 (0.00 %)	10 (66.7 %)	
Rarely	0 (0.00 %)	4 (8.51 %)	8 (24.2 %)			0 (0.00 %)	2 (8.33 %)	3 (16.7 %)		0 (0.00 %)	2 (8.70 %)	5 (33.3 %)	
Several times per month	0 (0.00 %)	2 (4.26 %)	0 (0.00 %)			0 (0.00 %)	0 (0.00 %)	0 (0.00 %)		0 (0.00 %)	2 (8.70 %)	0 (0.00 %)	
Several times per week	0 (0.00 %)	18 (38.3 %)	0 (0.00 %)			0 (0.00 %)	10 (41.7 %)	0 (0.00 %)		0 (0.00 %)	8 (34.8 %)	(0.00 %)	
Daily	0 (0.00 %)	23 (48.9 %)	0 (0.00 %)			0 (0.00 %)	12 (50.0 %)	0 (0.00 %)		0 (0.00 %)	11 (47.8 %)	0 (0.00 %)	
Past cannabis use				<0.001***	128				<0.001***				<0.001***
None	56 (100 %)	3 (7.69 %)	0 (0.00 %)			32 (100 %)	2 (9.52 %)	0 (0.00 %)		24 (100 %)	1 (5.56 %)	0 (0.00 %)	
Rarely	0 (0.00 %)	2 (5.13 %)	0 (0.00 %)			0 (0.00 %)	0 (0.00 %)	0 (0.00 %)		0 (0.00 %)	2 (11.1 %)	0 (0.00 %)	
Several times per month	0 (0.00 %)	3 (7.69 %)	3 (9.09 %)			0 (0.00 %)	2 (9.52 %)	1 (5.56 %)		0 (0.00 %)	1 (5.56 %)	2 (13.3 %)	
Several times per week	0 (0.00 %)	11 (28.2 %)	12 (36.4 %)			0 (0.00 %)	8 (38.1 %)	9 (50.0 %)		0 (0.00 %)	3 (16.7 %)	3 (20.0 %)	
Daily	0 (0.00 %)	20 (51.3 %)	18 (54.5 %)			0 (0.00 %)	9 (42.9 %)	8 (44.4 %)		0 (0.00 %)	11 (61.1 %)	10 (66.7 %)	

Table 1 (continued)

	Total group					ARMS				FEP			
	Nonusers, *N*=56	Current users, *N*=47	Past users, *N*=33	*p* value	*N*	Nonusers, *N*=32	Current users, *N*=24	Past users, *N*=18	*p* value	Nonusers *N*=24	Current users, *N*=23	Past users, *N*=15	*p* value
Cannabis-positive urine				<0.001***	62				<0.001***				<0.001***
No	28 (100 %)	1 (5.26 %)	15 (100 %)			16 (100 %)	1 (10.0 %)	7 (100 %)		12 (100 %)	0 (0.00 %)	8 (100 %)	
Yes	0 (0.00 %)	18 (94.7 %)	0 (0.00 %)			0 (0.00 %)	9 (90.0 %)	0 (0.00 %)		0 (0.00 %)	9 (100 %)	0 (0.00 %)	
Age at onset of cannabis use				0.160	33				1.000				0.119
<16 years		10 (52.6 %)	11 (78.6 %)				7 (63.6 %)	5 (71.4 %)			3 (37.5 %)	6 (85.7 %)	
>16 years		9 (47.4 %)	3 (21.4 %)				4 (36.4 %)	2 (28.6 %)			5 (62.5 %)	1 (14.3 %)	

*$p<0.05$, **$p<.01$, ***$p<0.001$

Within the total 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, years of education, 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 3 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 interaction 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/No-Go 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 Figs. 1 and 2 and supplementary Tables 3 and 4 report about the same differences separately for ARMS and FEP patients.

As shown in Fig. 2, FEP patients tended to have lower cognitive performance than ARMS individuals on most

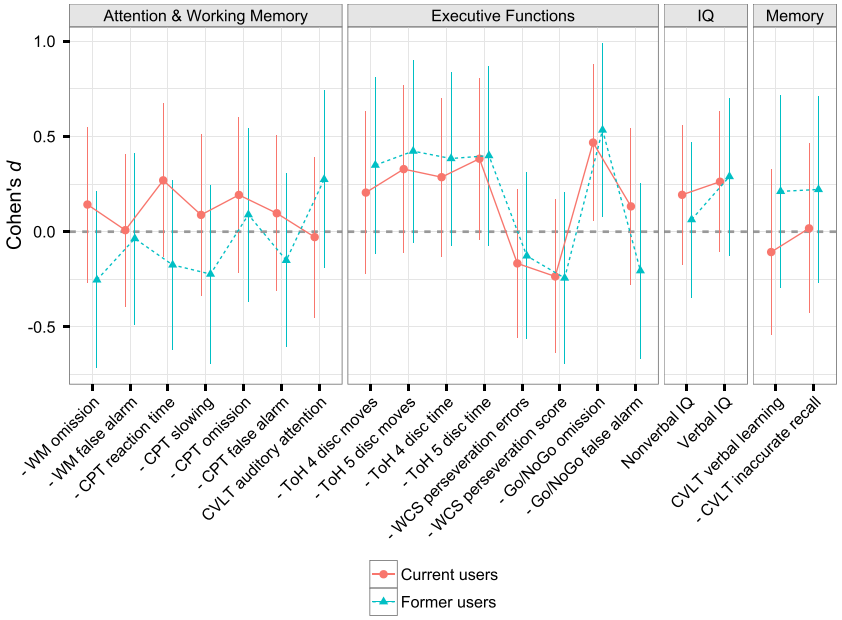

Fig. 1 Cognitive performance of current and former cannabis users compared to never users within the combined group of at-risk mental state (ARMS) and first episode psychosis (FEP) patients. The *dotted horizontal line* at zero represents the performance of never users. Differences are expressed in units of Cohen's *d* and are significant if the 95 % confidence interval (*vertical line*) does not overlap with zero. Variables with a minus sign were reversed such that high scores always represent good performance. Differences are adjusted for the influence of patient group, sex, age, and premorbid IQ and antipsychotics except for the outcome variable MWT-IQ for which we used years of education instead of premorbid IQ

cognitive measures. However, the differences between these two groups were only statistical trends for the number of omissions in the Go/No-Go 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

Fig. 2 Cognitive performance of first episode psychosis (FEP) patients compared to at-risk mental state (ARMS) patients. The *dotted horizontal line* at zero represents the performance of ARMS patients. Differences are expressed in units of Cohen's *d* and are significant if the 95 % confidence interval (*vertical line*) does not overlap with zero. Variables with a minus sign were reversed such that high scores always represent good performance. Differences are adjusted for the influence of cannabis group, sex, age, and premorbid IQ and antipsychotics except for the outcome variable MWT-IQ for which we used years of education instead of premorbid IQ

less than weekly use of cannabis) was not statistically significant for any of the cognitive performance measures, as can be seen in Fig. 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 Figs 3 and 4 and supplementary Tables 6 and 7 report about the same differences separately for ARMS and FEP patients.

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/No-Go 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 et al. 2008; Loberg and Hugdahl 2009; Yucel et al. 2010; Rabin 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 et al. 2010; Meijer 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 et al. 2007a), we assessed cannabis use with a semistructured 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 a 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/No-Go 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

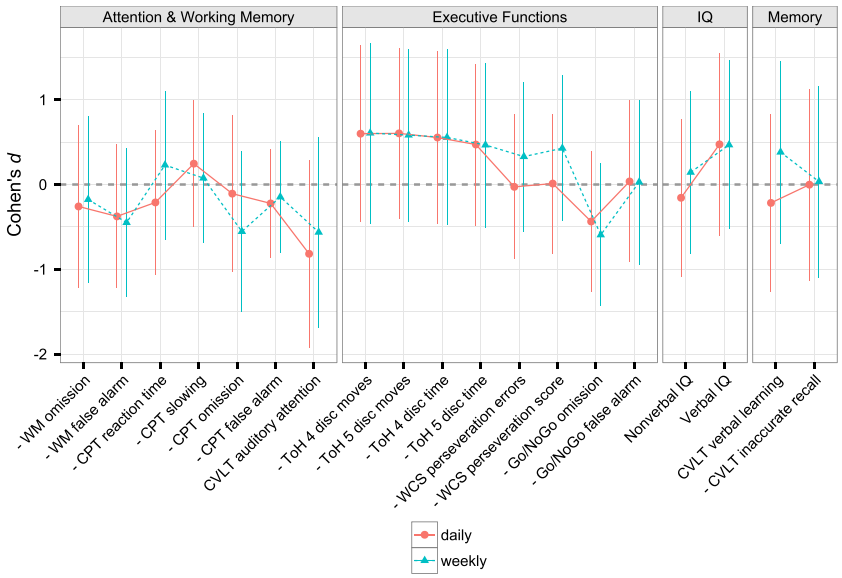

Fig. 3 Cognitive performance of weekly and daily current cannabis users compared to current cannabis users using cannabis less than weekly within the combined group of at-risk mental state (ARMS) and first episode psychosis (FEP) patients. The *dotted horizontal line* at zero represents the performance of current cannabis users using cannabis less than weekly. Differences are expressed in units of Cohen's *d* and are significant if the 95 % confidence interval (*vertical line*) does not overlap with zero. Variables with a minus sign were reversed such that high scores always represent good performance. Differences are adjusted for the influence of patient group, sex, age, and premorbid IQ and antipsychotics except for the outcome variable MWT-IQ for which we used years of education instead of premorbid IQ

not differentiate enough between groups with different cognitive functioning. On the other hand, we did not find differences in the cognitive measures that were not subject to floor or ceiling effects either.

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 et al. 2010). Data suggest diverging trends across Europe in the mean level of THC of cannabis in recent years, with a decrease or stabilization 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 et al. 2010; Meijer 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. (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 lifetime. 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 quite small (Meijer 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, Yucel 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 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.

Conflict of interest None

References

Andreasen NC (1989) The scale for the assessment of negative symptoms (SANS): conceptual and theoretic foundations. Br J Psychiatry 155:49–52

Banos JH, LaGory J et al (2004) Self-report of cognitive abilities in temporal lobe epilepsy: cognitive, psychosocial, and emotional factors. Epilepsy Behav 5(4):575–579

Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate—a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 57(1):289–300

Bhattacharyya S, Morrison PD et al (2010) Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 35(3):764–774

Bolla KI, Eldreth DA et al (2005) Neural substrates of faulty decision-making in abstinent marijuana users. NeuroImage 26(2):480–492

Box GEP, Cox DR (1964) An analysis of transformations. J R Stat Soc Ser B Stat Methodol 26(2):211–252

Brewer WJ, Francey SM et al (2005) Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. Am J Psychiatry 162(1):71–78

Brewer WJ, Wood SJ et al (2006) Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. Schizophr Bull 32(3):538–555

Coulston CM, Perdices M et al (2007a) The neuropsychological correlates of cannabis use in schizophrenia: lifetime abuse/dependence, frequency of use, and recency of use. Schizophr Res 96(1–3):169–184

Coulston CM, Perdices M et al (2007b) The neuropsychology of cannabis and other substance use in schizophrenia: review of the literature and critical evaluation of methodological issues. Aust N Z J Psychiatr 41(11):869–884

Coulston CM, Perdices M et al (2011) Cannabinoids for the treatment of schizophrenia? A balanced neurochemical framework for both adverse and therapeutic effects of cannabis use. Schizophr Res Treat 2011:501726

Delis DC, Kramer JH et al (1987) California Verbal Learning Test (CVLT). Psychological Corporation, San Antonio

Drühe-Wienholt CM, Wienholt W (1998) CKV: Computergestütztes Kartensortierverfahren. Swets und Zeitlinger Testservices, Frankfurt am Main

Enders CK (2010) Applied missing data analysis. Guilford, New York

Fusar-Poli P, Deste G et al (2012) Cognitive functioning in prodromal psychosis a meta-analysis. Arch Gen Psychiatry 69(6):562–571

Gedika G, Schöttke H (1994) Der Turm von Hanoi—TvH. Hogrefe Testsystem (HTS). Hogrefe, Göttingen

Giuliano AJ, Li H et al (2012) Neurocognition in the psychosis risk syndrome: a quantitative and qualitative review. Curr Pharm Des 18(4):399–415

Gonzalez-Pinto A, Alberich S et al (2011) Cannabis and first-episode psychosis: different long-term outcomes depending on continued or discontinued use. Schizophr Bull 37:631–639

Graham JW, Olchowski AE et al (2007) How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci 8(3):206–213

Heaton RK, Chelune GH et al. (1993). Wisconsin Card Sorting Test. Psychological Assessment Resources, Odessa (FL), Psychological Assessment Resources.

Horn W (1983) Leistungsprüfsystem (LPS). Göttingen Verlag für Psychologie, Toronto

King L (2008) Understanding cannabis potency ad monitoring cannabis products in Europe. A cannabis reader: global issues and local experiences, in European Monitoring Centre for Drugs and Drug Addiction Volume 1.

Korver N, Nieman DH et al (2010) Symptomatology and neuropsychological functioning in cannabis using subjects at ultra-high risk for developing psychosis and healthy controls. Aust N Z J Psychiatr 44(3):230–236

Koutsouleris N, Davatzikos C et al (2012) Early recognition and disease prediction in the at-risk mental states for psychosis using neurocognitive pattern classification. Schizophr Bull 38(6):1200–1215

Lehrl S (1991) Manual zum MWT-B. 3 überarbeitete Auflage. Perimed-spitta, Balingen

Leweke FM, Koethe D et al (2007) Cannabidiol as an antipsychotic agent. Eur Psychiatry 22:S21–S21

Little RJA, Rubin DB (1987) Statistical analysis with missing data. Wiley, New York

Loberg EM, Hugdahl K (2009) Cannabis use and cognition in schizophrenia. Front Hum Neurosci 3:53

Lukoff D, Nuechterlein KH et al (1986) Manual for the expanded brief psychiatric rating scale. Schizophr Bull 12:594–602

Medina KL, Hanson KL et al (2007) Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. J Int Neuropsychol Soc 13(5):807–820

Meier MH, Caspi A et al (2012) Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci USA 109(40):E2657–E2664

Meijer JH, Dekker N et al (2012) Cannabis and cognitive performance in psychosis: a cross-sectional study in patients with non-affective psychotic illness and their unaffected siblings. Psychol Med 42(4):705–716

Palmer BW, Dawes SE et al (2009) What do we know about neuropsychological aspects of schizophrenia? Neuropsychol Rev 19(3):365–384

Pflueger MO, Gschwandtner U et al (2007) Neuropsychological deficits in individuals with an at risk mental state for psychosis-working memory as a potential trait marker. Schizophr Res 97(1–3):14–24

Potvin S, Joyal CC et al (2008) Contradictory cognitive capacities among substance-abusing patients with schizophrenia: a meta-analysis. Schizophr Res 100(1–3):242–251

R Development Core Team (2012). R: a language and environment for statistical computing. Vienna, Austria, R Foundation for Statistical Computing.

Rabin RA, Zakzanis KK et al (2011) The effects of cannabis use on neurocognition in schizophrenia: a meta-analysis. Schizophr Res 128(1–3):111–116

Rapp C, Bugra H et al (2012) Effects of cannabis use on human brain structure in psychosis: a systematic review combining in vivo structural neuroimaging and post-mortem studies. Curr Pharm Des 18(32):5070–5080

Raykov T (2011) On testability of missing data mechanisms in incomplete data sets. Struct Equ Model A Multidiscip J 18(3):419–429

Riecher-Rössler A, Gschwandtner U et al (2007) The Basel early-detection-of-psychosis (FEPSY)-study-design and preliminary results. Acta Psychiatr Scand 115(2):114–125

Riecher-Rössler A, Aston J et al (2008) [The Basel screening instrument for psychosis (BSIP): development, structure, reliability and validity]. Fortschr Der Neurol Psychiatr 76(4):207–216

Riecher-Rössler A, Pflueger MO et al (2009) Efficacy of using cognitive status in predicting psychosis: a 7-year follow-up. Biol Psychiatry 66(11):1023–1030

Rodriguez-Sanchez JM, Ayesa-Arriola R et al (2010) Cannabis use and cognitive functioning in first-episode schizophrenia patients. Schizophr Res 124(1–3):142–151

Roser P, Vollenweider FX et al. (2010) Potential antipsychotic properties of central cannabinoid (CB1) receptor antagonists. World J Biol Psychiatry 11(2 Pt 2):208–219

Rosvold HE, Mirsky AF et al (1956) A continuous performance-test of brain-damage. J Consult Psychol 20(5):343–350

Ruiz-Veguilla M, Callado LF et al (2012) Neurological soft signs in psychotic patients with cannabis abuse: a systematic review and meta-analysis of the paradox. Curr Pharm Des 18(32):5156–5164

Sarne Y, Asaf F et al (2011) The dual neuroprotective-neurotoxic profile of cannabinoid drugs. Br J Pharmacol 163(7):1391–1401

Schnell T, Koethe D et al (2009) The role of cannabis in cognitive functioning of patients with schizophrenia. Psychopharmacology (Berlin) 205(1):45–52

Schwarcz G, Karajgi B et al (2009) Synthetic delta-9-tetrahydrocannabinol (dronabinol) can improve the symptoms of schizophrenia. J Clin Psychopharmacol 29(3):255–258

Segev A, Lev-Ran S (2012) Neurocognitive functioning and cannabis use in schizophrenia. Curr Pharm Des 18(32):4999–5007

Solowij N, Michie PT (2007) Cannabis and cognitive dysfunction: parallels with endophenotypes of schizophrenia? J Psychiatr Neurosci 32(1):30–52

Solowij N, Pesa N (2010) [Cognitive abnormalities and cannabis use]. Rev Bras Psiquiatr 32(Suppl 1):S31–40

van Buuren S, Groothuis-Oudshoorn K (2011) mice: multivariate imputation by chained equations in R. J Stat Softw 45(3):1–67

Van der Meer FJ (2012) Cannabis use in patients at clinical high risk of psychosis: impact on prodromal symptoms and transition to psychosis. Curr Pharm Des 18(32):5036–5044

Ventura J, Lukoff D et al (1993) Training and quality assurance with the brief psychiatric rating scale: "the drift busters"; Appendix 1. The Brief Psychiatric Rating Scale (expanded version). Int J Methods Psychiatric Res 3:221–224

Yucel M, Bora E et al (2010) The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. Schizophr Bull 38(2):316–330

Yung AR, Phillips LJ et al (1998) Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br J Psychiatry Suppl 172(33):14–20

Yung AR, McGorry PD et al (2007) PACE: a specialised service for young people at risk of psychotic disorders. Med J Aust 187(7 Suppl):S43–S46

Zimmermann P, Fimm B (1993) Testbatterie zur Aufmerksamkeitsprüfung (TAP). Version 1.02. Handbuch. Vera Fimm/Psychologische Testsysteme, Würselen