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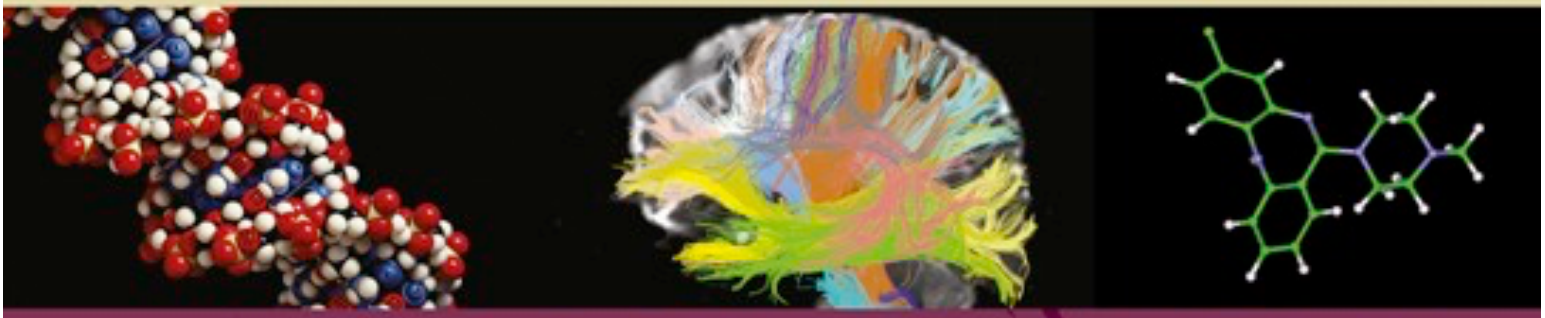

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Cannabis users have higher premorbid IQ than other patients with first onset psychosis

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ABSTRACT

Background: A number of studies have reported that patients with psychosis who use cannabis have better cognitive performance than those who do not. This is surprising as cannabis can impair cognition in healthy subjects. An obvious question is whether the better current performance of psychotic patients who have used cannabis is a reflection of their having a higher premorbid IQ than those psychotic patients who haven't used cannabis.
Aim: In a sample of patients at their first episode of psychosis, we tested the hypothesis that patients who smoked cannabis would have a higher premorbid IQ than patients who did not.
Methodology: 279 participants (119 patients and 160 healthy controls) were assessed in order to obtain current and premorbid IQ measures and detailed information on cannabis use. We examined the association between cannabis use and both premorbid and current IQ in patients and controls.
Results: Patients who had ever smoked cannabis had significantly higher current ($p < .001$) and premorbid IQ ($p = .004$) compared to patients who had never used cannabis. This difference was not found among controls.
Conclusions: These findings suggest that the better cognitive performance of patients with their first episode of psychosis who have used cannabis compared with those who haven't is due to the better premorbid IQ of the former.

1. Introduction

Cognitive impairment is a key feature of schizophrenia (Mohamed et al., 1999; Zanelli et al., 2010; Matheson et al., 2011) and also occurs, though to a lesser extent, in affective psychosis (Krabbendam et al., 2005; Kravariti et al., 2009). However, not all psychotic patients show cognitive impairment (Kremen et al., 2000). A recent epidemiological study of first-admission patients with psychotic disorders estimated that as many as 16% of schizophrenic, 20% schizoaffective, 42% of bipolar, and 42% of depressed patients may not be cognitively impaired (Reichenberg et al., 2009).

Cannabis use has been repeatedly shown to be a risk factor for the development of psychosis (Henquet et al., 2005; Moore et al., 2007; Potvin and Amar, 2008; Di Forti et al., 2009; Casadio et al., 2011). Three recent meta-analyses have reported that among patients with psychosis, those who have used cannabis show better cognitive performance than those who have not (Potvin et al., 2008; Yücel et al., 2010; Rabin et al., 2011). This is unexpected as it has been shown that cannabis use can impair cognition in healthy subjects (Fried et al., 2005; Meier et al., 2012).

Two different explanations have been advanced for this finding. The first suggests that those psychotic subjects who use cannabis have less premorbid cognitive impairment than those who do not. This could be because good premorbid functioning is necessary to acquire and sustain an illegal drug habit (Joyal et al., 2003; Stirling et al., 2005; Rodriguez-Sanchez et al., 2010) or because cannabis use increases the risk of psychosis in a subgroup of patients with less neurodevelopmental vulnerability (Løberg and Hugdahl, 2009; Schnell et al., 2009; de la Serna et al., 2010; Yücel et al., 2010; Leeson et al., 2012; Schnell et al., 2012).

To our knowledge, only one recent study (Leeson et al., 2012) has found higher premorbid IQ in patients who smoked cannabis – among 99 FEP subjects – using the Wechsler Test of Adult Reading (WTAR) as an estimated measure of premorbid IQ. Other studies (Jockers-Scherübl

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et al., 2007; Sevy et al., 2007; DeRosse et al., 2010; Ringen et al., 2010; Yücel et al., 2010; Ringen et al., 2013) that have incidentally examined premorbid IQ in psychosis in relation to cannabis use have reported inconsistent findings, probably due to their small sample size and other methodological problems.

A second possible explanation, based on research into animal models of Parkinson's disease and Alzheimer's disease (Ramirez et al., 2005; Chung et al., 2011; Martìn-Moreno et al., 2011), suggests that some cannabinoids have a neuroprotective action which may help to prevent psychosis-related cognitive decline (Jockers-Scherübl et al., 2007; Løberg and Hugdahl, 2009).

We set out to test the first hypothesis (i.e. that patients who have smoked cannabis show a higher premorbid IQ compared to those who did not) in a sample of FEP patients. We did not expect to find any such relationship between cannabis use IQ and premorbid IQ in controls. This is the first study comparing the relationship of cannabis use to premorbid IQ, in a representative group of FEP patients, including those with affective psychosis, and a matched control group, whilst controlling for important social and demographic variables.

2. Methods

2.1. Sample

Data were derived from the Genetics and Psychosis (GAP) study (Di Forti et al., 2009; Mondelli et al., 2009; Aas et al., 2011; Di Forti et al., 2012; O'Connor et al., 2012), a case–control study of first-episode psychosis, conducted in consenting patients aged 18–65 years admitted to the South London and Maudsley Mental Health NHS Foundation Trust (SLaM). The study was approved by the local research ethics committee.

We collected data on cannabis consumption and neuropsychological performance from 279 subjects (119 patients and 160 healthy controls) recruited between February 2006 and June 2011. Characteristics of the sample are presented in Table 1. All subjects underwent an extensive assessment which included collecting information about their socio-demographic characteristics and lifetime substance use. Subjects were administered tests of premorbid and present intellectual level as soon as possible based on their compliance and within the first six months after their admission (instruments used are indicated below).

2.2. Patients

The 119 patients met ICD-10 criteria for psychosis (F10–19, F20–F29 and F30–F33) (WHO, 1992), 33 of them had a diagnosis of affective psychosis vs. 86 diagnosed as non-affective psychosis. Exclusion criteria were applied as follows: organic psychosis, acute intoxication (F1x.0), learning disabilities, history of traumatic brain injury and lack of English fluency.

Table 1
Socio-demographic characteristics.

	Cases	N	Controls	N	*t*-test or χ^2	df	p
Age in years, mean (s.d.)	29.6 (8.5)	119	29.6 (10.8)	160	0.03	277	.971
Males, n (%)	84 (70.6)	119	83 (51.9)	160	9.9	1	**.002**
Ethnicity, n (%)		111		159	16.8	2	<**.001**
White	33 (29.7)		95 (59.7)				
Black	55 (49.5)		47 (29.6)				
Other	23 (20.7)		17 (10.7)				
English mother tongue, n (%)	86 (72.3)	117	133 (83.1)	160	4.7	1	.052
Years of education, mean (s.d.)	13.2 (3.7)	108	15.1 (2.9)	147	4.1	200.1	<**.001**
Unemployed, n (%)	63 (59.4)	106	27 (22.0)	123	33.5	1	<**.001**

Abbreviation: df = degree of freedom.

2.3. Controls

Healthy controls (n = 160) were recruited from the same catchment area as the patients. Controls were recruited through local newspapers and internet advertising, job centres, hospitals and a pre-existing volunteer database. A control sample representative of the general population in age, gender, ethnicity and employment status was obtained (Di Forti et al., 2009). The Psychosis Screening Questionnaire (PSQ) (Bebbington and Nayani, 1995) was administered to exclude subjects who had any psychotic symptomatology.

2.4. Assessments

2.4.1. Demographic variables

A modified version of the Medical Research Council (MRC) Socio-demographic Schedule (Di Forti et al., 2009) was administered to all subjects. Ethnicity was self-ascribed during the interview and grouped into “white”, “black” and “other”.

2.4.2. Clinical assessment

Diagnoses for patients were established using the Operational Criteria Checklists (OPCRIT) (McGuffin et al., 1991), a 90-item checklist linked to a computerised diagnostic algorithm that includes a structured clinical interview with questions and optional probes derived from the World Health Organization Schedules for Clinical Assessment in Neuropsychiatry (SCAN, version 2.1) (WHO, 1999). It is capable of generating diagnoses under a number of classification systems such as DSM-IV and ICD-10. Diagnoses of non-affective psychosis included schizophrenia, delusional disorder, schizophreniform disorder, schizoaffective disorder depressed and schizoaffective disorder bipolar, whilst affective psychosis included manic episode with psychosis and major depressive episode with psychotic features. Levels of positive and negative symptoms were assessed by administering the Positive and Negative Syndrome Scale (PANSS), thus deriving scores for positive, negative and general symptoms (Kay et al., 1987).

2.4.3. IQ assessment

Current IQ was estimated based on five subtests (Information, Digit Span, Matrix, Block Design and Digit Symbol) of the Wechsler Adult Intelligence Scale — Third Edition (WAIS-III) (Wechsler, 1997). Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR), a reading test normed with the WAIS-III, which is able to provide a broad estimate of general ability before the illness (Holdnack, 2001). WTAR has been shown to be stable in patients with traumatic brain injury (Green et al., 2008; Hanks et al., 2008) or exerting suboptimal effort (Whitney et al., 2010). Reading abilities are also widely used in order to infer premorbid IQ in psychosis, as related to measures of full scale IQ, verbal IQ, verbal comprehension (Hanks et al., 2008) and verbal memory (Whitney et al., 2010), the latter being more impaired than general IQ at first episode of psychosis (Mesholam-Gately et al., 2009). This discrepancy between verbal and non-verbal scores in psychotic patients (Wilk et al., 2005) has been shown in people with a genetic liability to develop schizophrenia (Kravariti et al., 2006).

2.4.4. Drug use assessment

By using the Cannabis Experience Questionnaire (modified version) (Di Forti et al., 2009), all subjects were assessed for lifetime cannabis use (used at least once), age at first use in years (then dichotomized according to mean age at first use), type of cannabis used most often (hash/imported herbal cannabis or – alternatively – skunk, high potency cannabis), frequency of use (everyday/less frequently), current use (customarily smoking cannabis/no), mode of use (social/isolated), self-estimated number of times that they used cannabis over the

Table 2
Pattern of cannabis use.

	Cases	N	Controls	N	*t*-test or χ^2	df	p
Ever used cannabis lifetime, n (%)	86 (72.3)	119	98 (62.0)	158	3.1	1	.074
Age in years of first use of cannabis[a], mean (s.d.)	16.4 (4.6)	82	16.1 (3.0)	98	0.70	135.5	.498
Current cannabis users[a], n (%)	34 (39.1)	87	36 (36.4)	99	0.1	1	.703
Frequency of use (everyday/less frequently)[a], n (%)	38 (48.7)	78	15 (17.0)	88	19.08	1	<**.001**
Type of cannabis used[a], n (%)		66		86	− 4.59	1	**.045**
Hash and imported herbal cannabis	23 (34.8)		44 (52.4)				
Sinsemilla (skunk)	43 (65.2)		42 (28.8)				
Mode of cannabis use[a], n (%)		77		92	1.65	2	.437
Socially	49 (63.6)		67 (72.8)				
Isolated	13 (16.9)		12 (13.0)				
Both	15 (19.5)		13 (14.1)				
Number of times of cannabis use lifetime[a], n (%)		60		88	1.29	3	.730
Once or twice only–fewer than 10 times	12 (20.0)		14 (15.9)				
Between 10 and 50	3 (5.0)		7 (7.9)				
Between 50 and 200	9 (15.0)		10 (11.4)				
Over 200 times	36 (60.0)		57 (64.8)				
Ever used other illicit drugs lifetime, n (%)	51 (45.1)	113	53 (34.6)	153	3.0	1	.083
Drugs use (general), n (%)		119		158	4.66	2	.187
No drugs	33 (27.7)		60 (38.0)				
Only cannabis	37 (31.1)		45 (38.5)				
Cannabis and other drugs	49 (41.2)		53 (33.5)				

Abbreviation: df = degree of freedom.
[a] In those who had ever used cannabis.

lifetime (operationalized as described in Table 2) and lifetime use of other drugs (yes/no).

2.5. Statistical analysis

Chi-square (χ^2) tests and *t*-tests were used where appropriate to compare socio-demographic characteristics between cases and controls. Equality of variance was tested using Levene's test. A significance level of 5% (two-tailed) was initially specified; this was adjusted using a Bonferroni correction in the analysis of covariance (ANCOVA).

Estimated current IQ (WAIS) and premorbid IQ (WTAR) scores were compared between the groups, first using a *t*-test and then using ANCOVA to adjust for confounders in order to check if cases were lower in IQ and premorbid IQ than controls. Potential confounders were selected a priori based on the literature. In order to avoid overfitting the model, significance tests (Pearson correlations, *t*-tests and chi-squared tests) were used to select which of these to include in the ANCOVA. These included: gender, mother tongue, ethnicity and years of education (years attended school). Next, we stratified by group and used an independent two-tailed *t*-test to compare mean IQ and premorbid IQ between people with any lifetime cannabis use and those without, and also between different patterns of cannabis use (Table 2). This analysis was carried out in order to test the specific hypothesis that patients with *lifetime* cannabis use were better in their premorbid IQ. A 2 × 2 factorial ANCOVA was run (groups [cases, controls] × cannabis [cannabis yes, cannabis no]) controlling for covariates as specified previously; the inclusion of a cannabis by group interaction term formally tested whether the relationship between cannabis and IQ and premorbid IQ differed in cases and controls.

Finally, a score measuring the difference between current IQ and premorbid IQ (current IQ minus premorbid IQ) was calculated for the patient group only. We then carried out an ANCOVA using this score as the dependent variable and lifetime cannabis use [yes, no] as fixed factor, whilst additionally controlling for years of education and mother tongue (dichotomized as English vs. Not English first language), which a preparatory analysis showed to be related to differences between IQ and premorbid IQ. This analysis tested the hypothesis of a smaller difference between IQ and premorbid IQ in patients with cannabis use, compared with patients without any use of cannabis. Statistical analyses were carried out using SPSS 15.0 for Windows (SPSS Inc., 1994).

3. Results

3.1. Socio-demographic characteristics

Table 1 shows socio-demographic characteristics of patients and controls. There were no differences in mean age at assessment between cases and controls. Statistically significant differences emerged between patients and controls in gender (higher percentage of males in cases than in controls), ethnicity (higher percentage of black and other ethnic minority groups among cases) and years of education (fewer years of education among cases). The case group also contained a greater percentage of unemployed people at the time of assessment. All of these differences were expected (see also Di Forti et al., 2009) and, therefore, used as covariates.

3.2. Pattern of cannabis use

Table 2 reports patterns of cannabis use by group. All patients who reported use of cannabis in their lifetime started using cannabis prior to the onset of psychosis. There were no significant differences in ever having used cannabis or other illicit drugs between cases and controls. Among those who had used cannabis, there were no significant differences between cases and controls in age of first use, current cannabis use, context of use (isolated or social), or the number of times that they had used cannabis.

Statistically significant differences between cases and controls were, however, found in the type and the frequency of cannabis used. Cases were more likely than controls to have preferentially smoked "skunk" which has a relatively high concentration of Δ9-THC (12–18%) (Potter et al., 2008), and were more likely to have used cannabis everyday than controls. There were no significant differences between cases who used cannabis and those who did not in gender, age, ethnicity, years of education, mother tongue nor in any of the PANSS subscales: negative ($t(111) = -1.187$, $p = .238$), positive ($t(111) = .677$, $p = .500$) and general psychopathology ($t(111) = -.386$, $p = .700$) scores (data not shown in tables).

3.3. Current IQ and premorbid IQ in cases and controls

Differences between cases and controls emerged in terms of current IQ ($t(247) = 8.99$, $p < .001$) and premorbid IQ ($t(181) = 10.81$,

Table 3
Comparing IQ and premorbid IQ across different patterns of cannabis use.

	Cases			Controls		
	Mean (s.d.)	Mean (s.d.)	p	Mean (s.d.)	Mean (s.d.)	p
Cannabis use lifetime (yes/no)						
IQ	93.3 (11.0)	85.5 (10.1)	**<.001**	106.3 (15.1)	106.9 (17.9)	.838
Premorbid-IQ	91.2 (16.5)	79.1 (11.5)	**.004**	102.5 (10.2)	101.0 (10.9)	.518
Current use[a] (yes/no)						
IQ	91.6 (12.8)	90.6 (18.5)	.796	103.6 (17.5)	107.5 (13.4)	.223
Premorbid-IQ	91.6 (11.1)	94.7 (10.7)	.285	101.6 (10.7)	102.7 (10.1)	.659
Type of cannabis[a] (skunk/hash)						
IQ	88.8 (13.3)	93.0 (16.8)	.310	107.8 (16.0)	103.2 (13.9)	.118
Premorbid-IQ	93.2 (9.9)	92.8 (12.8)	.922	105.0 (9.2)	99.0 (11.9)	.069
Age first use in years[a] (>16/≤16)						
IQ	87.1 (15.3)	93.0 (17.3)	.154	112.3 (16.1)	103.8 (14.0)	**.016**
Premorbid-IQ	89.8 (10.2)	95.4 (11.4)	.075	104.7 (10.3)	101.3 (10.1)	.216
Mode of use[a] (alone/social)						
IQ	89.0 (9.5)	90.7 (17.2)	.745	105.0 (21.9)	107.0 (14.0)	.696
Premorbid-IQ	89.5 (10.0)	94.8 (11.3)	.172	101.3 (11.8)	102.4 (9.5)	.759
Frequency[a] (everyday/less freq)						
IQ	88.5 (14.3)	94.9 (16.1)	.086	109.1 (16.1)	105.1 (15.0)	.378
Premorbid-IQ	92.2 (11.9)	94.6 (10.5)	.582	101.5 (12.4)	102.3 (9.4)	.805
N. of times[a] (over/under 200 times)						
IQ	88.2 (14.6)	86.5 (16.7)	.691	106.8 (16.6)	103.3 (15.5)	.358
Premorbid-IQ	89.9 (10.6)	90.2 (12.2)	.925	103.5 (10.3)	101.0 (10.7)	.427

[a] In those who had ever used cannabis.

$p < .001$). Cases had a mean current IQ of 87.9 (16.2) and controls of 106.6 (16.2); cases had a mean premorbid IQ of 91.2 (11.3) compared with 102.0 (10.5) in controls. ANCOVAs were subsequently carried out adjusting for gender, years of education, mother tongue and ethnicity. Age was not included since WAIS scores and WTAR already take this into account. After adjusting for the above covariates, patients still performed significantly worse than controls in IQ ($F(1,233) = 53.1$, adjusted $p < .001$, $\eta^2 = 0.186$) and premorbid IQ ($F(1,169) = 27.0$, adjusted $p < .001$, $\eta^2 = 0.138$).

3.4. Association of IQ and premorbid IQ with cannabis use when stratifying by case/control groups

In cases, IQ ($t(104) = 3.6$, $p < .001$) and premorbid IQ ($t(81) = 2.9$, $p = .004$) were significantly higher among patients who had used cannabis compared with those who had never used it (Table 3). In contrast, in the controls there were no statistically significant differences either in IQ ($t(141) = -0.2$, $p = .757$) or in premorbid IQ ($t(98) = 0.6$, $p = .156$) scores between those who did or did not use cannabis. ANCOVAs adjusting for gender, education, mother tongue and ethnicity, still gave similar results in the case group for both IQ ($F(1,86) = 21.6$, adjusted $p < .001$, $\eta^2 = 0.201$) and premorbid IQ ($F(1,66) = 10.6$, adjusted $p = .002$, $\eta^2 = 0.139$) (not shown in table). We did not find any such significant differences when analysing the control group (all $p > .05$).

3.5. Patterns of cannabis use and IQ

T-tests in the group of lifetime cannabis users were only performed to establish whether current cannabis use, type of cannabis used, frequency of use, mode of use, number of times used or age at first use were associated with IQ or premorbid IQ. None of these variables were found to have a significant association with either IQ or premorbid IQ among cases or controls (all $p > .05$). We only found that controls who had smoked cannabis after age 16, had higher IQ than controls that had smoked cannabis earlier in life ($p = .016$) (see also Meier et al., 2012) (Table 3).

3.6. IQ and premorbid IQ scores association with cannabis use: Case–control comparisons

3.6.1. IQ

Factorial ANCOVA confirmed a significant main effect of the group (case/control) on IQ scores ($F(1,222) = 53.3$, $p < .001$, $\eta^2 = 0.205$). There was also a significant main effect of cannabis use ($F(1,222) = 8.1$, $p = .005$, $\eta^2 = 0.036$). The interaction effect between cannabis use and the group was significant ($F(1,222) = 13.7$, $p < .001$, $\eta^2 = 0.058$), indicating that the IQ of cases and controls was related differently to cannabis use. Specifically, the IQ of patients was significantly related to cannabis use ($F(1,86) = 21.6$, $p < .001$, $\eta^2 = 0.201$), whilst the IQ of the controls was not ($F(1,132) = 0.7$, $p = .399$).

3.6.2. Premorbid IQ

A factorial ANCOVA showed a significant main effect of the group (case/control) on premorbid IQ scores ($F(1,161) = 34.3$, $p < .001$, $\eta^2 = 0.176$), a main effect of cannabis ($F(1,161) = 6.2$, $p = .013$, $\eta^2 = 0.038$), and a significant interaction between cannabis and the group ($F(1,161) = 3.9$, $p = .048$, $\eta^2 = 0.024$) indicating that premorbid IQ of cases and controls was related differently to cannabis use. Whilst premorbid IQ of patients was significantly related to cannabis use ($F(1,66) = 10.6$, $p = .002$, $\eta^2 = 0.139$), premorbid IQ of the controls was not ($F(1,91) = 0.1$, $p = .730$).

3.7. Difference between IQ and premorbid IQ

A difference score was calculated (IQ minus premorbid IQ) for each of the patients. Those in the non-cannabis group were found to have a difference between premorbid IQ and IQ of 6.1 points greater (95% CI: 0.3, 11.7; $p = .037$) than that of patients who had used cannabis ($F(1,75) = 6.6$, adjusted $p = .012$, $\eta^2 = 0.081$).

Diagnosis had no effect in any of our analyses on cannabis use and IQ, or premorbid IQ score.

4. Discussion

The aim of this study was to test the hypothesis that among psychotic patients, those who had smoked cannabis would have a higher

premorbid IQ than those who had not. Our main finding was in line with this hypothesis and showed that patients who had used cannabis in their lifetime had higher scores in both IQ and premorbid IQ compared to those patients who had never used cannabis.

4.1. Why is lifetime cannabis use associated with better premorbid IQ?

In our sample of cases any lifetime use of cannabis was associated with a better premorbid cognitive performance, in line with reports by Yücel et al. (2010), Meijer et al. (2012), Rabin et al. (2013) and Schnell et al. (2012). Cognition has been established as a predictor of real-world community functioning in schizophrenia (Green et al., 2000; Evans et al., 2003) and 69% of our sample of psychotic cannabis users reported a social use of cannabis, a similar proportion as in controls. Thus, our findings are compatible with the view that, among psychotic patients, the better premorbid cognition of the group who had smoked cannabis is likely to have facilitated their use of the drug in a normal recreational way, sharing it with their friends. The findings are also compatible with the view that patients that used cannabis were less neurodevelopmentally impaired than those who did not. Other studies compatible with this latter view have reported that patients at their first episode who have used cannabis have fewer neurological soft signs (Ruiz-Veguilla et al., 2012) and less abnormal MRI scans (Cunha et al., 2013) than those who have not.

4.2. Are IQ and premorbid IQ of patients and controls different in relation to cannabis use?

Looking at differences between cases and controls, we found, as expected, significantly lower current and premorbid IQ in patients on the overall. We also expected that cannabis use would be associated differently with IQ and premorbid IQ in patients and controls. Among cases, cannabis use was associated with a higher IQ and premorbid IQ, whilst among the controls, there was no significant difference. Previous studies compared cases and controls who used cannabis at age 16 or before and their performance in single tests: Jockers-Scherübl et al. (2007) found an interaction effect of group and cannabis on the "digit symbol" subtest from WAIS-R. Yücel et al. (2010) reported that "visual memory", "working memory", and "executive functioning" were better in patients who used cannabis, but no interaction analysis was made with a corresponding control group. Meijer et al. (2012) found that lifetime cannabis use was associated with better performance on acquired knowledge, facial affect recognition and face identity recognition, but they did not find any interaction effect with group status (patients, siblings and controls). To our knowledge, this is the first study that has investigated and found a relationship between IQ, premorbid IQ and cannabis use in cases but not in a comparison group of controls.

4.3. Difference between IQ and premorbid IQ in relation to cannabis use

As expected, the current IQ of patients was lower than their premorbid IQ on average (see also Dazzan et al., 2008). We calculated a difference score (IQ minus premorbid IQ) in order to see whether the estimated deterioration was associated with cannabis use (see also Leeson et al., 2011), and found this to be the case. This raises the possibility of a neuroprotective action of cannabis. However, those who used cannabis daily were neither less, nor more impaired than less frequent users; this was also the case when we compared patients that had started smoking cannabis at 16 or earlier (our mean age for cannabis use onset — the lowest age of first use in our sample was 5 years), and also when we compared patients that had smoked cannabis more or less than 200 times in their life, or patients that were currently smoking cannabis or not. Thus, we cannot make a definite statement on the question of any protective effect of cannabis use.

4.4. Limitations and strengths

We examined patients at their first episode of psychosis, which minimizes the influence from variables inherent to those with chronic illness and/or the effects of continuous pharmacological treatment on cognition. However, patients were not medication *naïve* and, as is well known, medication could have affected current neuropsychological performance (i.e. IQ) even in the short period between initial contact with the services and our cognitive testing. On the other hand, as already mentioned, WTAR – our main measure of interest – is also robust in patients exerting suboptimal effort due to medication effects.

The inclusion of a control group was another strength of our study, but, as some demographic differences show, our strategy of recruiting controls representative of the local population could have biased our findings. However, we corrected our analysis for these characteristics and differences in neuropsychological performances stayed significant. Otherwise, as already discussed in Di Forti et al. (2009), it seems unlikely that the difference in frequency and type of cannabis used between cases and control group was driven by a recruitment bias.

Cannabis use was self-reported but we measured the reliability of the self-reported data on current users in a random sample of 56 cases from the GAP sample, by carrying out a urinary drug screening (UDS). Of the 56 cases tested, 34 had reported they were not current users; 32 of these (88%) had a negative UDS, only 2 tested positive. Thus, the accuracy of self-report data on current use in our sample is high. For obvious reasons, a history of lifetime use of cannabis cannot be assessed by a biological test.

Finally, we are aware that reading-based tests have some limitations as a measure of premorbid IQ (Russell et al., 2000; O'Connor et al., 2012). However, WTAR is thought to be a more reliable measure of pre-morbid IQ (Green et al., 2008) compared to other tests like the NART (*National Adult Reading Test*) (Nelson and Willison, 1991) and is able to indicate a "hold" intellectual capacity (Cattel, 1971).

5. Conclusions

Our findings are in line with the hypothesis that among psychotic patients, cannabis users had a higher premorbid IQ than non-users (an association not witnessed among controls). Our cannabis-using patients also had a smaller difference between current IQ and premorbid IQ than non-using patients.

Kremen et al. (2008) point out that premorbid estimates should be understood as a measure of "potential" had a given subject not been destined to develop schizophrenia. Thus, individuals with a high premorbid IQ could be seen as less predisposed. Taking these findings together with the substantial evidence that cannabis use is a risk factor for psychosis, we suggest that cannabis may play a role in provoking psychosis in people who were less neurodevelopmentally impaired than is generally the case in psychosis.

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Contributors

Ferraro Laura: conception and design, analysis and interpretation of the data and draft of the article.

Robin M. Murray, Marta Di Forti, and Abraham Reichenberg: conception and design, revised the paper critically for important intellectual content and finally approved the version to be published.

Hannah Sallis helped with the analysis and interpretation of the data.

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Conflict of interests

They all have none to declare.

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