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The association between cannabis use and facial emotion recognition in schizophrenia, siblings, and healthy controls: Results from the EUGEI study

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Abstract
Schizophrenia is frequently accompanied with social cognitive disturbances. Cannabis represents one established environmental factor associated with the onset and progression of schizophrenia. The present cross-sectional study aimed to investigate the association of facial emotion recognition (FER) performance with cannabis use in 2039 patients with schizophrenia, 2141 siblings, and 2049 healthy controls (HC). FER performance was measured using the Degraded Facial Affect Recognition Task (DFAR). Better FER performance as indicated by higher DFAR-total scores was associated with lifetime regular cannabis use in schizophrenia ($B = 1.36$, 95% CI 0.02 to 2.69), siblings ($B = 2.17$, 95% CI 0.79 to 3.56), and HC ($B = 3.10$, 95% CI 1.14 to 5.06). No associations were found between DFAR-total and current cannabis use. Patients with schizophrenia who started to use cannabis after the age of 16 showed better FER performance than patients who started earlier ($B = 2.50$, 95% CI 0.15 to 4.84) and non-users ($B = 3.72$, 95 CI 1.96 to 5.49). Better FER performance was found also in siblings who started to use cannabis after 16 compared to non-users ($B = 2.37$, 95% CI 0.58 to 4.16), while HC using cannabis performed better than non-users at DFAR-total regardless of the age at onset. Our findings suggest that lifetime regular cannabis use may be associated with better FER regardless of the psychosis risk, but that FER might be moderated by age at first use in people with higher genetic risk. Longitudinal studies may clarify whether there is a cause-and-effect relationship between cannabis use and FER performance in psychotic and non-psychotic samples.

1. Introduction

Even though cognitive deficits are not included among the core features of schizophrenia, it has been estimated that approximately 80% of psychotic patients exhibit clinically significant impairments in this area (McCleery and Nuechterlein, 2019). Both neurocognition (e.g., attention, reasoning, speed of processing, memory) and social cognition (e.g., theory of mind, emotion processing) can be affected (Green et al., 2019), with significant negative impact on real-life functioning (Fett et al., 2011; Galderisi et al., 2020; Mucci et al., 2021). Among the domains of social cognition, facial emotion recognition (FER) has been extensively studied over the last years (Green et al., 2019). FER is defined as the ability to effectively identify emotions in others' facial expressions (Green et al., 2019) and represents a key skill for social interactions and functioning (Halverson et al., 2019). Evidence has shown that FER performance is impaired not only in patients with schizophrenia (Maat et al., 2015) but also in their first-degree relatives (Fusar-Poli et al., 2022; Martin et al., 2020).

A multitude of genetic (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2022) and environmental factors (Stilo and Murray, 2019), as well as their interaction (Guloksuz et al., 2019; Pries et al., 2020, 2019; van Os et al., 2020), are implicated in the etiopathology of schizophrenia. Among environmental factors, cannabis use has been associated with the onset, progression, and outcome of psychotic disorders (Belbasis et al., 2018; Hasan et al., 2020; van Os et al., 2021). The risk of psychosis is doubled in people with a history of lifetime cannabis use and quadrupled in the heaviest cannabis users compared with non-users (Marconi et al., 2016). Moreover, the onset of psychotic disorders is on average two to three years earlier in cannabis users (Large et al., 2011; Myles et al., 2012). Finally, cannabis use has been associated with increased relapse rates, more hospitalizations, and more pronounced positive symptoms in patients with psychosis (Hasan et al., 2020).

Although the link between cannabis use and schizophrenia has been shown consistently, the association between social cognition and cannabis use appears more complex. In healthy individuals, emotion recognition has been reported to be slower (Platt et al., 2010) and less accurate (Hindocha et al., 2014) in frequent cannabis users compared to non-users. In psychosis, findings are contrasting. Sánchez-Torres et al. (2013) reported a negative association between cannabis use and social cognition in patients with schizophrenia spectrum disorders. Conversely, other authors reported higher social cognitive skills in cannabis users than in non-users, both in chronic schizophrenia (Martin et al., 2016) and first-episode psychosis (Arnold et al., 2015). Moreover, fMRI findings showed that a higher number of neural regions associated with social cognition are activated in psychotic patients with comorbid substance use disorder (alcohol and/or cannabis) compared to patients without substance use (Potvin et al., 2007). Focusing on FER, one study demonstrated that lifetime cannabis use was associated with better performance in FER in patients with schizophrenia, siblings, and healthy controls (Meijer et al., 2012). To our knowledge, no other studies have been specifically conducted on the associ-

ation between FER and cannabis use in patients with psychosis.

The present study aimed to investigate the association of FER performance with cannabis use patterns in patients with schizophrenia, their unaffected siblings, and healthy controls.

2. Experimental procedures

The reporting of this study conforms to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (von Elm et al., 2008).

2.1. Study participants

Data were derived from the Workpackage 6 (WP6) of the European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EUGEI) (van Os et al., 2014) and the Genetic Risk and Outcome for Psychosis (GROUP) studies, collected using uniform assessment schedules between 2010 and 2015 in the Netherlands, Turkey, Spain, and Serbia (Korver et al., 2012). EUGEI WP6 ("vulnerability and severity") was a cross-sectional study specifically conducted to investigate gene-environment interactions underlying the vulnerability and severity of schizophrenia spectrum disorder and its intermediate phenotypes in a family-based setting (i.e., cases and their siblings). GROUP was a naturalistic longitudinal cohort study that started in 2004 in the Netherlands and Dutch-speaking part of Belgium and collected data of cases, their siblings and controls at baseline, 3, and 6 years follow-ups over an approximate 10-year period.

Both projects were approved by the Medical Ethics Committees of all participating sites and conducted in accordance with the Declaration of Helsinki. All respondents provided written informed consent and, in the case of minors, such a consent was also obtained from parents or legal guardians.

In the EUGEI WP6 sample, patients were diagnosed with schizophrenia spectrum disorders according to the DSM-IV-TR (average duration of illness since age of first contact with mental health services = 9.9 years) (Guloksuz et al., 2019). In the GROUP sample, over 65% of patients were diagnosed with schizophrenia and 11% with schizoaffective disorder (Korver et al., 2012). Diagnoses were confirmed by the Operational Criteria Checklist for Psychotic and Affective Illness (McGuffin et al., 1991) in EUGEI WP6, and by the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990) or the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992) in GROUP. Unrelated controls with no lifetime psychotic disorder were recruited from the same population as the cases. Exclusion criteria for all participants were a diagnosis of psychotic disorder due to another medical condition, a history of head injury with loss of consciousness, and an intelligence quotient (IQ) <70.

The current analyses used a merged dataset of GROUP baseline data and EUGEI WP6 cross-sectional data including 2039 patients with schizophrenia, 2141 siblings, and 2049 unrelated healthy controls.

2.2. Assessment of facial emotion recognition (FER)

The Degraded Facial Affect Recognition Task (DFAR) was used as a measure of FER (i.e., the main outcome). This performance-based social cognition task measures emotional face recognition in degraded photographs. Subjects were presented with photographs of four individuals (two males and two females), depicting emotional facial expression. Subjects were asked to indicate the expression of each face and to respond as accurately as possible. The photographs of the faces were passed through a filter resulting in a reduced visual contrast by 30%. This method was adopted to increase difficulty and enhance the contribution of perceptual expectancies and interpretation. Subjects were presented with 64 trials (16 for each condition: angry, happy, fearful and neutral) (van 't Wout et al., 2004). The percentage of total correct answers (DFAR-total) was the primary outcome of interest. Exploratory analyses were conducted on the percentages of correct answers per emotion domain (i.e., DFAR-neutral, happy, fearful, and angry). Higher scores on the DFAR indicate a better ability to recognize facial expressions of a particular emotion. As DFAR was considered the main outcome, subjects with missing data on DFAR-total scores and susbscales were excluded from the analyses.

2.3. Assessment of cannabis use

Cannabis use was assessed using three main instruments: the Cannabis Experiences Questionnaire (CEQ), modified version (Barkus et al., 2006) in EUGEI-WP6; the Composite International Diagnostic Interview (CIDI), L section (Robins et al., 1988), and urinalysis in GROUP. Three variables were considered: 1) lifetime regular cannabis use; 2) current cannabis use; 3) age at first cannabis use.

To evaluate lifetime cannabis use, following previous work (Erzin et al., 2021; Guloksuz et al., 2019; Pries et al., 2018, 2019; Radhakrishnan et al., 2019; van Winkel, 2011), a binary regular cannabis use variable was constructed by using the cut-off value of one or more per week during the lifetime period of most frequent use, according to CEQ or CIDI self-report.

In EUGEI-WP6, current cannabis use was assessed using the CEQ item 15.4 ("Do you currently use cannabis?"). In GROUP, participants were considered current users if THC was detected in urinalysis. Urine was screened for the presence of THC with a cut off of 50 ng/ml, in order to infer a detection window of 1 month.

Age at onset of cannabis use was evaluated using the CEQ (EUGEI-WP6) or CIDI (GROUP). Conforming to previous research (Dahlgren et al., 2016; Gruber et al., 2012; Sagar et al., 2015), the sample was divided into three categories: non-users; early onset users (<16 years old); late onset users ($\geq$ 16 years old).

2.4. Statistical analyses

Stata software version 16.0 was used for the analysis (StataCorp, 2019). Analyses were stratified by the sub-

Table 1 Characteristics of participants.

	Patients ($n = 2039$)	Siblings ($n = 2141$)	Healthy controls ($n = 2049$)	Total ($N = 6229$)
Age, *M* (SD)	30.56 (8.77)	31.12 (9.45)	32.96 (10.58)	31.54 (9.68)
Sex, male n (%)	1454 (71.31)	965 (45.07)	1016 (49.59)	3435 (55.15)
Country, n (%)				
Turkey	587 (28.79)	619 (28.91)	1029 (50.22)	2235 (35.88)
Spain	410 (20.11)	494 (23.07)	428 (20.89)	1332 (21.38)
Serbia	52 (2.55)	54 (2.52)	46 (2.24)	152 (2.44)
Netherlands	990 (48.55)	974 (45.49)	546 (26.65)	2510 (40.30)
Education, n (%)				
No qualifications	175 (8.85)	103 (4.92)	42 (2.09)	320 (5.26)
With qualifications	523 (26.45)	379 (18.11)	383 (19.05)	1285 (21.13)
Tertiary	513 (25.95)	400 (19.11)	431 (21.44)	1344 (22.11)
Vocational	549 (27.77)	688 (32.87)	638 (31.74)	1875 (30.84)
University	217 (10.98)	523 (24.99)	516 (25.67)	1256 (20.66)
DFAR-total, *M* (SD)	66.42 (13.71)	72.43 (11.82)	73.91 (15.86)	70.95 (14.23)
DFAR-neutral, *M* (SD)	71.82 (23.13)	77.84 (18.51)	79.40 (20.67)	76.38 (21.07)
DFAR-happy, *M* (SD)	85.18 (16.47)	88.36 (13.50)	87.33 (17.56)	86.98 (15.95)
DFAR-angry, *M* (SD)	62.05 (22.24)	69.41 (20.65)	70.29 (23.50)	67.29 (22.44)
DFAR-fearful, *M* (SD)	46.84 (21.46)	54.37 (20.53)	58.88 (21.87)	53.39 (21.84)
Patterns of cannabis use, n (%)				
Lifetime regular use	739 (38.37)	312 (15.18)	193 (9.67)	1244 (20.81)
Current use	197 (10.54)	135 (6.79)	114 (5.72)	446 (7.63)
Age at first use $<$16 years old	206 (13.42)	128 (7.02)	123 (6.46)	457 (8.68)
Age at first use $\geq$16 years old	363 (23.65)	333 (18.26)	252 (13.23)	948 (18.01)

groups: patients, unaffected siblings, and healthy controls. Linear regression models were fitted with DFAR-total (primary outcome) and domain scores (secondary exploratory analyses) as the dependent variables and cannabis use patterns as the independent variables. All analyses were a priori adjusted for age, sex, country (Turkey, Spain, the Netherlands, and Serbia), and took into account of clustering of observations within families using the Stata "cluster" option. We reported unstandardized regression coefficients (*B*). The analyses were also conducted on multiple imputed data (See **Supplementary Table S1** for the missing data frequencies). Following the previous analyses in this dataset (Guloksuz et al., 2019; Pries et al., 2020), the multiple imputation chained equation (Royston and White, 2011) was applied with 20 imputations restricted to in-range values (relative efficiency $\geq$ 99%) and analyses were run on multiple imputed data and pooled using Rubin's rules (Rubin, 2004).

3. Results

3.1. Descriptive statistics

General characteristics of the sample, DFAR scores, and patterns of cannabis use are reported in Table 1.

3.2. Association between DFAR and lifetime regular cannabis use

Adjusted linear regressions evaluating the association between DFAR scores and lifetime regular cannabis use are presented in Table 2. DFAR-total scores were positively associated with lifetime regular cannabis use in patients with schizophrenia ($B = 1.36$, 95% CI 0.02 to 2.69, $p = 0.046$), siblings ($B = 2.17$, 95% CI 0.79 to 3.56, $p = 0.002$), and healthy controls ($B = 3.10$, 95% CI 1.14 to 5.06, $p = 0.002$).

In secondary exploratory analyses, a positive association was found between lifetime cannabis use and DFAR-neutral in siblings ($B = 3.56$, 95% CI 1.55 to 5.57, $p = 0.001$) and healthy controls ($B = 3.93$, 95% CI 1.37 to 6.49, $p = 0.003$). DFAR-happy was also associated with lifetime cannabis use in patients ($B = 1.71$, 95% CI 0.06 to 3.37, $p = 0.04$) and healthy controls ($B = 2.83$, 95% CI 0.41 to 5.25, $p = 0.02$). Results from the imputed data are reported in **Table S2**.

3.3. Association between DFAR and current cannabis use

As reported in Table 3, no significant associations between DFAR-total scores and current cannabis use were found. Secondary analyses showed that current cannabis use was positively associated with DFAR-happy in patients with schizophrenia ($B = 2.25$, 95% CI 0.33 to 4.16, $p = 0.02$) but not in the other groups. A sensitivity analysis conducted in 894 patients, 891 siblings, and 520 healthy controls, for which results from urinalysis were available, confirmed the lack of significant associations between DFAR-total scores and current cannabis use. In this subgroup, secondary exploratory analyses showed significantly lower DFAR-fearful scores in patients with schizophrenia who were currently using cannabis compared with non-users ($B = -4.32$, 95% CI -7.66 to -0.98, $p = 0.01$) and significantly higher DFAR-happy scores in siblings who were currently using cannabis compared with non-users ($B = 2.85$, 95% CI 0.53 to 5.18,

Table 2 Association between the DFAR scores and lifetime regular cannabis use.

	Patients			Siblings			Healthy controls		
	B	**95% CI**	**P**	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**
DFAR-total (primary outcome)	1.36	0.02, 2.69	0.046*	2.17	0.79, 3.56	0.002*	3.10	1.14, 5.06	0.002*
Subscales (secondary exploratory analyses)									
DFAR-neutral	0.91	−1.20, 3.02	0.40	3.56	1.55, 5.57	0.001*	3.93	1.37, 6.49	0.003*
DFAR-happy	1.71	0.06, 3.37	0.04*	1.15	−0.40, 2.71	0.15	2.83	0.41, 5.25	0.02*
DFAR-fearful	2.00	−0.15, 4.15	0.07	1.36	−1.22, 3.94	0.30	2.17	−0.89, 5.24	0.16
DFAR-angry	0.83	−1.45, 3.11	0.48	2.61	−0.06, 5.28	0.05	3.30	−0.07, 6.67	0.05

Legend: CI = Confidence Interval; DFAR = Degraded Facial Affect Recognition task; * $P < 0.05$. All models were adjusted for age, sex, country (Turkey, Spain, the Netherlands, and Serbia), and took into account of clustering of observations within families.

Table 3 Association between DFAR scores and current cannabis use.

	Patients			Siblings			Healthy controls		
	B	**95% CI**	**P**	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**
DFAR-total (primary outcome)	−0.06	−1.66, 1.55	0.95	0.53	−1.76, 2.83	0.65	2.08	−0.64, 4.80	0.13
Subscales (secondary exploratory analyses)									
DFAR-neutral	−0.92	−3.92, 2.08	0.55	0.22	−2.88, 3.32	0.89	2.92	−0.51, 6.36	0.09
DFAR-happy	2.25	0.33, 4.16	0.02*	0.70	−2.19, 3.60	0.63	0.51	−2.92, 3.95	0.77
DFAR-fearful	−2.57	−5.51, 0.37	0.09	1.10	−2.68, 4.87	0.57	0.44	−3.33, 4.21	0.82
DFAR-angry	1.01	−1.96, 3.98	0.51	0.11	−3.98, 4.21	0.96	4.16	−0.10, 8.43	0.06

Legend: CI = Confidence Interval; DFAR = Degraded Facial Affect Recognition task; * $P < 0.05$. All models were adjusted for age, sex, country (Turkey, Spain, the Netherlands, and Serbia), and took into account of clustering of observations within families.

$p = 0.02$). Results from the sensitivity analysis are reported in **Table S3**. Results from the imputed analyses are reported in **Table S4**.

3.4. Association between DFAR and age at first cannabis use

Linear regression models revealed significantly higher DFAR-total scores in patients ($B = 3.72$, 95% CI 1.96 to 5.49, $p < 0.001$), siblings ($B = 2.37$, 95% CI 0.58 to 4.16, $p = 0.01$) and healthy controls ($B = 4.25$, 95% CI 1.96 to 6.53, $p < 0.001$) who started using cannabis after the age of 16 years old compared to the reference group: non-users (Table 4). Moreover, patients with schizophrenia who started using cannabis after 16 years of age had significantly higher total scores than those who started earlier ($B = 2.50$, 95% CI 0.15 to 4.84, $p = 0.04$). DFAR-total were higher in healthy controls who started using cannabis before 16 years old ($B = 3.92$, 95% CI 0.95 to 6.89, $p = 0.01$) compared to non-users.

Secondary exploratory analyses for DFAR subscales showed similar patterns of association as for DFAR-total, with for DFAR-neutral significantly higher scores in patients ($B = 5.20$, 95% CI 2.39 to 8.01, $p < 0.001$), siblings ($B = 4.10$, 95% CI 1.68 to 6.51, $p < 0.001$), and healthy controls ($B = 5.39$, 95% CI 2.42 to 8.37, $p < 0.001$) who started using cannabis after the age of 16 compared to non-users. Additionally, patients with schizophrenia who started using cannabis after the age of 16 had significantly higher scores than those who started earlier ($B = 5.18$, 95% CI 1.44 to 8.92, $p = 0.007$). In healthy controls, a better performance in DFAR-neutral was found also in cannabis users who started before the age of 16 compared to non-users ($B = 6.09$, 95% CI 2.21 to 9.97, $p = 0.002$). Patients with schizophrenia who started using cannabis at or after 16 years had a better DFAR-happy performance than non-users ($B = 2.96$, 95% CI 0.81 to 5.10, $p = 0.007$). A similar positive association was found for healthy controls who started using cannabis after 16 years of age compared with non-users ($B = 2.78$, 95% CI 0.06 to 5.49, $p = 0.04$). Scores in both DFAR-fearful ($B = 3.02$, 95% CI 0.15 to 5.89, $p = 0.04$) and DFAR-angry ($B = 3.65$, 95% CI 0.78 to 6.52, $p = 0.01$) were significantly higher in patients with schizophrenia who started using cannabis after the age of 16 compared to non-users. In siblings, no significant associations with the age at onset of cannabis use were found. In healthy controls, DFAR-angry scores were greater in cannabis users who started at or after 16 years than non-users ($B = 6.27$, 95% CI 2.63 to 9.92, $p < 0.001$). Results from the imputed analyses are reported in **Table S5**.

4. Discussion

The present study aimed to evaluate the association between FER and lifetime regular cannabis use, current cannabis use, and age at first cannabis use in patients with schizophrenia, their unaffected siblings, and healthy controls. The results show that a history of lifetime regular cannabis use, but not current cannabis use, is associated with better performance in total FER in all three groups. Moreover, this association seems to be moderated by the age at onset of cannabis use in patients and siblings. Patients

Table 4 Association between DFAR scores and age at first cannabis use.

		Patients			Siblings			Healthy controls		
		B	95% CI	P	B	95% CI	P	B	95% CI	P
DFAR-total (primary outcome)	< 16 years vs non-users†	1.23	−0.88, 3.33	0.25	0.48	−1.98, 2.93	0.70	3.92	0.95, 6.89	0.01*
	≥ 16 years vs non-users	3.72	1.96, 5.49	<0.001*	2.37	0.58, 4.16	0.01*	4.25	1.96, 6.53	<0.001*
	≥ 16 years vs < 16 years	2.50	0.15, 4.84	0.04*	1.89	−0.94, 4.73	0.19	0.33	−2.62, 3.28	0.83
Subscales (secondary exploratory analyses)										
DFAR-neutral	< 16 years vs non-users†	0.01	−3.56, 3.59	0.99	1.28	−2.43, 5.01	0.50	6.09	2.21, 9.97	0.002*
	≥ 16 years vs non-users	5.20	2.39, 8.01	<0.001*	4.10	1.68, 6.51	0.001*	5.39	2.42, 8.37	<0.001*
	≥ 16 years vs < 16 years	5.18	1.44, 8.92	0.007*	2.81	−1.20, 6.82	0.17	−0.70	−4.42, 3.02	0.71
DFAR-happy	< 16 years vs non-users†	1.98	−0.64, 4.61	0.14	1.21	−2.04, 4.46	0.46	3.66	−0.05, 7.36	0.05
	≥ 16 years vs non-users	2.96	0.81, 5.10	0.007*	1.83	−0.29, 3.95	0.09	2.78	0.06, 5.49	0.04*
	≥ 16 years vs < 16 years	0.97	−1.92, 3.87	0.51	0.61	−3.03, 4.26	0.74	−0.88	−4.55, 2.79	0.64
DFAR-fearful	< 16 years vs non-users†	1.70	−1.71, 5.11	0.33	−1.48	−5.24, 2.29	0.44	1.78	−2.45, 6.01	0.41
	≥ 16 years vs non-users	3.02	0.15, 5.89	0.04*	0.85	−1.84, 3.54	0.54	2.60	−0.76, 5.97	0.13
	≥ 16 years vs < 16 years	1.32	−2.45, 5.10	0.49	2.33	−1.73, 6.39	0.26	0.82	−3.36, 5.01	0.70
DFAR-angry	< 16 years vs non-users†	1.04	−2.50, 4.58	0.56	0.77	−3.38, 4.93	0.71	4.28	−0.71, 9.27	0.09
	≥ 16 years vs non-users	3.65	0.78, 6.52	0.01*	2.59	−0.43, 5.62	0.09	6.27	2.63, 9.92	0.001*
	≥ 16 years vs < 16 years	2.61	−1.20, 6.41	0.18	1.82	−2.85, 6.49	0.44	1.99	−2.93, 6.92	0.43

Legend: CI = Confidence Interval; DFAR = Degraded Facial Affect Recognition task; * $P < 0.05$; †The second group is the reference group. All models were adjusted for age, sex, country (Turkey, Spain, the Netherlands, and Serbia), and took into account of clustering of observations within families.

and their unaffected siblings, in fact, showed no significant differences compared to non-users when age at onset of cannabis use was lower than 16 years. In contrast, healthy controls who used cannabis showed better performance in FER regardless the age they started using cannabis.

Our findings are in line with previous studies showing that long-term cannabis use is positively associated with social cognition (Arnold et al., 2015), and more specifically to FER (Meijer et al., 2012). One possible explanation is that regular cannabis users need to maintain superior social cognitive skills to obtain the illicit substance (Potvin et al., 2008). Another hypothesis is that genetic vulnerability to schizophrenia may be less pronounced in cannabis-using patients with schizophrenia than in those who have never used cannabis (Meijer et al., 2012). Indeed, it has been shown that premorbid cognitive functioning is better in psychotic patients that use cannabis than in non-users (Ferraro et al., 2013), suggesting lower vulnerability in the former group. Consequently, it could be hypothesized that people with relatively lower genetic vulnerability (i.e., cannabis users) present better FER performance.

It is worth mentioning that the degree of the association between lifetime regular cannabis use and FER was greater in siblings than patients and even greater in healthy controls, as indicated by larger unstandardized regression coefficients (B). These differences might be driven by specific patterns of gene-environment and environment-environment interactions. It is also likely that unmeasured genetic and environmental vulnerability might explain the stronger association in siblings and healthy controls. In fact, it cannot be excluded that other environmental risk or protective factors not investigated in the present study may contribute to the FER performance. For instance, it has been recently shown that individuals at ultra-high risk for psychosis with a history of peer-bullying performed better in DFAR-total; conversely, those who reported emotional abuse had decreased DFAR-total scores (Tognin et al., 2020). Future studies may clarify the individual and synergistic impact of different environmental factors on FER ability.

The composition of cannabis itself could further explain the association between lifetime regular cannabis use and more accurate FER performance. Cannabis contains over a

hundred different cannabinoids, the most important being delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is known to be responsible for the main psychotropic effect; CBD is a non-psychotropic compound with antipsychotic and pro-cognitive properties (Colizzi and Bhattacharyya, 2017). Cannabinoids exert their properties on human organism by acting on the endocannabinoid system (ECS), a complex network of lipids that seems imbalanced in psychotic disorders (Minichino et al., 2019). Interestingly, there is also evidence that the ECS is a key modulator of emotions and cognition (Campolongo and Trezza, 2012; Marco and Laviola, 2012; Zanettini et al., 2011). In fact, cannabinoid receptors are highly expressed in regions involved in perceptual emotional processing, such as the occipital and temporal lobes, as well as in regions involved in emotion recognition and generation of emotional reactions the amygdala and orbital frontal cortex (Bossong et al., 2013; Herkenham et al., 1991; Katona et al., 2001).

The acute administration of CBD and THC causes different effects in healthy subjects (Colizzi and Bhattacharyya, 2017; Rossi et al., 2020). To the best of our knowledge, no study has specifically evaluated the separate effects of CBD or THC on FER performance in patients with schizophrenia. Only, Hindocha et al. (2015) have investigated the acute effect of CBD and THC in a sample of 48 participants (half occasional, half heavy users) that were divided into two groups according to the level of schizotypal traits (high vs. low). In their study, THC impaired FER performance, whereas CBD improved accuracy of FER and significantly reduced the negative effect of THC on face recognition. Schizotypy or frequency of cannabis use did not impact FER performance. Although our study was different in terms of the design (observational vs. experimental), the study population (schizophrenia, siblings, and healthy controls vs. high/low schizotypy), the period of cannabis use (long-term vs. acute administration), and cannabis exposure (cannabis as a whole compound vs. CBD and THC separately), we cannot exclude the possibility that the regular use of CBD may counteract the detrimental effects of THC in the whole cannabis compound. Indeed CBD has shown some benefits for psychoses (Schoevers et al., 2020) and other psychiatric disorders (Bonaccorso et al., 2019; Fusar-Poli et al., 2020). Nevertheless, the increasing use of cannabis with high THC concentration seen over the last 15 years (ElSohly et al., 2016; Freeman et al., 2021) makes this hypothesis unlikely. Animal models have also shown that CBD may act as a partial dopamine agonist, which might account for the clinical antipsychotic effects (Seeman, 2016). Future randomized control trials are required to investigate the effects of CBD on social cognition in the population with psychosis. These studies should evaluate not only the effects of acute administration but also the longer-term effects of CBD on FER and other social cognitive domains.

It is worth mentioning that current cannabis use was not associated with total FER performance in any of the three groups in our study, in line with the previous findings (Meijer et al., 2012). However, the proportion of current cannabis users was relatively smaller compared to lifetime regular users (7.63% vs. 20.81% of the sample for which data were available) and might lack statistical power.

The age at first cannabis use influenced the impact of cannabis on FER in patients with schizophrenia and siblings, but not in controls. Specifically, compared with the non-users as the reference group, FER in all three groups were greater in those with a cannabis use onset after 16, whereas starting cannabis at a younger age was associated with better FER only in the control group. This finding may indicate that the effects of cannabis use on social cognition are age-dependent in people with higher psychosis vulnerability (Gorey et al., 2019). This could be related to the common use of products with lower CBD:THC ratios among adolescents (Ueno et al., 2021). Therefore, subjects with higher psychosis vulnerability could be particularly affected by THC at a younger age without the potentially beneficial effect of CBD. Indeed adolescence represents a sensitive neurodevelopmental window in which ECS modulation may predispose to the onset of schizophrenia (Zamberletti and Rubino, 2021).

FER deficits seem to be more pronounced for perception of negative than positive emotions both in patients with schizophrenia (Addington et al., 2006) and their first-degree relatives (Martin et al., 2020). In our sample, lifetime regular cannabis use was not only significantly associated with better performance in DFAR-total scores but also with the neutral (siblings and controls) and happy (patients and controls) subscales. On the contrary, no significant association between cannabis use and emotions with negative valence (i.e., fearful and angry) was observed. This finding provides further support to the hypothesis that cannabinoids interact with emotional content, inducing a shift from a bias for negative emotional content towards positive emotional content (Bossong et al., 2014, 2013). On the one hand, they suggest a possible role for the ECS in abnormal emotional processing; on the other hand, they provide indirect evidence for an involvement of ECS in FER deficits experienced by patients with schizophrenia (Bossong et al., 2013).

To our knowledge, this is the largest study that specifically focused on the association between cannabis use and FER. Moreover, it is the first to examine the association between cannabis use and the recognition of specific emotions, as well as the association between FER and age of first cannabis use. Nevertheless, some limitations should be discussed. First, the study had a cross-sectional design, thus not allowing us to infer any causal link between cannabis use and FER performance. Future longitudinal analyses might additionally evaluate whether differences in pharmacological treatment (duration, combination, dose) influence FER performance in large first-episode psychosis cohorts. Second, the patterns of cannabis use were collected using information reported by participants and might be subjected to recall bias, thus potentially underestimating the actual prevalence of cannabis use. Third, current cannabis use was evaluated differently in the two datasets (i.e., self-report in the EUGEI and urinalysis in the GROUP). However, results from the sensitivity analysis conducted in the GROUP participants were in accordance with the main findings and substantially with exploratory analysis. Finally, we did not take into account the amount and type of cannabis (e.g., hash, herbal, home-grown skunk, etc.) and thus the THC concentration. Therefore, any hypothesis regarding the impact of different cannabinoids on social cognition is merely speculative.

In conclusion, our findings revealed that the lifetime regular use of cannabis may be associated with better accu-

racy in emotion recognition in patients with schizophrenia, their unaffected siblings, and healthy controls, regardless of the psychosis expression. This association appeared to be dependent on the age of first cannabis use (after 16 years old) in the groups with greater genetic vulnerability to schizophrenia (i.e., patients and siblings). Our findings are not in conflict with the large amount of evidence in support of the harmful effects of cannabis on physical and mental health, as well as the negative social consequences (Campeny et al., 2020). They provide further support for the involvement of the ECS in the patoethiology of schizophrenia (Minichino et al., 2019) and the importance of evaluating social cognitive outcomes while testing the effects of CBD in populations with psychosis (Colizzi and Bhattacharyya, 2017). Further prospective observational studies are required to investigate whether cannabis use is causally linked to FER, and if so, studies with experimental designs should explore the underlying mechanisms.

Ethical standards

The projects were approved by the Medical Ethics Committees of all participating sites and conducted in accordance with the Declaration of Helsinki. All respondents provided written informed consent and, in the case of minors, such consent was also obtained from parents or legal guardian.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request under the condition of the approval of the EUGEI and GROUP steering committees.

Appendix

Genetic Risk and Outcome of Psychosis (GROUP) Investigators in EUGEI (GROUP-EUGEI) investigators are: Behrooz Z. Alizadeh[a], Therese van Amelsvoort[b], Richard Bruggeman[a,], Wiepke Cahn[c,d], Lieuwe de Haan[e], Bart P. F. Rutten[b], Jurjen J. Luykx[c,f,g], Jim van Os[c,b,h], and Ruud van Winkel[b,i]

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Conflicts of Interest

Celso Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. Maria Paz Garcia-Portilla has been a consultant to and/or has received honoraria/grants from Angelini, Alianza Otsuka-Lundbeck, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, and SAGE Therapeutics.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.08.003.

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