

Hemispheric Language Asymmetry in First Episode Psychosis and Schizotypy: The Role of Cannabis Consumption and Cognitive Disorganization

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Cannabis use has been related to an elevated psychosis risk and attenuated cognitive functioning. Cannabis-related cognitive impairments are also observed in populations along the psychosis dimension. We here investigated whether a potential behavioral marker of the psychosis dimension (attenuated functional hemispheric asymmetry) is even further attenuated in individuals using cannabis (CU) vs those not using cannabis (nCU). We tested 29 patients with first-episode psychosis (FEP; 11 CU) and 90 healthy controls (38 CU) on lateralized lexical decisions assessing left-hemisphere language dominance. In patients, psychotic symptoms were assessed by Positive & Negative Symptom Scale (PANSS). In controls, self-reported schizotypy was assessed (The Oxford-Liverpool Inventory of Feelings and Experiences: O-LIFE). Results indicated that nCU FEP patients had a relative reduced hemispheric asymmetry, as did controls with increasing cognitive disorganization (CogDis) scores, in particular when belonging to the group of nCU controls. Positive, disorganized and negative PANSS scores in patients and negative and positive schizotypy in controls were unrelated to hemispheric asymmetry. These findings suggest that cannabis use potentially balances rather than exacerbates uncommon hemispheric laterality patterns. Moreover, in healthy populations, the potential stabilization of typical hemispheric asymmetry in CU might be most relevant to individuals with elevated CogDis. We discuss the potential beneficial and harmful effects of cannabis use along the psychosis dimension together with propositions for future studies that should account for the mediating role of additional substances (eg nicotine), cannabis composition (eg cannabidiol content), and individual differences (eg physical health, or absence of significant polysubstance use).

Key words: cannabis/drugs/laterality/cognition/schizotypy/psychosis-proneness

Introduction

Psychotic disorders have serious personal¹ and societal² implications. Early detection may ameliorate or even prevent some of these adverse consequences, because it relates to more favorable outcomes including milder forms and shorter illness duration.³ It is therefore important to determine risk factors that enable detection of high-risk individuals. Here we consider reduced functional hemispheric asymmetry (hitherto: HA), individuals' cannabis use and symptom profiles in individuals along the psychosis dimension.

HA refers to the fact that certain cognitive functions are differently processed by the cerebral hemispheres, eg language is predominantly processed by the left hemisphere.⁴ In schizophrenia, the establishment of this HA seems hampered.⁵ Behavioral studies showed reduced left-hemisphere language dominance not only in schizophrenia⁶ but also in healthy schizotypal individuals.^{7,8} The schizotypy concept assumes that psychotic symptoms occur along a continuum, with severest symptoms being exhibited by patients with schizophrenia and mildest symptoms by the least affected schizotypal individual from the healthy population.^{9–11} Schizotypy is commonly assessed via self-report questionnaires comprising symptom dimensions known from schizophrenia, ie positive, negative and disorganized symptoms.^{10,12,13} Longitudinal studies showed that high schizotypy scores associate with an increased risk for the development of psychosis.^{9,14}

Schizotypy is consequently a valuable risk factor to consider.

Another risk factor for the development of psychosis is cannabis use.^{15,16} Acute tetrahydrocannabinol (THC) administration, the psychoactive compound in cannabis, can induce psychotic symptoms in healthy individuals, and exaggerate symptoms in patients.¹⁷ Despite this risk potential, cannabis is a popular drug along the schizophrenia spectrum, eg in schizophrenia^{18,19} and schizotypy.^{20,21} Given this link, cannabis may also influence performance in cognitive measures such as HA.

Research investigating the link between cannabis and HA is sparse. Inconclusive brain imaging studies showed (1) increased right-hemisphere activation in cannabis users (CU) when compared with noncannabis users (nCU) during tasks requiring attentional control,²² (2) increased right-hemisphere cerebral blood flow with acute THC-ingestion,²³ and (3) increased hippocampal volume in the left over right hemisphere in alcohol and marijuana using individuals compared with alcohol using individuals.²⁴ Also, some recent studies reported comparable dichotic listening performance (assessing HA) after THC and placebo consumption.^{25,26} Better known are links between cannabis use and cognitive impairments in functions such as memory, executive functioning, and attention.^{27,28} Of interest here, such cognitive impairments are common in schizophrenia²⁹ and schizotypy.^{30,31} Overall, if both cognitive impairments and reduced HA are behavioral markers of psychosis, and cannabis use is a risk factor for psychosis impacting on the brain, one could suggest that both cognitive impairments and reduced HA are even more pronounced in both psychotic and high schizotypal CU.

Few published studies measured schizotypy, cannabis, and cognition simultaneously.^{32,33} These showed that cannabis use was related (1) to exacerbated attentional disinhibition and elevated schizotypal personality questionnaire subscale scores for positive and disorganized schizotypy,³² and (2) to enhanced verbal fluency performance in a healthy subsample irrespective of their schizotypy scores.³³ These few studies indicate that cannabis use does not associate with both cognitive functioning and elevated schizotypy subscale scores,³³ or only with positive and disorganized subscale scores.³² On the other hand, recent studies indicated that cognitive disorganization (CogDis) might be key to both cognitive attenuations (including reduced HA)^{34–38} and also associated with drug use,³⁷ whereas positive schizotypy seems of minor clinical relevance.^{39,40} Negative schizotypy seems most heterogeneous when relating it to cognitive functions (including HA),^{32,41–43} and substance use.^{35,36,44}

To test for HA as a behavioral marker of psychosis, and the high-risk potential of cannabis use, we tested whether functional HA for language is most

attenuated in CU when compared with nCU in 2 populations along the psychosis dimension, ie first-episode psychosis (FEP) patients and healthy controls. We expected this to be most pronounced with increasing CogDis for the following reasoning, particularly in healthy controls: if CogDis is a vulnerability factor in high risk individuals,^{34,45,46} and cannabis exerts harmful effects in vulnerable populations, cannabis' harmful effects might be most pronounced in high CogDis individuals.

Method

Participants

The fluent English speaking FEP patients and healthy right-handed controls had normal or corrected to normal vision. Right-handedness was determined according to a standardized handedness questionnaire.⁴⁷ Each right-hand preference was given a score of “1,” each either-hand preference “0.5,” and each left-hand preference “0.” We calculated the mean of the sum of these scores, and defined as right-handed those participants who scored at least 7.5.³⁵ For patients, both left- and right-handers were included to maximize sample size. The 29 FEP patients (12 females) presented at treatment centers in Nottingham, Bristol, Birmingham, and London. They were part of the ethically approved PsyGrid cohort (www.psygrid.org). According to the inclusion and exclusion criteria, participants were aged 16–65 years, entered secondary care for the first time with psychotic symptoms, had sufficient English command and had no suspected organic brain disease or history of learning disability.⁴⁸ The diagnoses were made according to the criteria of experienced psychotic symptoms over the previous month accompanied by a decrease in functioning. The healthy sample was recruited through local advertisements and the University of Bristol “Experimental Hours” scheme for course credits. The latter group performed additional cognitive tasks (to be reported elsewhere)⁴⁹ and a lateralized facial decision task.³⁵ We do not report on the latter task, because results were highly heterogeneous across numerous studies. In contrast, laterality measures obtained when assessing lateralized language functions have been more reliable.⁴ These individuals were also asked about their highest finished education. The University of Bristol ethics committee approved this study. All participants provided written informed consent prior participation.

Psychotic Symptoms and Premorbid IQ in Patients

Psychotic symptoms in FEP patients were assessed with the Positive & Negative Symptom Scale (PANSS).⁵⁰ We here considered the positive and negative symptom scales, as well as factor-analytic solutions for the CogDis scale comprising poor attention, difficulties in abstract thinking,

and conceptual disorganization.⁵¹ Trained clinical interviewers at each centre enquired about psychotic symptoms over the previous week. Interviewing skills and inter-rater reliability (ICC) were regularly checked. The ICC was 0.95 (95% CI 0.67–1.0) for positive symptoms and 0.92 (95% CI 0.51–1.0) for negative symptoms. Patients also completed the National Adult Reading Test (NART), assessing premorbid reading ability by measuring the number of irregular words correctly pronounced⁵² (the more correct pronunciations, the higher the verbal IQ).

Schizotypy and Educational Level in Healthy Participants

The 159 true-false item Oxford-Liverpool Inventory of Feelings and Experiences^{10,53} assesses Unusual Experiences (UnEx, positive schizotypy, 30 items such as “Are your thoughts sometimes so strong that you can almost hear them?”), Introvertive Anhedonia (IntAn, negative schizotypy, 27 items such as “Do you prefer watching television to going out with people?”), and CogDis (24 items such as “Are you easily confused if too much happens at the same time?”). The higher the sum score, the higher the schizotypy score. Normative values can be found in Mason et al.^{10,53} Participants were also asked about their highest finished education (ie secondary school, college, university, or other).

Drug Use and Medication

Within PsyGrid, patients were only asked which drugs they mainly use and with which frequency, ie occasional (less than weekly), regular (at least weekly), or frequent [(almost) everyday] use. The same criteria for frequency were also applied to healthy controls. In both groups, other drugs were only used occasionally. At study entry, 2 patients were medically treated (once Mirtazapine, once Benzodiazepine), 16 patients had incomplete medication records, and 11 were medication-free. The duration between presenting at the treatment centers and actual study entry ranged between 1 and 3 months.

In the healthy sample, we excluded volunteers who reported excessive alcohol use (>50/>35 units of alcohol per week for men/women, respectively), and/or alcohol use within 12h prior testing. In the study information, we informed participants that we would perform urine drug screening. At study entry, we asked about illegal substance use within the past 3 months. To encourage honest responding, we kept volunteers unaware that the urine drug test would only detect cannabis metabolites until about 2 weeks after its consumption. Participants were excluded if they indicated illicit drug use (apart from cannabis) in the past 3 months (>twice) and/or within the last 2 weeks. We kept participants with a negative THC-derivate urine test if they had reported occasional use within the past 30 days, and/or indicated regular or frequent use in the past 30 days, but not within the past

2 weeks. Participants were excluded, if they indicated regular or frequent cannabis use within the past 2 weeks despite a negative drug test. We also excluded healthy nCU if they did not report nicotine and cannabis use in the past 30 days but showed a positive drug test.

Lateralized Lexical Decision Task

Our Lateralized Lexical Decision Task (LDT) paradigm is based on common procedures used for lateralized half-field studies⁵⁴ and has been used before.^{8,35} The stimuli consisted of 4- and 5-letter words matched for neighborhood and CELEX frequency.⁵⁵ A fixation cross was displayed in the centre of the screen for 1000 ms, followed by the presentation of 2 strings of letters on either side of the screen for 150 ms. After this, a blank screen was presented. For a maximum of 4000 ms, participants had to indicate whether they saw a word on the left (pressing the left shift key with their left index finger) or right (pressing the right shift key with their right index finger), or saw no meaningful English word on either side of the screen (pressing the space bar with both thumbs, see³⁵ for further details). Each word was matched with a nonword of the same length. The remaining non-words were matched to result in an additional set of nonword pairs. There were 72 trials with three 24-trial conditions: (1) word left/nonword right, (2) nonword left/word right, and (3) nonword/nonword. The word pairs were displayed in black (33 point Courier New Bold font) on a grey background on the computer screen. Each letter string was presented with their center 25 mm from central fixation (visual eccentricity: 2.5 degrees of visual angle per half-field). Prior to the experimental task, each participant undertook a practice block consisting of 10 trials with words and nonwords not used in the experimental trial. The order of the stimuli was randomized between participants. We assessed the number of correct lexical decisions and the mean reaction times for correct lexical decisions for the left visual field (LVF) and right visual field (RVF) separately.

Data Analysis

We excluded individual response latencies faster than $2 \times$ SD from the individual means in the LDT.^{35,36} Additional exclusion criteria included age and random responding. We excluded participants older than 40 years or missing age information (1 CU control, 2 CU patients, 1 nCU patient). We excluded 1 nCU control and 1 nCU patient performing at or below chance level for both LVF and RVF performance. Missing PANSS values (13.8% of all cases; Little’s Missing Completely at Random test: $X^2 = 11.57$, $df = 14$, $P = .64$) were estimated according to EM-methods of the SPSS missing value analysis.⁵⁶

Kolmogorov-Smirnov tests revealed normal distribution for the LDT LVF %, the The Oxford-Liverpool

Table 1. Age and Handedness for FEP Patients and Controls

	Controls (<i>N</i> = 90)				Patients (<i>N</i> = 29)			
	Cannabis users (<i>N</i> = 38)		Nonusers (<i>N</i> = 52)		Cannabis users (<i>N</i> = 11)		Nonusers (<i>N</i> = 18)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	21.97	3.97	21.67	3.49	25.64	6.55	24.11	4.90
Handedness	11.51	0.71	11.24	0.84	8.86	4.70	8.19	3.92

Inventory of Feelings and Experiences (O-LIFE) CogDis scale, and for the PANSS positive and negative symptom scores. All other variables (O-LIFE UnEx, O-LIFE IntAn, PANSS CogDis, age, handedness, and other laterality variables) were not normally distributed. Consequently, we ran all correlational analyses using Spearman's rho. *F*-tests are fairly robust to violations of normality.⁵⁷ Thus, we calculated $2 \times 2 \times 2$ mixed sample ANCOVAs controlling for age and handedness, with visual field (LVF, RVF) as the related samples factor, and mental health group (patients, healthy controls) and cannabis use (yes, no) as the independent samples factors on mean reaction times for correct lexical decisions. The same ANCOVA was also calculated for percent correct lexical decisions. Effect sizes are reported throughout. All *P* values were 2-tailed, the α -level was set at .05.

Results

Participants

Of the 11 CU FEP, 2 were occasional CU, 3 used cannabis on a regular basis and 6 on a frequent basis. Of the 38 CU controls, 3 were occasional users, 16 were regular users and 19 were frequent users (the latter 2 groups yielded positive urine tests). Pearson-Chi square analyses revealed that the frequency of occasional, regular and frequent users did not differ between patients and controls [$\chi^2(3, N = 119) = 1.49, P = .68$]. The NART scores were comparable for CU and nCU patients ($t(27) = 0.45, P = .66$). CU controls did not differ from nCU controls on measures of highest finished education [$\chi^2(2, N = 90) = 1.63, P = .44$].

Univariate analysis of variances with cannabis use and nonuse (CU, nCU) and mental health group (patients, controls) as between-subjects factors on age and handedness, separately, revealed that age did not differ between CU and nCU [$F(1,115) = 0.98; P = .32, \text{partial } \eta^2 = 0.01$], nor did handedness [$F(1,115) = 0.99; P = .32, \text{partial } \eta^2 = 0.01$]. However, patients were significantly older than controls [$F(1,115) = 10.93; P < .01, \text{partial } \eta^2 = 0.09$], and were less right-handed than controls [$F(1,115) = 36.27; P < .001, \text{partial } \eta^2 = 0.24, \text{table 1}$]. There was no significant interaction between cannabis use and mental health neither for age [$F(1,115) = 0.44; P = .51, \text{partial } \eta^2 < 0.01$] nor handedness [$F(1,115) = .18; P = .68, \text{partial } \eta^2 < .01, \text{table 1}$].

Table 2. Spearman's Rho Correlations for the Association Between LDT Performance Measures, Age, and Handedness in the Entire Sample (*N* = 119)

	Age	Handedness
LVF ^a % ^b	-0.05	-0.20*
RVF ^c %	-0.00	-0.05
LVF RT	0.12	-0.16**
RVF RT	0.23*	-0.16**

Note: LDT, Lexical Decision Task; LVF, left visual field; RVF, right visual field; RT, reaction time.

^aLeft visual field; ^bPercent correct; ^cRight visual field.

*Significant at $P \leq .05$; **significant at $P \leq .10$.

Spearman's rho correlations revealed that age and handedness correlated with at least one laterality measure (table 2). Therefore, these variables were controlled for in subsequent analyses.

The Relationship Between Cannabis Use and Mental Health on HA

The mixed-samples ANCOVA on percent correct responses showed a significant drug use * mental health * visual field interaction [$F(1,113) = 4.13, P = .04, \text{partial } \eta^2 = 0.04$]. The same mixed-samples ANCOVA split by cannabis use revealed a significant mental health * visual field interaction in nCU [$F(1,66) = 5.45, P = .02, \text{partial } \eta^2 = 0.08$], but not in CU [$F(1,45) = 1.56, P = .22, \text{partial } \eta^2 = 0.03$]. Paired-samples *t*-tests split by mental health in nCU revealed significantly better RVF than LVF performance in controls ($t(51) = -5.77, P < .001, \text{Cohen's } d_z = -0.80$), but not in patients ($t(17) = -0.85, P = .41, \text{Cohen's } d_z = -0.20; \text{table 3}$).

All other comparisons were nonsignificant (all $P > .05$). The same ANCOVA on reaction times showed that patients were significantly slower than controls [$F(1,113) = 4.89, P = .03, \text{partial } \eta^2 = 0.04, \text{table 3}$]. All other comparisons were nonsignificant (all $P > .05$).

Psychotic (-Like) Symptoms and HA

The *t*-tests on PANSS scores separately showed that CU patients had more positive symptoms than nCU patients (table 4). Negative and CogDis symptoms were

Table 3. Means and SD for LDT Performance for the Total Sample and the Study Groups Separately

			LVF ^a % ^b	RVF ^c %	LVF RT	RVF RT
All	<i>N</i> = 119	Mean	55.60	72.58	827.09	807.25
		SD	22.97	15.04	210.49	228.07
Controls	CU (<i>N</i> = 38)	Mean	54.28	69.30	801.60	797.66
		SD	22.29	14.58	156.77	177.65
	nCU (<i>N</i> = 52)	Mean	55.29	76.20	761.59	730.96
		SD	23.77	13.13	137.90	130.87
Patients	CU (<i>N</i> = 11)	Mean	51.14	75.38	1021.01	990.28
		SD	25.01	16.08	205.17	383.94
	nCU (<i>N</i> = 18)	Mean	62.04	67.36	951.59	936.06
		SD	21.34	18.43	341.91	311.47

Note: CU, using cannabis; nCU, not using cannabis; RT, reaction time.

^aLeft visual field; ^b% correct; ^cRight visual field

Table 4. PANSS and O-LIFE Scores and Their Distribution, Split by Mental Health Group and Cannabis Use

		Patients		Controls		<i>t</i>	<i>P</i>	Cohen's <i>d</i>
		CU (<i>N</i> = 11)	nCU (<i>N</i> = 18)	CU (<i>N</i> = 38)	nCU (<i>N</i> = 52)			
		Mean (SD)	Mean (SD)	Mean (SD)	Mean			
PANSS	Positive	18.28 (6.9)	13.06 (4.4)	n/a	n/a	2.25	.04	0.99
	CogDis ^a	6.10 (3.36)	4.45 (1.86)	n/a	n/a	1.72	.10	0.68
	Negative	14.68 (5.69)	13.5 (4.53)	n/a	n/a	0.62	.54	0.25
O-LIFE	UnEx ^b	n/a	n/a	7.39 (5.82)	5.63 (3.91)	1.62	.11	0.37
	CogDis	n/a	n/a	10.74 (5.71)	11.04 (5.1)	-0.26	.79	-0.06
	IntAn ^c	n/a	n/a	3.95 (3.21)	4.85 (3.72)	-1.2	.23	-0.26

Note: CU, using cannabis; nCU, not using cannabis; PANSS, Positive & Negative Symptom Scale.

^aCognitive disorganization, ^bUnusual experiences, ^cIntrovertive anhedonia.

comparable between groups (table 4). Partial Spearman's rho correlations controlling for age and handedness indicated no association between PANSS subscale scores and the laterality measures (all *P* > .09; table 5). In controls, *t*-tests comparing the O-LIFE subscale scores between CU and nCU were all nonsignificant (table 4).

In controls, partial Spearman's rho correlations controlling for age and handedness indicated that increasing CogDis scores correlated with an enhanced LVF accuracy and a marginally decreased LVF RT (table 5). When testing these relationships for CU and nCU controls separately, increasing CogDis scores correlated with an enhanced LVF accuracy in nCU only (table 5). In patients, the same analysis revealed no significant correlations (see also table 5).

Discussion

We investigated the relationship between cannabis use, psychotic (-like) symptoms and HA, a purportedly biological marker along the psychosis spectrum. Using a lateralized LDT, we investigated firstly if CU relates to a more pronounced attenuation in HA than nCU in FEP and controls, respectively, and secondly if any such

relationship in controls would be particularly true for CogDis. Results showed that nCU FEP patients had a reduced HA, as did controls with increasing CogDis, in particular when belonging to the group of nCU. Positive, negative and CogDis PANSS scores in patients and IntAn and UnEx scores in controls were unrelated to functional HA.

Reduced HA, in particular for language, might be a behavioral marker for schizophrenia.⁵⁸ Behavioral studies strengthened this notion reporting reduced left-hemisphere dominance for language in both schizophrenia⁶ and healthy schizotypy.^{7,8} Supporting the influence of drug use,^{35,36} we only observed this laterality reduction in nCU FEP and controls with increasing CogDis, in particular when belonging to the group of nCU.

The first finding is initially surprising, we expected cannabis (mainly smoked with nicotine) to reduce left hemisphere language dominance for several reasons. Firstly, epidemiological studies show enhanced cannabis use along the schizophrenia spectrum (eg schizophrenia,^{18,19} schizotypy).^{20,21} Secondly, acute THC administration can induce psychotic symptoms in healthy participants, and exacerbate symptoms in patients.¹⁷ Thirdly, cannabis use in patients associates with an unfavorable illness

Table 5. Partial Spearman's Rho Correlations Controlling for Age and Handedness Investigating the Association Between Psychotic (-Like) Symptoms and LDT Performance Measures, Split by Mental Health Status and Drug Use

		LVF ^d % ^e	RVF ^f %	LVF RT	RVF RT
Controls (<i>N</i> = 90)	UnEx ^a	0.02	0.07	0.01	0.03
	CogDis ^b	0.25*	0.03	-0.19**	-0.08
	IntAn ^c	0.05	0.05	-0.07	-0.05
CU (<i>N</i> = 38)	UnEx	-0.14	-0.04	0.07	0.11
	CogDis	0.19	0.02	-0.11	0.08
	IntAn	0.22	0.08	0.06	0.1
nCU (<i>N</i> = 52)	UnEx	0.17	0.13	0.01	0.03
	CogDis	0.29***	0.06	-0.15	-0.1
	IntAn	-0.05	0.01	-0.14	-0.12
Patients (<i>N</i> = 29)	Positive	-0.15	0.12	0.10	0.07
	CogDis	0.26	0.23	-0.11	-0.01
	Negative	0.14	0.28	0.05	-0.08
CU (<i>N</i> = 11)	Positive	-0.17	0.05	-0.09	-0.05
	CogDis	0.17	0.07	0.26	0.34
	Negative	0.17	-0.09	0.02	0.24
nCU (<i>N</i> = 18)	Positive	0.23	-0.20	-0.13	-0.04
	CogDis	0.43	0.20	-0.29	-0.23
	Negative	0.14	0.38	-0.05	-0.28

Note: CU, using cannabis; nCU, not using cannabis; RT, reaction time.

P* = .02; *P* = .07; ****P* = .04

^a Unusual experiences, ^b cognitive disorganization, ^c introverted anhedonia, ^d left visual field, ^e percent correct, ^f right visual field.

outcome, ie earlier onset, more frequent hospitalization and relapse.⁵⁹ Finally, cannabis use can be harmful for cognition in FEP²¹ and healthy controls.^{27,28} Yet, we observed a reduced functional HA in nCU (instead of CU) FEP and in controls with increasing CogDis, in particular in nCU. Functional HA was comparable for CU FEP, nCU controls and CU controls, with no significant influence of CogDis in the latter sample. Thus, cannabis use was associated with the commonly observed [and not “psychotic-(like)”] laterality pattern.

Studies testing the influence of cannabis use on functional HA are scarce. Some results indicate that THC when compared with placebo is associated with greater RH activation.⁶⁰ Others found comparable dichotic listening performance after THC and placebo consumption.^{25,26} Given the scarcity of HA studies, we considered links between cannabis use and cognition more widely. These studies revealed various cognitive impairments in CU when compared with nCU including memory, attention and executive functions.^{27,28} Such cognitive impairments seem common in schizophrenia²⁹ and also schizotypy^{30,31} indicating that cannabis use along the psychosis dimension might link to even worse cognitive impairments. Yet, cognitive functions are usually superior in CU when compared with nCU patients.^{61,62} Cannabis use may be related to enhanced prefrontal neurotransmission and consequently superior cognitive performance in patients.⁶³ Finally, cannabis use enhanced verbal fluency performance in healthy participants low on trait creativity.³³ Thus, CU might actually restore cognitive functioning (including common patterns of HA as observed here).

To conjecture the kind of restorative processes, the neuronal underpinnings of cannabis use seem widespread anatomically and functionally.⁶⁴ What seems, however, common is that neuronal activity and connectivity has been found to be altered in CU when compared with nCU, being potentially indicative of compensatory functions.^{64,65} Given that left-hemisphere dysfunctions have long been linked to psychotic conditions,^{8,58} cannabis might facilitate the activation and strengthening of such relatively impaired neuronal networks, and as such help to compensate for neuronal deficits, ie left-hemisphere deficits in the current case. We do not know whether any such compensation might become established over time^{65,66} and/or exerts its action in the short-term.⁶⁷ In particular for visual lexical decisions, potential mechanisms restoring asymmetry might not necessarily imply better cognitive functioning.⁶⁸ Moreover, we do not know whether observed changes in chronic CU are directly explained by cannabis use or point to vulnerability markers associated with the long-term use of cannabis.⁶⁶

Alternatively or complementarily, premorbid IQ and years of education did not differ between CU and nCU patients and controls, respectively. Thus, intellectual abilities are unlikely to explain our findings.⁶⁹ We propose that our cannabis effects result from (1) beneficial properties of certain cannabinoid components and (2) individual differences such as enhanced psychopathological vulnerability yielding different sensitivities to cannabis use. Firstly, neuroprotective (antioxidant, anti-inflammatory) properties of some cannabis components have been identified.^{70,71} Cannabidiol is such a neuroprotective

component.⁷² Fewer psychotic experiences in the general population^{73,74} and putative benefits for cognitive functioning⁷⁵ have been associated with cannabis high in cannabidiol. This substance may activate neuroprotective effects outlasting acute intoxication periods and counteracting negative consequences of psychopathological changes.

Secondly, research exploring which patients may benefit from CU regarding cognitive functioning has been rather scarce. Other outcome measures, however, may hint at which individuals may benefit from CU. For instance, some patient subgroups seem to experience symptom alleviation with synthetic THC-administration,⁷⁶ ie patients with no significant polysubstance use, good physical health, and severe, longstanding illness refractory to standard treatment. The sample size in this report was, however, small (4 participants). Other outcome variables such as psychopathological symptoms in patients seem unrelated to CU after controlling for variables such as additional substance use, or baseline illness severity.⁷⁷

In schizotypy, cognitive impairments are commonly linked to schizotypal subdimensions, and when considering HA and drug use, reduced HA seems particularly linked with CogDis (as measured by the O-LIFE).^{10,35,36} We conjecture that CogDis is the schizotypal subdimension related to psychopathological risk. Independent patient studies reported on increased right hemisphere functioning with enhanced CogDis,⁷⁸ or cognitive attenuations.⁴⁶ Moreover, CogDis has been shown to be sensitive to relatively well-established endophenotypes of psychosis in healthy schizotypal populations.^{34–38} Importantly, the basic symptom criterion “cognitive disturbances” together with ultra-high risk symptoms are crucial for predicting psychosis.⁴⁵ CogDis also seems to mediate the relationship between positive and negative symptoms.⁷⁹ Thus, our CogDis findings are also supporting independent notions that positive schizotypy is of minor relevance to psychopathology,^{39,40} and negative schizotypy relates inconsistently with cognitive and behavioral measures (including HA).^{35–37,80}

Limitations

The current multicenter study protocol provided only limited drug use information in patients. More information would be important, because polydrug use has been associated with better cognitive performance in patients.⁶³ Also, CU patients frequently consume other substances, mainly nicotine.⁸¹ Nicotine use has been linked to increased transition rates in high-risk samples.⁸² An increased nicotine exposure via cannabis smoking might actually associate with reduced HA in patients, and not cannabis alone. Nicotine dependence in a student population correlated with enhanced right hemisphere language functions³⁵ and right ear advantage in a dichotic

listening task (men only).⁸³ Moreover, nicotine exposure increased RH thalamic blood flow in overnight abstinent smokers.^{84,85}

Additionally, the absence of a relationship between CogDis scores and HA in patients may be due to a difference in scale composition. The O-LIFE CogDis-scale also comprises social anxiety items,¹⁰ whereas this is not the case for most factor-analytic solutions of the PANSS.⁵¹ We therefore suggest that future studies use the same, or develop a comparable instrument to measure the construct of CogDis in healthy and mentally ill populations.

Conclusions

We investigated the relationship between psychotic (-like) symptoms, cannabis use and HA, a purportedly biological marker along the psychosis spectrum. More specifically, we set out to investigate if (1) CU relates to a less pathological HA profile in FEP and (2) if in healthy controls CogDis would relate to a more pathological laterality profile, particularly pronounced in CU when compared with nCU. We found that a psychotic-like attenuation of the typical LH language dominance was found in both nCU FEP and healthy controls with increasing CogDis, in particular when belonging to the group of nCU. These findings suggest that cannabis use may stabilize laterality patterns in vulnerable populations, ie patients with FEP and healthy individuals scoring high on CogDis. Future studies should address the additional role of nicotine, cannabidiol, and other substances on functional HA and pathological risk, as well as the role of individual differences in cannabis use and their effect on mental health.

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