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The impact of cannabidiol treatment on resting state functional connectivity, prefrontal metabolite levels and reward processing in recent-onset patients with a psychotic disorder

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ABSTRACT

The first clinical trials with cannabidiol (CBD) as treatment for psychotic disorders have shown its potential as an effective and well-tolerated antipsychotic agent. However, the neurobiological mechanisms underlying the antipsychotic profile of CBD are currently unclear. Here we investigated the impact of 28-day adjunctive CBD or placebo treatment (600 mg daily) on brain function and metabolism in 31 stable recent-onset psychosis patients (<5 years after diagnosis). Before and after treatment, patients underwent a Magnetic Resonance Imaging (MRI) session including resting state functional MRI, proton Magnetic Resonance Spectroscopy (^{1}H-MRS) and functional MRI during reward processing. Symptomatology and cognitive functioning were also assessed. CBD treatment significantly changed functional connectivity in the default mode network (DMN; time × treatment interaction $p = 0.037$), with increased connectivity in the CBD (from 0.59 ± 0.39 to 0.80 ± 0.32) and reduced connectivity in the placebo group (from 0.77 ± 0.37 to 0.62 ± 0.33). Although there were no significant treatment effects on prefrontal metabolite concentrations, we showed that decreased positive symptom severity over time was associated with both diminishing glutamate ($p = 0.029$) and N-acetyl-aspartate (NAA; neuronal integrity marker) levels ($p = 0.019$) in the CBD, but not the placebo group. CBD treatment did not have an impact on brain activity patterns during reward anticipation and receipt or functional connectivity in executive and salience networks. Our results show that adjunctive CBD treatment of recent-onset psychosis patients induced changes in DMN functional connectivity, but not prefrontal metabolite concentrations or brain activity during reward processing. These findings suggest that DMN connectivity alteration may be involved in the therapeutic effects of CBD.

1. Introduction

Psychosis is a serious mental disorder characterized by disturbances of thought, perception and cognition. Because available treatments are only modestly effective and cause serious adverse effects (Tandon et al., 2008), there is a pressing need for novel treatments.

The first clinical trials with the non-intoxicating cannabinoid compound cannabidiol (CBD) as treatment for psychosis have shown its potential as an effective and well-tolerated antipsychotic agent (Leweke et al., 2012; McGuire et al., 2018). Leweke et al. (2012) showed that mono-therapy of four weeks of daily CBD (maximum of 800 mg/day; N = 20) decreased both positive (e.g. hallucinations and delusions) and negative (e.g. apathy) symptoms in acute psychosis patients to a similar extent as the conventional antipsychotic amisulpride (N = 19), but with significantly fewer side effects. Another clinical trial in stable psychosis patients with six weeks of CBD (1000 mg/day) as add-on therapy to

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conventional antipsychotic medication demonstrated significant improvement in both positive symptoms and global clinical impression after CBD (N = 43) compared to placebo (N = 46) (McGuire et al., 2018). Conversely, Boggs et al. (2018) did not observe any significant effects of six weeks of additional CBD treatment (1000 mg/day; N = 18) of outpatients with chronic schizophrenia on positive symptoms and cognition compared to placebo (N = 18).

Robust pathophysiological features of psychosis patients include functional brain dysconnectivity (O'Neill et al., 2019), altered glutamate metabolite levels and γ-aminobutyric acid (GABA) concentrations (Nakahara et al., 2022) and abnormal brain activity during reward processing (Zeng et al., 2022). First, converging evidence indicates decreased resting state connectivity as key feature in patients, in particular in functional brain networks including default mode, central executive and salience network (Pettersson-Yeo et al., 2011; O'Neill et al., 2019). Importantly, reduced functional network connectivity in patients has been shown to ameliorate with antipsychotic treatment (Wang et al., 2017; Chopra et al., 2021). Second, meta-analyses including numerous Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) studies converge on the conclusion that psychosis patients exhibit increased levels of glutamate metabolites and reduced GABA concentrations across several brain regions (Merritt et al., 2016; Nakahara et al., 2022). Longitudinal studies indicate that antipsychotic treatment is associated with significant reductions in glutamate metabolite levels, while changes in GABA concentrations were not shown (Egerton et al., 2017; Kubota et al., 2020). Finally, several meta-analyses including functional MRI studies that applied a reward paradigm reported abnormal brain activity patterns associated with both reward anticipation and receipt in psychosis patients (Radua et al., 2015; Zeng et al., 2022). In particular, patients demonstrated significantly reduced activity in the ventral striatum during reward anticipation, which was associated with more severe negative symptoms. During reward receipt, patients exhibited significant activity abnormalities in striatum and prefrontal cortex (Radua et al., 2015; Zeng et al., 2022). Reduced striatal activity during reward anticipation was ameliorated after both six weeks of antipsychotic treatment (Nielsen et al., 2012; Wulff et al., 2020) and one year of psychological treatment (Smucny et al., 2022).

An increasing number of neuroimaging studies examined the acute effects of CBD on brain function in psychosis (Batalla et al., 2021). For example, in both individuals at clinical high risk for psychosis and patients with established psychosis, a single dose of CBD attenuated activation of the insula during reward anticipation (Wilson et al., 2019; Gunasekera et al., 2022). In addition, CBD administration to at-risk individuals resulted in an activation level in the striatum, parahippocampal gyrus and midbrain during a verbal memory task that was intermediate between the response in healthy controls without any drug and at-risk individuals after placebo (Bhattacharyya et al., 2018). Finally, as shown with ^{1}H-MRS, hippocampal glutamate concentrations were significantly decreased in psychosis patients after CBD administration compared to placebo (O'Neill et al., 2021). However, although the above-mentioned studies provide evidence for the acute brain effects of CBD in the context psychosis, the neurobiological mechanisms underlying the antipsychotic profile of CBD are currently unknown.

In the current randomised, double-blind, placebo-controlled, between-subjects intervention study, we investigated the impact of 28-day adjunctive CBD or placebo treatment (600 mg daily) on brain function and metabolism of recent-onset patients with a psychotic disorder as measured with MRI. Resting state functional connectivity, prefrontal metabolite concentrations including glutamate and GABA, brain activity patterns during reward anticipation and receipt as well as symptomatology and cognition were determined before and after treatment. We anticipated that CBD treatment would attenuate abnormalities in brain function and metabolism as previously established in psychosis patients.

2. Material and methods

This study was approved by the Medical Research Ethics Committee of the UMC Utrecht (protocol number NL58805.041.16), and the study was conducted in accordance with the Declaration of Helsinki. All participants provided informed, written consent.

2.1. Participants

A total of 32 recent-onset patients (<5 years) with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of schizophrenia or a related psychotic disorder (schizophreniform disorder, schizoaffective disorder, psychosis not otherwise specified) were recruited from the University Medical Center (UMC) Utrecht. 31 patients completed the study protocol, one patient dropped out (see Supplemental CONSORT flow diagram). All patients were treated with a stable dose of one antipsychotic agent in the month prior to study inclusion. They did not use corticosteroids, non-steroidal anti-inflammatory drugs or medication other than antipsychotics that had a clinically relevant interaction with CBD (e.g. carbamazepine, fluvoxamine) within 2 weeks prior to study inclusion. Patients were excluded in case of neurological disorders, history of head injury, IQ < 70, MRI contraindications and pregnancy. Additional exclusion criteria were intake of CBD within a month before study inclusion, daily use of alcohol or drugs within three months prior to study entry, and a positive urine test on any drug of abuse except cannabis.

2.2. Design and procedure

Using a randomised, double-blind, placebo-controlled, between-subjects study design, patients were treated with 600 mg oral CBD or placebo daily (Trigal Pharma, Vienna, Austria) for 28 days, in addition to their regular antipsychotic medication. CBD was given as 200 mg capsules of which three were taken daily at once. Placebo capsules were matched in size and appearance. All measurements were performed at the UMC Utrecht on two identical test days before and after treatment. Both study days included assessments of symptomatology, cognition and brain function using MRI. Antipsychotic medication was converted to chlorpromazine equivalents according to standard guidelines (Leucht et al., 2003). Premorbid IQ was assessed with the Dutch version of the National Adult Reading Test (Schmand et al., 1991). Venous blood samples were taken on both test days to measure CBD, THC and 11-nor-9-carboxy-THC (THC-COOH) plasma concentrations.

2.3. Drug adherence and adverse events

Drug adherence and adverse events were assessed in weekly telephone calls and at follow-up. Measures of drug adherence included number of returned capsules, self-report on medication intake and the Medication Adherence Questionnaire (Morisky et al., 1986).

2.4. Clinical and cognitive assessments

Symptomatology and psychosocial functioning was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), Hamilton Depression Scale (HAM-D) (Hamilton, 1960)), Young Mania Rating Scale (YMRS) (Young et al., 1978)), Clinical Global Impression (CGI) (Guy, 1976), Global Assessment of Functioning scale (GAF) (Hall, 1995), and Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992). Cognitive functioning was examined using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004), with all individual test scores converted into standardized (t and z) and composite scores corrected for age and gender (Keefe et al., 2008). Substance use was determined with the WHO Assist 3.0 (WHO Assist Working Group, 2002).

2.5. Monetary incentive delay task

Reward anticipation and receipt was measured using a previously applied modified version of the Monetary Incentive Delay task (Vink et al., 2016). In short, trials were potentially rewarding (30 trials) or non-rewarding (30 trials), as indicated by a cue at the start of the trial. Participants were instructed to respond as fast as possible to a target presented after the cue. They could win 2 euros in a potentially rewarding trial when they responded during target presentation. Subsequent feedback notified participants of their performance. Target duration was individually adjusted to ensure that each participant could succeed in 50% of the trials. This adjustment was based on twenty practice trials, presented before the start of the task (Fig. 1).

2.6. Magnetic Resonance Imaging

MRI data were collected on a Philips 3.0 T MRI scanner (Philips Medical Systems, Best, the Netherlands). Sequences included a T1-weighted structural image for both registration purposes and ^{1}H-MRS voxel placement, resting state functional MRI (240 functional images), ^{1}H-Magnetic Resonance Spectroscopy and functional MRI during a reward task (366 functional images). All MRI specifics including scanning parameters and pre-processing procedures are described in the Supplemental Methods.

2.7. Resting state functional MRI

One participant did not have a complete resting state functional MRI data set due to scanner difficulties. No patients were excluded due to excessive motion, defined as mean relative displacement (Root-Mean Squared-Framewise Displacement) $>$ 0.55 mm (Satterthwaite et al., 2013), resulting in 14 participants in the placebo and 16 participants in the CBD group.

Resting state functional connectivity was assessed within and between three large-scale functional brain networks: default mode network (DMN), executive control network (ECN) and salience network (SAL). Individual time series were extracted from the core nodes of each of the three networks as previously defined: medial prefrontal cortex and posterior cingulate cortex for DMN (two nodes), bilateral dorsolateral prefrontal cortex and posterior parietal cortex (four nodes) for ECN, and anterior cingulate cortex and bilateral anterior insula (three nodes) for SAL (Fig. 2A) (Young et al., 2017). Correlation coefficients were calculated and normalised using Fisher Z-transformation, indicating functional connectivity strength.

2.8. ^{1}H-Magnetic Resonance Spectroscopy

^{1}H-MRS spectra were obtained in the medial prefrontal cortex using MEGA-PRESS (Fig. 2B) (Mullins et al., 2014). Water-scaled values of GABA, glutamate, Glx (combined measure of glutamate and glutamine), glutathione, N-acetyl-aspartate and NAA + NAAG (combined measure of N-acetyl-aspartate and N-acetyl-aspartyl-glutamate) were obtained and corrected for CSF voxel content (Supplemental Methods) (Bossong et al., 2018). Table S1 shows scan quality parameters and voxel tissue composition. One participant was excluded from data analysis due to poorly fitted metabolite peaks, resulting in 14 participants in the placebo and 16 participants in the CBD group.

2.9. Reward functional MRI

Two participants did not have complete reward functional MRI data sets due to scanner difficulties and one participant was excluded due to excessive motion (mean relative displacement $>$0.55 mm) (Satterthwaite et al., 2013), resulting in 13 participants in the placebo and 15 participants in the CBD group.

Group activity maps were created for reward anticipation (anticipation reward vs anticipation neutral) and reward receipt (receipt hit win vs receipt hit neutral). For whole-brain voxel-wise group analyses, follow-up minus baseline images were used in paired sample t-tests in SPM12 (CBD vs placebo). Results were FWE-corrected at cluster-level (p

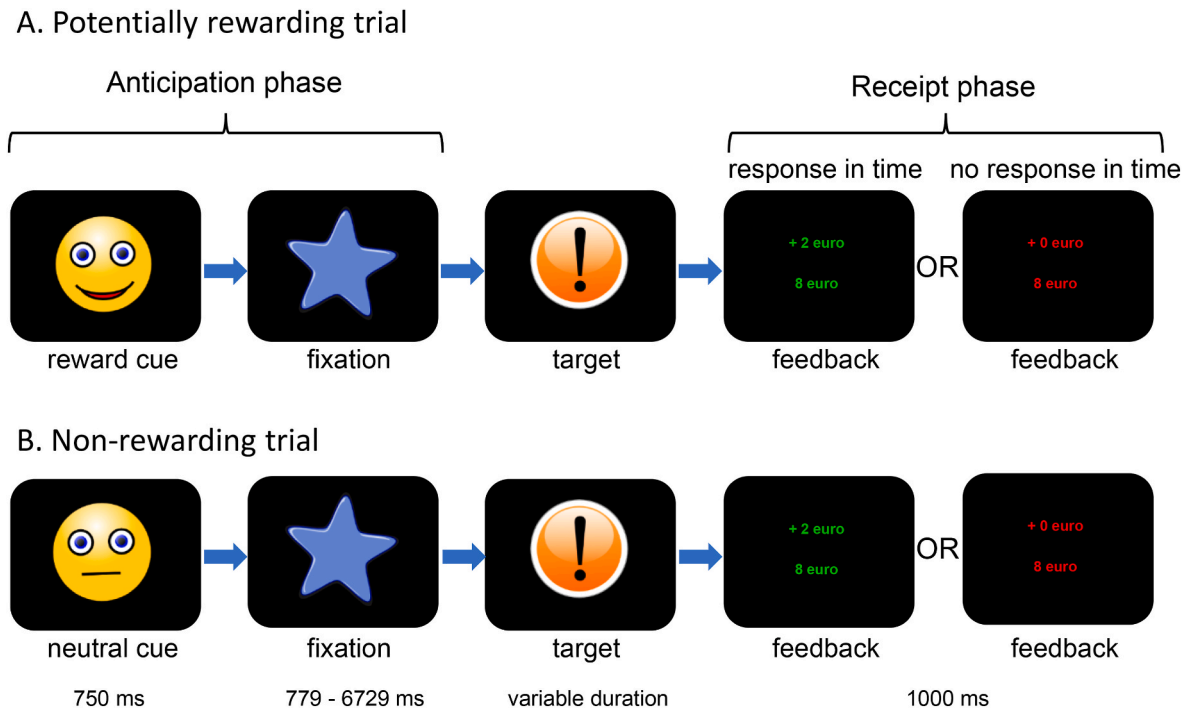

Fig. 1. Schematic representation of the applied modified version of the Monetary Incentive Delay task. Each trial started with the presentation of a cue signalling either a potentially rewarding (A) or a non-rewarding neutral trial (B). After the cue, a target was presented to which subjects had to respond as fast as possible by pressing a button. The time between cue and target presentation (anticipation phase) varied between trials. At the end of each trial, visual feedback on performance was provided (receipt phase).

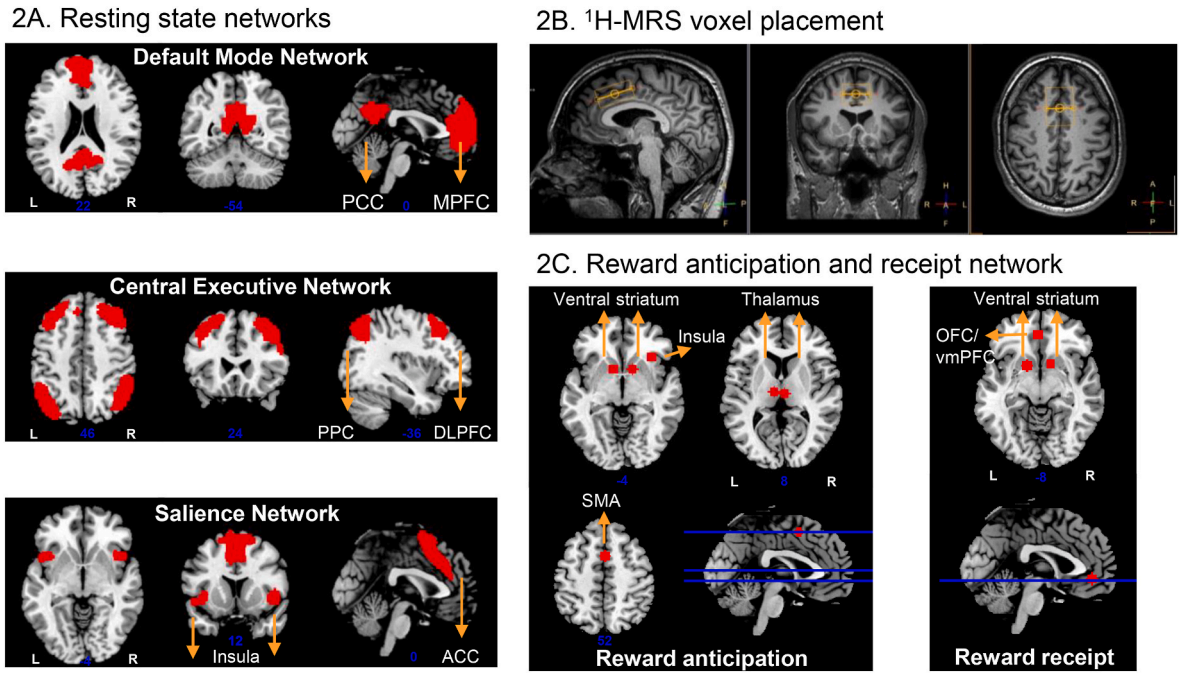

Fig. 2. The effect of CBD treatment was examined on 2 A) functional connectivity within and between resting state networks, 2 B) prefrontal metabolite concentrations as measured with ^{1}H-MRS, 2C) activity patterns in brain networks significantly involved in reward anticipation and receipt. ACC, Anterior Cingulate Cortex; DLPFC, Dorsolateral Prefrontal Cortex; L, left; R, right; MPFC, Medial Prefrontal Cortex; OFC/vmPFC, Orbitofrontal Cortex/ventro-medial Prefrontal Cortex; PCC, Posterior Cingulate Cortex; PPC, Posterior Parietal Cortex; SMA, Supplementary Motor Cortex.

< 0.05). For a region of interest approach, regression coefficients (mean beta values) were extracted from 6 mm spheres placed around MNI coordinates of brain regions significantly involved in reward anticipation and receipt, based on an extensive meta-analysis (Fig. 2C; Table S5) (Oldham et al., 2018).

2.10. Statistical analysis

Group differences in baseline clinical and demographic variables and in measures of drug adherence and adverse events were assessed using two-sample independent t or chi-square tests. To examine the impact of CBD treatment on cannabinoid plasma concentrations, clinical and cognitive assessments, resting state functional connectivity, prefrontal metabolite concentrations and reward processing, multivariate approaches to repeated measures ANOVA were used, with time (baseline and follow-up) as within-subject and treatment (placebo and CBD) as between-subject factors. Reward task performance was analysed with task condition (neutral and reward) as additional within-subject factor. $P < 0.05$ was considered statistically significant.

To examine 1) correlations between prefrontal metabolite concentrations and 2) correlations between brain function (i.e. prefrontal metabolite concentrations, functional network connectivity and reward network activity) and measures of symptomatology and cognition (i.e. PANSS positive symptom score, HAM-D total score, GAF score, BACS composite score), treatment effects (follow-up minus baseline values) were calculated. Regression slopes were statistically compared between treatment groups using General Linear Model univariate analyses with treatment group as fixed factor and variables of interest as dependent variable and covariate, respectively. A significant interaction effect between treatment group and covariate of interest indicated a significantly different relationship between dependent variable and covariate for both treatment groups. Correlation metabolite analyses were corrected for multiple comparisons (Glu-GABA, Glu-NAA, Glu-GSH, GABA-NAA, GABA-GSH; thresholded $p < 0.01$). Correlation analyses between brain function and symptomatology aimed for improved interpretation of neuroimaging findings and were therefore considered exploratory. All analyses were performed in SPSS, version 25 (SPSS Inc).

3. Results

3.1. Demographics, drug adherence and adverse events

There were no significant group differences between the placebo and CBD group in any of the demographic or clinical variables at baseline (Table 1). Groups did not show significant differences in drug adherence, as indicated by the reported number of missed capsules (placebo 1.0 ± 1.9 vs CBD 3.5 ± 7.2 capsules, $p = 0.196$), returned capsules (8.4 ± 4.9 vs 9.6 ± 10.0 capsules, $p = 0.672$), and Medication Adherence Questionnaire score (53% high and 40% medium adherence vs 63% high and 25% medium adherence, $p = 0.630$). There was a significant interaction effect between time and treatment in CBD plasma concentrations ($F(1,25) = 40.39$, $p < 0.001$), which indicates increasing CBD plasma concentrations over time in the CBD ($N = 16$, from 0.01 ± 0.03 to 39.36 ± 20.20 ng/ml) but not the placebo group ($N = 11$, from 0.02 ± 0.04 to 0.40 ± 1.13 ng/ml). Both the total number of reported adverse events (20 in the placebo and 38 in the CBD group) and the percentage of patients that reported at least one adverse event (80% for placebo vs 100% for CBD, $p = 0.060$) were higher with CBD treatment (Table S2). Somnolence (placebo: six patients, CBD: seven patients) and nausea (placebo: one patient, CBD: eight patients) were the most commonly reported adverse events. In both groups, most events were mild (80% for placebo and 89% for CBD).

3.2. Clinical and cognitive measures

CBD treatment did not impact any of the clinical or cognitive assessments, as there were no significant interaction effects between time and treatment (Table S3).

3.3. Substance use

THC plasma concentrations showed a significant interaction effect

Table 1
Baseline demographic and clinical characteristics.

	Placebo (n = 15)	Cannabidiol (n = 16)	p value
Age, years	27.5 (6.6)	24.7 (6.3)	.228
Gender (male/female)	10/5	11/5	.901
Years of education	14.3 (3.4)	14.6 (5.7)	.894
NART IQ	105.1 (6.0)	101.7 (8.6)	.207
Handedness (right/left)	13/2	15/1	.505
Body Mass Index	23.3 (4.3)	23.0 (3.0)	.804
Illness duration, years	2.5 (1.6)	2.6 (1.9)	.879
Diagnosis, number (%)			.230
Schizophrenia	5 (33)	10 (63)	
Schizophreniform disorder	1 (7)	0	
Schizoaffective disorder	1 (7)	2 (13)	
Psychosis NOS	8 (53)	4 (25)	
Antipsychotic medication, number (%)			.203
Typical	4 (27)	1 (6)	
Atypical	9 (60)	14 (88)	
None	2 (13)	1 (6)	
Chlorpromazine dose equivalents (mg/day)	259 (188)	294 (171)	.617
PANSS			
Positive symptom scor	13.7 (6.0)	12.8 (4.8)	.662
Negative symptom score	13.0 (4.9)	10.8 (3.8)	.174
General symptom score	28.3 (7.0)	28.0 (5.6)	.907
Total symptom score	54.9 (14.0)	51.6 (11.0)	.468
GAF score	56.7 (13.5)	60.1 (9.7)	.416
SOFAS score	56.7 (13.5)	62.3 (12.2)	.187
HAM-D score	11.2 (5.4)	8.4 (3.8)	.101
Substance use			
Cigarettes per day	6.0 (6.9)	6.8 (7.6)	.775
Alcoholic drinks in the last 30 days	10.9 (15.2)	23.7 (42.6)	.283
Frequency of cannabis use in the last 30 days, median (range)[a]	1 (1–5)	1 (1–5)	.730
THC plasma concentration (ng/ml)	1.29 (2.28)	0.56 (0.91)	.313

Results are indicated as mean (SD), unless stated otherwise. GAF, Global Assessment of Functioning scale; HAM-D, Hamilton Depression Rating Scale; IQ, Intelligence Quotient; NART, National Adult Reading Test; NOS, Not Otherwise Specified; PANSS, Positive And Negative Syndrome Scale; SOFAS, Social and Occupational Functioning Assessment Scale; THC, Δ9-tetrahydrocannabinol.

[a] Cannabis use frequency in the last 30 days indicated as 1 = never; 2 = once, 3 = a few times (<once per week), 4 = once a week, 5 = a few times per week (<once per day), 6 = daily.

between time and treatment (F (1,25) = 5.310, p = 0.030), with more strongly increasing THC levels in the placebo than in the CBD group (from 1.21 ± 2.38 to 2.45 ± 3.90; from 0.56 ± 0.91 to 0.63 ± 1.41 ng/ml, respectively). Plasma concentrations of the metabolite THC-COOH showed a trend towards a significant interaction effect between time and treatment (F (1,25) = 3.813, p = 0.062; from 0.36 ± 0.70 to 0.82 ± 1.22 with placebo and from 0.20 ± 0.34 to 0.27 ± 0.59 with CBD). There was no significant interaction effect between time and treatment in total WHO ASSIST score for cannabis use (F (1,29) = 0.9013, p = 0.347; from 8.4 ± 11.5 to 6.7 ± 9.1 with placebo and from 8.2 ± 11.3 to 9.3 ± 12.3 with CBD).

3.4. Resting state functional connectivity

CBD treatment significantly changed functional connectivity in the DMN (i.e. connectivity between medial prefrontal cortex and posterior cingulate cortex), as indicated by a significant interaction effect between time and treatment (F (1,28) = 4.775, p = 0.037). DMN connectivity decreased from 0.77 ± 0.37 to 0.62 ± 0.33 in the placebo group, but increased from 0.59 ± 0.39 to 0.80 ± 0.32 with CBD treatment (Table 2, Fig. 3A). There were no significant interaction effects between time and treatment in functional connectivity within the ECN (F (1,28) = 1.389, p = 0.248) or SAL network (F (1,28) = 0.182, p = 0.673), or between the three functional networks (DMN-ECN, DMN-SAL and ECN-SAL; all p > 0.05) (Table 2).

3.5. ^{1}H-Magnetic Resonance Spectroscopy

CBD treatment did not affect prefrontal metabolite concentrations measured with ^{1}H-MRS, as indicated by an absence of any significant interactions between time and treatment (all p > 0.05) (Table 3). Correlation analyses between prefrontal metabolite concentrations revealed a significantly different relationship between NAA and both GABA (p = 0.008) and glutamate concentrations (p = 0.01) for both treatment groups, with increasing NAA levels associated with increasing GABA and glutamate levels in the placebo (r = 0.568 and r = 0.758) but not the CBD group (r = −0.479 and r = 0.069) (Fig. 3B). Other metabolites did not show significantly different correlations between treatment groups (all p > 0.01).

Table 2
The impact of CBD treatment on resting state functional connectivity.

	Placebo (n = 14)		CBD (n = 16)		ANOVA F (1,28)		
	Baseline	Follow-up	Baseline	Follow-up	Time (p, F)	Treatment (p, F)	Time*treatment (p, F)
Overall Network Connectivity							
DMN (MPFC-PCC)	0.77 (±.37)	.59 (±.39)	.62 (±.33)	.80 (±.32)	.988 (.000)	.740 (.112)	**.037 (4.775)**
ECN	.92 (±.35)	.90 (±.34)	.76 (±.28)	.88 (±.18)	.417 (.678)	.585 (.305)	.248 (1.389)
SAL	.90 (±.39)	.89 (±.34)	.82 (±.32)	.87 (±.23)	.774 (.084)	.104 (2.823)	.673 (.182)
Within Network Connectivity							
ECN							
PPCL-DLPFCL	1.05 (±.41)	1.01 (±.39)	1.14 (±.31)	1.13 (±.27)	.700 (.151)	.356 (.880)	.831 (.046)
PPCL-PPCR	.91 (±.39)	.92 (±.47)	.57 (±.40)	.82 (±.30)	.125 (2.495)	.070 (3.550)	.162 (2.064)
PPCL-DLPFCR	.81 (±.46)	.85 (±.41)	.54 (±.38)	.76 (±.33)	.114 (2.658)	.165 (2.034)	.274 (1.247)
PPCR-DLPFCL	.67 (±.39)	.61 (±.38)	.45 (±.42)	.60 (±.23)	.555 (.357)	.265 (1.292)	.204 (1.690)
PPCR-DLPFCR	1.13 (±.37)	.95 (±.44)	1.17 (±.41)	1.06 (±.25)	.085 (3.197)	.503 (.461)	.626 (.244)
DLPFCR-DLPFCL	.77 (±.30)	.71 (±.47)	.72 (±.25)	.83 (±.34)	.105 (2.800)	.068 (3.609)	.564 (.340)
SAL							
IL-IR	1.06 (±.44)	.93 (±.42)	.93 (±.29)	.92 (±.22)	.322 (1.015)	.500 (.466)	.424 (.658)
IL-ACC	.87 (±.56)	.96 (±.48)	.89 (±.42)	1.05 (±.33)	.189 (1.817)	.691 (.162)	.683 (.170)
IR-ACC	.77 (±.38)	.79 (±.31)	.64 (±.37)	.63 (±.34)	.930 (.008)	.148 (2.217)	.943 (.005)
Between Network Connectivity							
DMN-ECN	.71 (±.38)	.74 (±.29)	.69 (±.37)	.77 (±.29)	.444 (.603)	.953 (.004)	.711 (.140)
DMN-SAL	.50 (±.48)	.60 (±.37)	.25 (±.45)	.47 (±.37)	**.042 (4.521)**	.164 (2.046)	.468 (.542)
ECN-SAL	.75 (±.44)	.72 (±.37)	.38 (±.52)	.57 (±.48)	.404 (.719)	.067 (3.627)	.242 (1.427)

Results are indicated as mean (SD). ACC, Anterior Cingulate Cortex; DMN, Default Mode Network; DLPFCL, Dorsolateral Prefrontal Cortex Left; DLPFCR, Dorsolateral Prefrontal Cortex Right; ECN, Executive Control Network; IL, Anterior Insula Left; IR, Anterior Insula Right; MPFC, Medial Prefrontal Cortex; PCC, Posterior Cingulate Cortex; PPCL, Posterior Parietal Cortex Left; PPCR, Posterior Parietal Cortex Right; SAL, Salience Network.

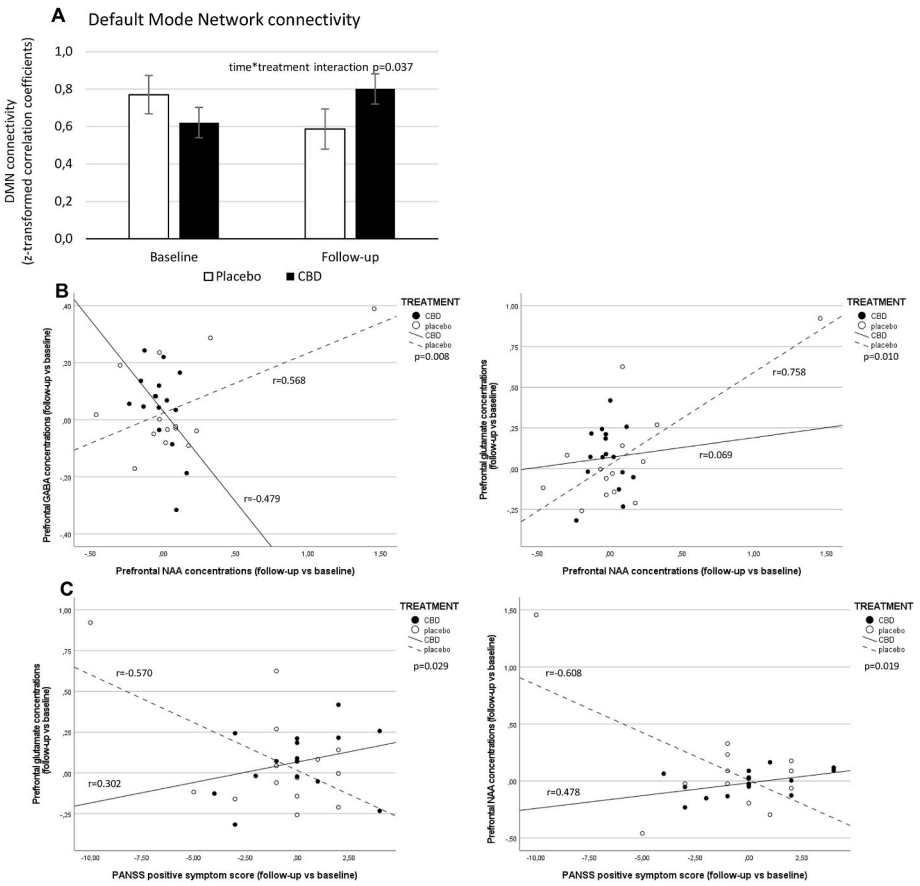

Fig. 3. CBD treatment significantly changed DMN functional connectivity (A). There was a significantly different relationship for both treatment groups B) between N-acetyl-aspartate (NAA) and both GABA and glutamate levels and C) between PANSS positive symptom scores and both glutamate and NAA levels.

Table 3
The impact of CBD treatment on prefrontal metabolite concentrations.

	Placebo (n = 14)		CBD (n = 16)		ANOVA F (1,28)		
	Baseline	Follow-up	Baseline	Follow-up	Time (p, F)	Treatment (p, F)	Time*treatment (p, F)
GABA	1.12 (±.10)	1.17 (±.14)	1.09 (±.11)	1.14 (±.16)	.140 (2.31)	.415 (.69)	.983 (.00)
Glutamate	2.79 (±.26)	2.89 (±.35)	2.91 (±.25)	2.98 (±.29)	.146 (2.24)	.246 (1.41)	.901 (.02)
Glx (Glu + Gln)	3.39 (±.30)	3.56 (±.32)	3.47 (±.34)	3.56 (±.31)	.068 (3.60)	.716 (.14)	.595 (.29)
Glutathione	0.93 (±.10)	.87 (±.13)	.94 (±.11)	.92 (±.15)	.261 (1.32)	.425 (.66)	.441 (.61)
NAA	3.98 (±.32)	4.08 (±.41)	4.04 (±.25)	4.02 (±.24)	.477 (.52)	.991 (.00)	.327 (1.00)
NAA + NAAG	3.98 (±.32)	4.09 (±.43)	4.04 (±.25)	4.02 (±.24)	.463 (.55)	.964 (.00)	.321 (1.02)

Results are indicated as mean (SD). GABA, gamma-aminobutyric acid; Gln, glutamine; Glu, glutamate; GSH, Glutathione; NAA, N-acetylaspartate; NAAG, N-acetyl-aspartyl-glutamate.

3.6. Reward processing

Reward task performance.

Task condition had a significant effect on reaction time ($F(1,27) = 13.68$, $p = 0.001$), with longer reaction times for neutral trials (232 ± 39 ms) compared with reward trials (214 ± 46 ms). There were no other significant effects (Table S4).

Brain activity during reward anticipation and receipt.

Region of interest analyses did not reveal any significant interaction effects between time and treatment on activity in any of the brain areas or their combined networks (all $p > 0.05$) (Table 4). Whole-brain voxel-wise paired sample t-tests did not show any significant differences in brain activity patterns between placebo and CBD treatment during reward anticipation or receipt (FWE-corrected at cluster-level, $p > 0.05$).

3.7. Correlations with symptomatology and cognition

Exploratory correlation analyses revealed a significantly different relationship between PANSS positive symptom scores and both prefrontal glutamate ($p = 0.029$) and NAA concentrations ($p = 0.019$) for both treatment groups, with diminishing PANSS scores associated with decreasing glutamate and NAA levels in the CBD ($r = 0.302$ and $r = 0.478$) but not the placebo group ($r = -0.570$ and $r = -0.608$) (Fig. 3C). There were no other significant differences in relationships between brain function and measures of symptomatology and cognition between treatment groups (all $p > 0.05$).

4. Discussion

To our knowledge, this is the first randomised, double-blind, placebo-controlled clinical trial that investigated the impact of adjunctive

Table 4
The impact of CBD treatment on brain activity during reward anticipation and receipt.

	Placebo (n = 13)		CBD (n = 15)		ANOVA F (1,26)		
	Baseline	Follow-up	Baseline	Follow-up	Time (p, F)	Treatment (p, F)	Time*treatment (p, F)
Reward anticipation							
Anticipation Network	0.19 (±.29)	.15 (±.25)	.29 (±.28)	.19 (±.24)	.142 (2.298)	.443 (.608)	.516 (.434)
Ventral Striatum R	.15 (±.32)	.12 (±.18)	.22 (±.17)	.13 (±.17)	.259 (.294)	.567 (.336)	.592 (.294)
Ventral Striatum L	.16 (±.29)	.15 (±.15)	.18 (±.19)	.12 (±.15)	.403 (.722)	.561 (.347)	.946 (.005)
Thalamus R	.14 (±.44)	.05 (±.56)	.43 (±.52)	.21 (±.34)	.101 (2.897)	.154 (2.161)	.498 (.473)
Thalamus L	.10 (±.33)	.08 (±.35)	.25 (±.38)	.16 (±.28)	.404 (.719)	.266 (1.292)	.599 (.283)
Supplementary Motor Area R	.34 (±.41)	.28 (±.43)	.45 (±.42)	.32 (±.48)	.214 (1.631)	.604 (.275)	.687 (.166)
Anterior Insula R	.27 (±.29)	.24 (±.28)	.22 (±.23)	.16 (±.24)	.528 (.410)	.259 (.294)	.824 (.050)
Reward receipt							
Receipt Network	.28 (±.69)	−.025 (±.99)	.30 (±.46)	.24 (±.27)	.281 (1.213)	.434 (.632)	.484 (.505)
Ventral Striatum R	−.02 (±.77)	.23 (±.92)	.03 (±.57)	.00 (±.41)	.541 (.383)	.619 (.254)	.452 (.583)
OFC/vmPFC L	.68 (±.73)	.04 (±1.42)	.87 (±.70)	.65 (±.41)	.066 (3.695)	.111 (2.718)	.358 (.874)
Ventral Striatum L	.17 (±.1.04)	−.34 (±.1.16)	.01 (±.62)	.06 (±.48)	.320 (1.029)	.613 (.261)	.218 (1.594)

Results are indicated as mean (SD). Regions of interest based on Oldham et al. (2018). Also see Fig. 2. L, left; R, right.

CBD treatment on resting state functional connectivity, prefrontal metabolite concentrations and reward processing in recent-onset patients with a psychotic disorder. Here we demonstrated that CBD treatment was associated with increased connectivity in the default mode network compared to placebo. Although there were no significant treatment effects on prefrontal metabolite concentrations, we showed that increased N-acetyl-aspartate (NAA) concentrations over time were related to both rising GABA and glutamate levels in the placebo, but not the CBD group. In addition, decreasing PANSS positive symptom scores were associated with both diminishing glutamate and NAA levels in the CBD, but not the placebo group. CBD treatment did not affect brain activity patterns during reward anticipation and receipt or functional connectivity in executive and salience networks.

Our findings show that CBD treatment significantly changed functional connectivity in the DMN of early psychosis patients. These results are consistent with the notion that functional brain dysconnectivity represents an important feature of psychotic disorders. An increasing amount of evidence indicates that psychosis patients exhibit impaired resting state connectivity, in particular in important functional brain systems such as the DMN (Pettersson-Yeo et al., 2011; O'Neill et al., 2019). The DMN is involved in internal modes of cognition, such as examining one's own thoughts, emotions and perceptions, and therefore likely contributes to psychosis vulnerability (Pettersson-Yeo et al., 2011; O'Neill et al., 2019). Our results indicate that CBD treatment attenuate impaired DMN connectivity, which may be one of the mechanisms involved in the therapeutic effects of CBD. This is in line with previous resting state studies that showed that impaired DMN connectivity in psychosis patients ameliorated with antipsychotic treatment (Wang et al., 2017; Chopra et al., 2021). Although this is the first study examining the impact of longer-term CBD treatment on resting state functional connectivity in patients with psychosis, our findings are also consistent with functional MRI studies that demonstrated attenuating effects of acute single-dose CBD administration to clinical high-risk individuals and patients with established psychosis on brain activity patterns related to reward processing and verbal memory (Bhattacharyya et al., 2018; Wilson et al., 2019; Gunasekera et al., 2022).

We did not find significant effects of CBD treatment on prefrontal metabolite concentrations. This contrasts our hypotheses, because meta-analyses of ^{1}H-MRS studies indicated that early psychosis patients exhibit increased levels of glutamate metabolites and reduced GABA concentrations (Merritt et al., 2016; Nakahara et al., 2022). Most longitudinal studies with conventional antipsychotic treatment demonstrated reductions in glutamatergic brain metabolite levels (Egerton et al., 2017; Kubota et al., 2020), although unchanged prefrontal Glx concentrations have also been reported (Liemburg et al., 2018; Kraguljac et al., 2019). One possible explanation for our findings is that the antipsychotic effect of CBD is not necessarily dependent on alterations in prefrontal glutamate and GABA concentrations. However, this seems unlikely as CBD appears to act on CB_1/CB_2, serotonin type 1 A ($5HT_{1A}$), vanilloid type 1 (TRPV-1) and GPR55 receptors (Gururajan and Malone, 2016), thereby playing an important role in the on-demand regulation of glutamate and GABA neurotransmission (Bossong and Niesink, 2010).

There was a significantly different relationship of NAA and both GABA and glutamate levels between treatment groups, with increasing NAA concentrations associated with rising GABA and glutamate levels in the placebo, but not the CBD group. NAA is commonly interpreted as a marker of neuronal integrity (Moffett et al., 2007). Previous ^{1}H-MRS studies demonstrated positive correlations between NAA and glutamatergic metabolite concentrations in the anterior cingulate and prefrontal cortex of patients with psychosis (Kraguljac et al., 2012; Liemburg et al., 2016). Interestingly, Kegeles et al. (2012) showed that prefrontal NAA levels were positively related to glutamatergic metabolite concentrations in unmedicated psychosis patients but not in medicated patients or healthy controls, whereas prefrontal NAA and GABA levels were correlated in both medicated and unmedicated patients but not controls. In addition, in our study, there was a significant difference in the relationship of PANSS positive symptom scores and both glutamate and NAA levels between treatment groups, with decreasing positive symptom severity associated with both diminishing glutamate and NAA concentrations in the CBD group. This finding suggests that alterations in prefrontal glutamate and NAA concentrations might be involved in the therapeutic effects of CBD. This is consistent with meta-analyses showing that lower brain glutamate levels of psychosis patients are associated with antipsychotic exposure (Merritt et al., 2021) and with earlier ^{1}H-MRS studies reporting that reduced levels of glutamate brain metabolites are related with symptomatic improvement after conventional antipsychotic treatment (Egerton et al., 2017; Merritt et al., 2019), although opposite treatment effects have also been demonstrated (De la Fuente et al., 2013).

Against our expectations, CBD treatment did not affect brain activity during reward anticipation or receipt. We anticipated that CBD would in particular affect striatal and prefrontal responses related to reward processing, because these functional abnormalities were previously established in psychosis patients (Radua et al., 2015; Zeng et al., 2022). Moreover, our results contrast with findings from previous functional MRI studies that demonstrated ameliorating effects of both conventional antipsychotic and psychological treatment on striatal activity during reward anticipation in patients (Nielsen et al., 2012; Wulff et al., 2020; Smucny et al., 2022). This may indicate that the antipsychotic profile of CBD does not rely on the manipulation of reward processing. Two previous neuroimaging studies with acute CBD administration to at-risk individuals and patients with established psychosis also failed to demonstrate striatal CBD effects during reward anticipation, although they did show attenuated insular activation in both groups (Wilson et al., 2019; Gunasekera et al., 2022). In addition to differences in study design (acute vs longer-term treatment, illness stage), discrepant

findings could be explained by the a priori selection of investigated brain regions. We did not show an impact of CBD treatment on brain areas that are significantly involved in reward anticipation and receipt, which mainly include striatal, thalamic and prefrontal regions (Oldham et al., 2018).

We demonstrated a stronger increase in THC plasma concentrations in the placebo than in the CBD group. Although this is a preliminary finding which warrants further investigation, it may be an indication that CBD treatment affects cannabis use. CBD at comparable doses has shown promising results for the treatment of cannabis use disorder (Freeman et al., 2020). Future research should further elucidate how CBD exposure impacts cannabis use, and how that relates to clinical and functional outcome of psychosis patients.

This study has several limitations. First, sample sizes were moderate resulting in limited statistical power, although appropriate to address the main study objectives in this pharmacological neuroimaging study. Second, illness severity of patients included in our study was relatively low, limiting the possibility for symptomatic improvement with CBD treatment. Third, adjunctive CBD treatment was used instead of a monotherapy design. However, this maximizes clinical impact as it follows previous clinical trials on the therapeutic effects of CBD in psychosis (Boggs et al., 2018; McGuire et al., 2018) and allocation of psychosis patients to placebo seems ethically questionable.

In conclusion, this study shows that adjunctive CBD treatment of recent-onset patients with a psychotic disorder induces changes in default mode functional connectivity, but not prefrontal metabolite concentrations or brain activity patterns during reward processing. These findings support the notion that CBD treatment attenuate impaired default mode connectivity of patients with psychosis, which may be involved in the therapeutic effects of CBD.

Author statement

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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