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Cannabidiol attenuates insular activity during motivational salience processing in patients with early psychosis

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Original Article

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Abstract

Background. The mechanisms underlying the antipsychotic potential of cannabidiol (CBD) remain unclear but growing evidence indicates that dysfunction in the insula, a key brain region involved in the processing of motivationally salient stimuli, may have a role in the pathophysiology of psychosis. Here, we investigate whether the antipsychotic mechanisms of CBD are underpinned by their effects on insular activation, known to be involved in salience processing.

Methods. A within-subject, crossover, double-blind, placebo-controlled investigation of 19 healthy controls and 15 participants with early psychosis was conducted. Administration of a single dose of CBD was compared with placebo in psychosis participants while performing the monetary incentive delay task, an fMRI paradigm. Anticipation of reward and loss were used to contrast motivationally salient stimuli against a neutral control condition.

Results. No group differences in brain activation between psychosis patients compared with healthy controls were observed. Attenuation of insula activation was observed following CBD, compared to placebo. Sensitivity analyses controlling for current cannabis use history did not affect the main results.

Conclusion. Our findings are in accordance with existing evidence suggesting that CBD modulates brain regions involved in salience processing. Whether such effects underlie the putative antipsychotic effects of CBD remains to be investigated.

Introduction

Reward processing includes the attribution of 'motivational salience', incorporating both approach behaviour towards a rewarding outcome, and the avoidance of an aversive outcome (Berridge, 2012) which has been linked to mesolimbic dopaminergic neurons (Berridge, 2012; Ferguson, Ahrens, Longyear, & Aldridge, 2020). One of the prevailing theories of psychosis suggests that the attribution of motivational significance or salience to contextually irrelevant or neutral stimuli may be associated with the onset of psychotic symptoms (Chapman, 1966; Kapur, 2003; McGhiee & Chapman, 1961), consistent with the idea that this may be induced by elevated dopaminergic release within mesolimbic reward pathways causing aberrant stimulus-reinforcement (Miller, 1976).

Traditionally, the aberrant salience hypothesis has focused on the striatum and midbrain, with patients with psychosis presenting with increased dopamine levels (Howes et al., 2012) and attenuated striatal activation during the anticipation of reward, indicative of the abnormal processing of reward-based stimuli (Radua et al., 2015). Recent evidence has implicated a 'salience' network, functioning to select internal and externally generated signals for higher-order processing (Seeley, 2019; Seeley et al., 2007; Uddin, 2015) and in particular, the insular cortex, a core component within the network for its role in psychosis (Wylie & Tregellas, 2010). The insula functions as a network hub that coordinates information across multiple cognitive domains and processes (Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017). A range of insular abnormalities have been reported in established psychotic disorders including altered activation (Moran et al., 2013; Palaniyappan, Simmonite, White, Liddle, & Liddle, 2013; Smieskova et al., 2014), volume (Goodkind et al., 2015; Sheffield et al., 2021; Shepherd, Matheson, Laurens, Carr, & Green, 2012), and connectivity (Li et al., 2019; O'Neill, Mechelli, & Bhattacharyya, 2019; Sheffield, Rogers, Blackford, Heckers, & Woodward, 2020; Tian, Zalesky, Bousman, Everall, & Pantelis, 2019). In the clinical high risk for psychosis state, compared to healthy controls, there have also been reports of altered insula activation (Wilson et al., 2019), volume (Borgwardt et al., 2007; Chan, Di, McAlonan, & Gong, 2011; Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008; Lee et al., 2016; Takahashi et al., 2009b), and functional connectivity with other salience network regions

(Li et al., 2019; Wang et al., 2016; Wotruba et al., 2014). Moreover, correlation between symptom severity and degree of insular atrophy (Takahashi et al., 2009a), or activation, indexed using fMRI (Smieskova et al., 2014; Thusius, Romanowicz, Mlynek, & Sola, 2018; Walter et al., 2016; Wilson et al., 2019) have been reported. These findings have consistently highlighted insular pathology across early stages of psychosis and suggest that insular dysfunction may hold a prominent role in the onset of psychotic symptoms.

There is growing interest in the antipsychotic potential of cannabidiol (CBD), a non-addictive substance present in the extract of *Cannabis sativa*, following evidence that it may oppose the psychotomimetic and neurophysiological effects of delta 9-tetrahydrocannabinol (THC) in healthy individuals (Bhattacharyya et al., 2010; Englund et al., 2013; Gunasekera, Davies, Martin-Santos, & Bhattacharyya, 2021) complemented by preliminary evidence of antipsychotic efficacy in patients with psychosis in some (Leweke et al., 2012; McGuire et al., 2018) but not all (Boggs et al., 2018) clinical trials, as well as an excellent tolerability profile across different age groups (Chesney et al., 2020; Velayudhan, McGoohan, & Bhattacharyya, 2021).

Consistent with this, there is a growing body of work investigating mechanisms that may underlie the antipsychotic potential of CBD. We have recently shown that CBD may normalise impaired activation of the medial temporal lobe, midbrain, striatum, and insula in the clinical high-risk state for psychosis (Bhattacharyya et al., 2018; Davies et al., 2020; Wilson et al., 2019) and established psychosis (O'Neill et al., 2021a, 2021b). However, the precise neurocognitive mechanisms underlying the therapeutic potential of CBD remain unclear (Bonaccorso, Ricciardi, Zangani, Chiappini, & Schifano, 2019; Davies & Bhattacharyya, 2019; Velayudhan et al., 2014), particularly when considering its effect on motivational salience (Gunasekera, Diederen, & Bhattacharyya, 2022). In a previous study in people at clinical high risk for psychosis, we have reported that CBD attenuated insular hyperactivation while processing motivationally salient stimuli during the anticipation phase of the monetary incentive delay task (MIDT) (Wilson et al., 2019), a reward processing paradigm adapted for fMRI (Knutson, Westdorp, Kaiser, & Hommer, 2000). This study investigated people at clinical high risk for psychosis, as opposed to those with established psychosis, and employed a between-group design. Hence, one cannot completely rule out the possibility that between-group (placebo-treated and CBD-treated patient groups) differences observed in the study were a result of between-subject variability rather than truly an effect of treatment with CBD. These limitations prevented direct examination of the effects of CBD, compared to placebo, with brain activation and psychopathology change in the same participants.

Therefore, we investigated the effects of CBD on brain activation, indexed using the blood-oxygen-level-dependent (BOLD) haemodynamic response measured using functional resonance imaging (fMRI) during motivational salience processing in patients with early psychosis (PSY). Here, we defined early psychosis as a psychotic mental disorder diagnosis within 5 years of presentation to clinical services (Malla et al., 2017). Using a within-subject design, we investigated whether acute CBD administration would attenuate abnormal brain activation within PSY, compared to placebo. We also compared PSY patients under placebo to a group of healthy controls studied under identical conditions but not receiving any treatment. This was conducted to help understand whether the acute effects of CBD, compared to placebo, on brain activation in psychosis patients overlapped with brain regions that were differentially activated in placebo-treated psychosis patients compared to healthy controls (i.e. regions affected by psychosis) and to examine whether the direction of any CBD-related change in activation in patients was consistent with a likely therapeutic benefit. We used the MIDT paradigm which comprises of 'anticipation' and 'feedback' conditions. Here we have focused on the anticipation condition, as in our previous study (Wilson et al., 2019). Meta-analytic findings have identified robust insular engagement during the anticipation of both reward and loss (Wilson et al., 2018). Therefore, consistent with our previous study (Wilson et al., 2019) and other work (Nielsen et al., 2012a, 2012b), we examined all motivationally salient (reward and loss avoidance) conditions of the MIDT. Based on results in our previous study in patients at clinical high-risk psychosis, we predicted that PSY participants would express greater levels of activation in the insula, compared with healthy controls, and that a single dose of CBD would attenuate this abnormal brain activity. Exploratory analyses examined effects at the whole-brain level and within a hippocampus-midbrain-striatum mask.

Methods

The methods are reported in full in the online Supplementary Methods and have been summarised below in the interest of brevity.

The study protocol was approved by the appropriate research ethics committee (reference: 14/LO/1861). All participants took part after providing written informed consent. Participants with early psychosis were recruited from mental health services in South London, United Kingdom. Fifteen participants attended for 2 study days, and 14 completed two fMRI scanning sessions [see (O'Neill et al., 2021b)]. Patients were included if they had a psychotic mental disorder diagnosis (meeting criteria for schizophrenia, schizophreniform, or brief psychotic disorder, but no other Axis I diagnoses) within 5 years of illness onset and did not have a diagnosis of alcohol or a substance use disorder (excluding cannabis). Nineteen healthy control (HC) participants, who were not administered CBD or placebo were also included. Additional inclusion/ exclusion criteria as well as advice regarding caffeine, alcohol and other drugs use and urine drug screening and smokerlyzer tests on study days for both participant groups are reported in online Supplementary Methods.

We employed a within-subject, crossover, double-blind randomised placebo-controlled design, in patients, over 2 sessions with a 1-week interval to allow for the washout of CBD. Psychosis participants were administered either a 600 mg CBD (approx. 99.9% pure) or an identical gelatine placebo (PLB) capsule. One hundred and eighty minutes after drug administration participants underwent fMRI scanning and performed the MIDT. Blood samples were obtained at three-time points: (T1) 60 min before drug administration, (T2) 60 min post drug administration, (T3) 270 min post-drug administration. The Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987) was used to assess psychopathology at timepoints T1 and T3.

The data presented in this study is part of a larger study which utilised a number of neuroimaging approaches (O'Neill et al., 2021a, 2021b). For the overall study, an initial power calculation was conducted (please see online Supplementary Methods), however, this focused on brain activation during a verbal learning task

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(O'Neill et al., 2021b) rather than specifically for the MIDT that we report here.

Monetary incentive delay task

Participants completed two runs of the MIDT (see online Supplementary Fig. S1 for task schematic) each consisting of 48 individual trials (approximately 16 min in two consecutive 8-min runs). The MIDT was comprised of four reward valence conditions signalled by learned visual cues: neutral (£0.00), small reward (£0.20), large reward (£2.00), and loss (£2.00). A total of 12 trials were used for each. All participants started with £10.00 and were provided with payment based on the actual monetary reward they earned over the two runs of the task on each study day. Participants underwent standardised training prior to entering the scanner.

Data analysis

Imaging analysis

Functional MRI data were pre-processed and analysed using SPM8. Data pre-processing steps consisted of functional image realignment, anatomical scan co-registration, spatial normalisation into a standard MNI space via unified segmentation, and smoothing via Gaussian filter (FWHM = 8 mm). Using general linear model regression with factors time-locked to task events convolved with a canonical hemodynamic response function, the regression coefficient (beta weight) for each condition at each voxel was determined. Twelve regressors were included in the task design: 4 anticipatory conditions (win small, win large, loss, neutral), 7 feedback conditions (feedback was displayed for neutral, and for the hit or miss of win small, win large and loss conditions), and 1 regressor that modelled all 4 anticipation conditions collapsed together. As we were interested in the effect of group on salience processing, we examined this across all reward valence conditions (win small, win large, and loss, each contrasted with neutral) during anticipation.

Group comparisons of HC-*v.*-PSY-PLB and PSY-PLB-*v.*-PSY-CBD were analysed using a flexible factorial model in SPM8. The between-group model was created by specifying the factors 'Group' and 'Reward Valence Conditions'. The within-group model was created in the same way with the additional 'Subject' factor specified in the design matrix. Using F contrasts (1 1 1 −1 −1 −1) the group by reward anticipation effect was determined. Contrast weights were extracted to determine contrast directions.

Brain activation was examined using region of interest (ROI) analysis. Two ROI masks were created using Pick Atlas in SPM8: a primary bilateral insula mask and a secondary mask comprising the hippocampus, midbrain and striatum (composed of bilateral medial hippocampi, subicula, caudate, putamen, pallidum and midbrain). Effects at the whole-brain level were also investigated. All neuroimaging results are reported using a family-wise error threshold.

Linear regression analysis was then conducted to determine if a relationship between mean contrast estimates during motivational salience processing (across anticipation win small, win large, and avoid lose conditions; extracted from the insula anatomical ROI) and PANSS total score change on study day (T1 minus T3) was significantly different under CBD compared with the placebo condition.

Performance analysis

Two group comparisons (HC-*v.*-PSY-PLB and PSY-PLB-*v.*-PSY-CBD) were carried out using Python 3.8.8 (Python Software Foundation, 2016) (code available at https://github.com/bgunasekera/Hemp/blob/main/megafile_analysis.py). Pairwise comparisons were applied on mean monetary reward (£), accuracy (correct responses %), reaction time (ms) and false-starts [a response < 100 ms was considered a false start (Brosnan, Hayes, & Harrison, 2017)]. *t* tests were conducted for mean monetary reward, analysis of variance (ANOVA) for mean reaction time, and binary logistic regression for accuracy, and false-starts. Repeated measures were specified for PSY-PLB-*v.*-PSY-CBD during *t* test and anova comparisons.

Results

Socio-demographic and substance use history of the participant groups have been reported before (O'Neill et al., 2021b) and are summarised again in Table 1. Although, one patient tested positive on urine drug screen for phencyclidine (PCP) on both study days, this was disregarded as the person was receiving venlafaxine, which has been reported to induce false PCP positive results (Landy & Kripalani, 2015). Antipsychotic medication was being used by all participants, except for one who had discontinued use of their prescribed olanzapine medication.

Clinical characteristics, and the change in symptoms as a result of treatment of the participants taking part in this study have been reported before (O'Neill et al., 2021a) and are summarised here again (Table 2). On each study day, prior to drug administration, there was no significant difference in total PANSS between PSY-CBD and PSY-PLB groups ($z = -1.07$, $p = 0.14$). Following drug administration, compared to baseline, patients reported an improvement in total PANSS score which was significantly greater under CBD than under PLB ($z = -2.14$; $p = 0.02$).

Behavioural performance

Mean monetary reward

At the end of the MIDT, the HC group won a significantly higher amount of monetary reward relative to PSY-PLB (Table 3; $p = 0.03$). No significant differences were observed when comparing PSY-PLB with PSY-CBD.

Accuracy

Across both sets of comparisons (HC *v.* PSY-PLB and PSY-PLB v. PSY-CBD), there was a main effect of stimulus type (salient *v.* neutral) on task accuracy, such that accuracy percentage was higher for salient compared to neutral stimuli ($p < 0.001$ and $p = 0.007$ respectively). In separate pairwise comparisons, there was also a main effect of group (HC *v.* PSY and PSY-CBD *v.* PSY-PLB) on task accuracy (Table 3), such that the PSY-PLB group were less accurate than HC ($p < 0.001$) and PSY-CBD ($p = 0.005$) across all types of stimuli. No significant interactions between group and salience were observed in either of the comparisons (HC *v.* PSY or PSY-CBD *v.* PSY-PLB) (Table 3).

Reaction time

Across both sets of comparisons (HC *v.* PSY-PLB and PSY-PLB *v.* PSY-CBD), there was a main effect of stimulus type (salient *v.* neutral) on RT such that RT was lower for salient compared to neutral stimuli ($p < 0.001$ and $p = 0.03$). In separate pairwise

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Table 1. Sociodemographic and clinical measures (previously also reported in O'Neill et al. (2021a, 2021b) *patient was prescribed olanzapine but was not taking it)

Characteristic	HC ($n = 19$) Mean (s.d.)	PSY ($n = 15$) Mean (s.d.)		*Statistics*
Age (years)	23.9 (4.2)	27.7 (4.6)		(HC *v.* PSY) $p = 0.02$
Sex (%male)	57.9	66.7		(HC *v.* PSY) $p = 0.61$
Handedness (%right)	94.7	86.7		(HC *v.* PSY) $p = 0.43$
Education (years)	17.0 (1.6)	14.2 (2.3)		(HC *v.* PSY) $p < 0.001$
Antipsychotic medication (atypical/typical/none)	–	14/0/1*		
CPZ equivalent dose mg/day	–	225.1 (96.2)		
Number of hospital admissions	–	1.5 (1.0)		
Urine Drug Screen (UDS) results: Clean	19	Session 1	Session 2	
		6	6	
THC		8	8	
Morphine		0	0	
Benzodiazepines		0	0	
PCP		1	1	
Cannabis: Lifetime use (n) (Current regular use)		15 (9)		
Cannabis use frequency (past/present):				
Daily	–	6		
1> per week	–	4		
1> monthly	–	0		
Few times a year	–	1		
Once/twice in lifetime	–	4		
Alcohol: Lifetime use (n) (Current use)	16 (16)	11 (7)		Difference in lifetime use – (HC *v.* PSY) $p = 0.44$
Alcohol use frequency (past/present):				Difference in lifetime use – (HC *v.* PSY) $p = 0.073$
Daily	0	1		
1>per week	7	3		
1>monthly	6	3		
Few times a year	3	3		
Never	3	4		
Missing	0	1		
Nicotine: Lifetime use (n) (Current use)	3 (2)	7 (6)		Difference in lifetime use – (HC *v.* PSY) $p = 0.05$
Nicotine use frequency (past/present):				Difference in frequency – (HC *v.* PSY) $p = 0.05$
Daily	2	6		
1> per week	0	0		
1> monthly	0	1		
Few times a year	0	0		
Never	0	8		
Missing	1	0		
Carbon monoxide in break mean ppm (%)	–	Session 1	Session 2	mean ppm: $p = 0.64$
		9.7 (2.2)	9.2 (2.2)	

All HC individuals had a lifetime cannabis use of less than 10 times.

comparisons, there was also a main effect of group in HC *v.* PSY on RT, such that the PSY-PLB group were slower than HC ($p < 0.001$) across all types of stimuli but this was not present in PSY-PLB *v.* PSY-CBD. No significant interactions between group and salience were observed in either of the comparisons (HC *v.* PSY or PSY-CBD *v.* PSY-PLB) (Table 3).

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Table 2. Symptom scores for HC and PSY patients at baseline, and post-drug for both study days [previously reported in (O'Neill et al., 2021a)]

Characteristic	PSY-PLB	PSY-CBD	Statistics (*p*)
	Mean (s.d.)		
T1 PANSS positive symptoms	12.5 (5.6)	12.9 (5.7)	0.5
T1 PANSS negative symptoms	12.4 (6.4)	12.5 (6.6)	0.39
T1 PANSS total symptoms	48.8 (18.9)	51 (20.0)	0.14
T3 PANSS positive symptoms	11.7 (5.0)	10.7 (3.4)	0.62
T3 PANSS negative symptoms	11.5 (6.1)	10.2 (3.1)	0.87
T3 PANSS total symptoms	44.6 (18.1)	41.5 (11.0)	0.82
Positive symptom change (T1–T3)	0.9(2.2)	2.2 (4.1)	0.20
Negative symptom change (T1–T3)	0.9 (2.8)	2.3 (4.2)	0.07
Total symptom change (T1–T3)	4.2 (7.6)	9.5 (14.2)	0.02

PSY-PLB, psychosis participants with placebo; PSY-CBD, psychosis participants with cannabidiol; PANSS, Positive and Negative syndrome scale; STAI-S, State-Trait Anxiety Inventory state subscale. T1 = 60 min prior to drug administration, T3 = 270 min post-drug administration. Non-parametric Sign test was used to compare paired medians.

False-starts (response⩽100 ms)

Across both sets of comparisons (HC *v.* PSY-PLB and PSY-PLB *v.* PSY-CBD), there was no main effect of stimulus type (salient *v.* neutral) on the percentage difference of false starts. In separate pairwise comparisons, there was a main effect of group (HC *v.* PSY) such that the PSY-PLB group had a higher percentage of false starts ($p < 0.001$) across all types of stimuli. This relationship was not seen in the PSY-PLB *v.* PSY-CBD pairwise comparison. No significant interactions between group and salience were observed in either of the comparisons (HC *v.* PSY or PSY-CBD *v.* PSY-PLB) (Table 3).

Imaging

Hc-v.- PSY-PLB

No differences were observed when comparing PSY-PLB with HC during the salience *v.* neutral contrast (PSY-PLB > HC) within the bilateral insula or the bilateral hippocampus-midbrain-striatum ROI masks or at the whole-brain level.

Within the PSY group, nine participants were current cannabis users. Therefore, sensitivity analyses were conducted to control for the confounding effect of previous cannabis exposure by including this as a covariate within the analysis. The result remained the same after controlling for current cannabis use.

PSY-PLB-v.- PSY-CBD

Within the bilateral insula ROI mask (Fig. 1*a* and *b*), activation was significantly attenuated in the left insula following CBD compared with placebo during the salience *v.* neutral contrast (PSY-PLB > PSY-CBD) (p-FWE = 0.047, $x = -36$, $y = 12$, $x = 12$, $k = 33$).

The result remained unchanged after controlling for current cannabis use (p-FWE = 0.045; $x = -36$, $y = 12$, $x = 12$; $k = 34$).

There was no significant difference in the relationship between the contrast estimate extracted from the bilateral insula anatomical ROI and change (T1 minus T3) in PANSS total score on study day between the CBD and placebo treatment conditions (estimate = 5.87, s.e. = 11.20, $p = 0.61$, CI −15.2 to 27.0).

No areas of significant activation were observed within the hippocampus-midbrain-striatum ROI or at the whole-brain level.

Discussion

In this study we compared brain activation differences between healthy controls and those with early psychosis while processing motivationally salient stimuli and examined the acute effects of CBD, relative to placebo, in psychosis, focusing primarily on changes within the insula cortex, based on previous work. Contrary to our first prediction, we failed to identify differences in brain activation while processing motivationally salient stimuli in early psychosis compared to healthy controls. In accordance with our second hypothesis, we found an attenuation of insula activity in participants with early psychosis following a single dose of CBD, compared with placebo. In the psychosis group, these effects were accompanied by a lower mean monetary reward won during the task, as well as poorer performance accuracy, faster reaction time and premature action initiation across all salience conditions compared to healthy controls. An attenuating effect of CBD on insular activation in psychosis patients was accompanied by a concomitant improvement in performance accuracy across all salience conditions compared with placebo. Exploratory whole-brain analyses, as well as those focusing on the striatum-hippocampus-midbrain ROI, did not reveal any significant difference in pairwise comparisons across the combined salience conditions.

The neuroimaging results comparing healthy controls with early psychosis are inconsistent with our previous report that investigated the neural substrates involved in the antipsychotic effect of CBD in the context of reward processing in people at clinical high risk for psychosis (Wilson et al., 2019). Using the MIDT, Wilson et al. (2019) identified increased activation in the left insula/parietal operculum in clinical high risk for psychosis participants under placebo compared to healthy controls not receiving any study drug. One explanation for not seeing a similar effect in the present study may be due to the confounding effects of dopamine antagonism in our early psychosis cohort who were taking antipsychotic medication at the time of study, unlike in the report by Wilson and colleagues where participants were antipsychotic-naïve. Another study investigating early psychosis participants reported a negative correlation between left insular activation during salience processing and cumulative antipsychotic medication dose (Walter et al., 2016). A further study, also using a salience processing task, identified reduced

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Table 3. Behavioural performance

				Pairwise analysis	
	HC	PSY-CBD	PSY-PLB	HC-*v.*-PSY-PLB	PSY-PLB -*v.*-PSY-CBD
Mean monetary reward £GBP (s.d.)	41.0 (6.3)	31.7 (19.1)	25.7 (24.8)	$p = 0.03$[a]	$p = 0.32$[b]
Accuracy (successful hits on target) %					
Overall	63.5	54.6	49.6	Group Exp(B) 1.87 CI 1.58–2.20 $p = <0.001$[c] Salience Exp(B) 1.71 CI 1.38–2.12 $p = <0.001$[c] Group *salience Exp(B) 0.82 CI 0.59–1.13 $p = 0.23$[c]	Group Exp(B) 0.78 CI 0.65–0.92 $p = 0.005$[c] Salience Exp(B) 1.40 CI 1.10–1.79 $p = 0.007$[c] Group *salience Exp(B) 1.24 CI 0.87–1.76 $p = 0.24$[c]
Neutral	53.9	44.4	43.4		
Salience	66.7	58.0	51.7		
Mean reaction time (ms) >100 ms (s.d.)*					
Overall	243.1 (44.9)	249.1 (54.7)	259.5 (65.6)	Group $F = 41.28$ $p = <0.001$[d] Salience $F = 29.17$ $p = <0.001$[d] Group *salience $F = 0.46$ $p = 0.50$[d]	Group $F = 4.00$ $p = 0.07$[e] Salience $F = 5.76$ $p = 0.03$[e] Group *salience $F = 0.84$ $p = 0.38$[e]
Neutral	254.3 (49.4)	256.0 (58.4)	268.2 (69.6)		
Salience	239.7 (43.0)	247.1 (53.5)	256.8 (64.1)		
False starts %					
Overall	0.9	6.9	5.2	Group Exp(B) 0.19 CI 0.10–0.33 $p = <0.001$[c] Salience Exp(B) 2.16 CI 0.49–9.53 $p = 0.31$[c] Group salience* Exp(B) 0.55 CI 0.11–2.68 $p = 0.46$[c]	Group Exp(B) 0.75 CI 0.52–1.09 $p = 0.13$[c] Salience Exp(B) 1.18 CI 0.67–2.08 $p = 0.58$[c] Group*salience Exp(B) 0.92 CI 0.43–2.0 $p = 0.84$[c]
Salience	0.9	6.9	5.2		
Neutral	0.0	4.6	2.7		

HC, healthy controls; PSY-CBD, early psychosis cannabidiol group; PSY-PLB, early psychosis placebo group.
[a]Independent *t* test.
[b]Paired *t* test.
[c]Binary logistic regression.
[d]Analysis of variance.
[e]Repeated measures analysis of variance.
In the calculation of accuracy, responses <100 ms after target presentation were considered as an inaccurate response, and subsequently excluded from reaction time analysis, in accordance with previous work (Wilson et al., 2019).

insula–anterior cingulate connectivity in early psychosis, relative to healthy controls, observed only in untreated patients and not in antipsychotic treated patients (Schmidt et al., 2016). These reports complement meta-analytic findings that antipsychotic medicated early psychosis patients are more likely to show structural abnormalities of grey matter volume in the left insula (Radua et al., 2012). Therefore, antipsychotic treatment may partly ameliorate insular activation abnormalities in patients with psychosis, such that they may no longer be detectable in comparison with healthy controls. Nevertheless, by employing a within-subject design in the present study, as opposed to a between-group design by Wilson et al. (2019), we were able to extend those results to clearly demonstrate that a single dose of CBD can attenuate salience processing-related insular activation in patients with established psychosis. In accordance with previous results (Wilson et al., 2019), we also found a shorter RT to salient compared to neutral stimuli across all participant groups, consistent with the idea that faster responding during MIDT may indicate greater salience perception (Mir et al., 2011).

Evidence suggests that atypical insula engagement, within the salience network, is a feature of psychotic disorders (Palaniyappan & Liddle, 2012; Walter et al., 2016). Upon detection of a salient stimulus, the insula facilitates task-related information processing by initiating appropriate transient control signals to brain areas mediating attentional, working memory, and higher-order cognitive processes, while disengaging the default mode network to facilitate goal-directed behaviour (Uddin, 2015). Significantly, previous studies have associated aberrant left insular activation with psychosis (Raij, Mäntylä, Mantere, Kieseppä, & Suvisaari, 2016; Thusius et al., 2018; Walter et al., 2016; Wilson et al., 2019).

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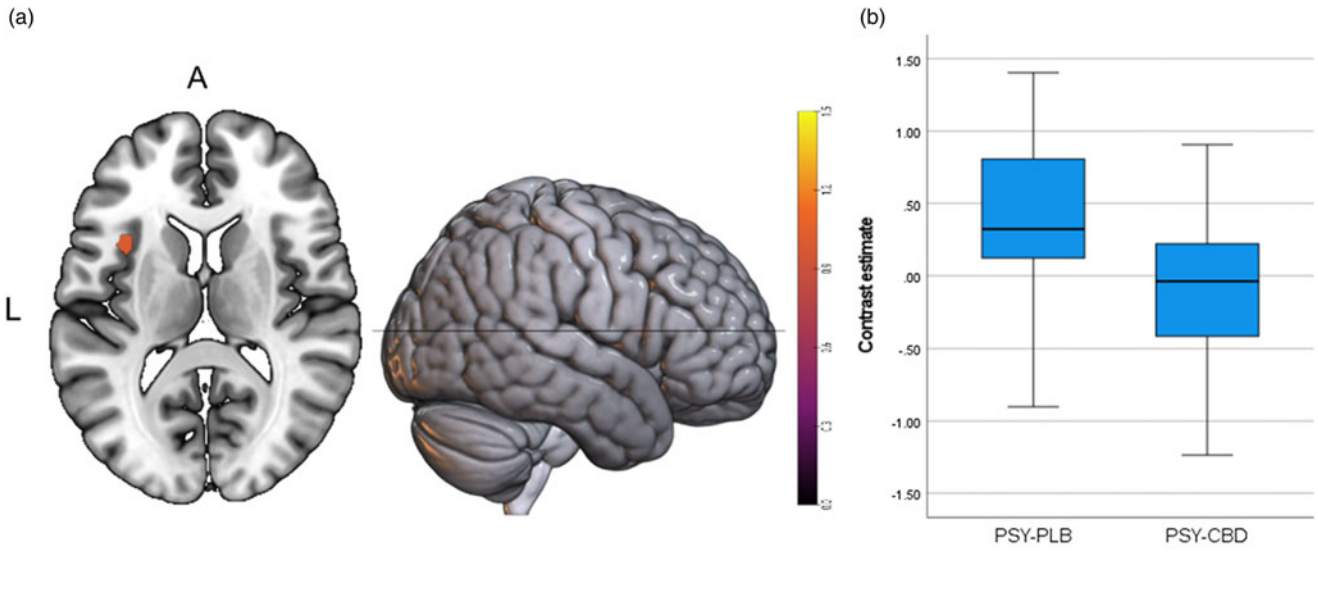

Fig. 1. (*a*) PSY-PLB > PSY-CBD comparison, (*b*) Box plot of extracted contrast weight estimates showing attenuated activation in CBD group compared with the placebo group. $p < 0.05$ FWE-corrected, L = left, A = anterior.

Finally, we found no activation within the striatum, hippocampus, or midbrain in our exploratory analyses. This is in line with our previous report in people at clinical high risk of psychosis (Wilson et al., 2019). In other reports from the same clinical high-risk cohort as that in Wilson and colleagues, we have identified altered striatal and parahippocampal gyrus activation in psychosis compared to healthy participants and their modulation by CBD following verbal learning and fear paradigms (Bhattacharyya et al., 2018; Davies et al., 2020). Therefore, as we have indicated before (Wilson et al., 2019), these results are likely reflective of the different cognitive paradigms employed in these studies, e.g. MIDT in the present study and in Wilson et al. (2019), verbal memory in Bhattacharyya et al. (2018) and fear processing in Davies et al. (2020). In particular, these differences may arise from the distinct roles of the insula and striatum in the processing of salient stimuli. While the striatum may be involved in the attribution of motivational salience to stimuli (Kapur, 2003), the insula has been suggested to be involved in proximal salience which occurs during the evaluation of stimuli (Palaniyappan & Liddle, 2012). The concept of proximal salience should be considered as an extension of aberrant salience to include the disruption of cognition and volition in psychosis (Palaniyappan & Liddle, 2012). It has been suggested that insular dysconnectivity induces the inappropriate assignment of proximal salience. Specifically, this is when external stimuli generate activity within the salience network that updates expectations which then lead to initiation or modification of action. This, in turn, is thought to contribute to the onset of perceptual and cognitive distortions, disorganisation, and psychomotor slowing (Palaniyappan & Liddle, 2012).

While the precise molecular mechanisms that may underlie the effects of CBD reported here remain unclear, a number of potential candidate mechanisms have been suggested, such as negative allosteric modulation of CB1 receptors (Laprairie, Bagher, Kelly, & Denovan-Wright, 2015), weak antagonism of CB2 receptors (Thomas et al., 2007), partial agonism of D2 receptors (a mechanism also shown by aripiprazole) (Tuplin & Holahan, 2017), inhibition of anandamide hydrolysis (Bisogno et al., 2001), and stimulation of vanilloid receptor type 1 (Bisogno et al., 2001) and 5-HT1A receptors (Sartim, Guimarães, & Joca, 2016). In any case, direct or indirect modulation of endogenous anandamide signalling by CBD may be a potential mechanism of antipsychotic action that is consistent with independent evidence of altered CB1 receptor levels across a number of brain regions including in the insula of schizophrenia patients (Ceccarini et al., 2013; Ranganathan et al., 2016).

Limitations

The results presented must be considered in light of the modest sample size highlighted by the power calculation reported. The data presented in this study is a subset of a larger study which utilised a number of neuroimaging approaches where an initial power calculation was conducted, however, this focused on medial temporal activation during a verbal learning task (O'Neill et al., 2021b) rather than estimating power specifically for the MIDT that we employed here. Therefore, although the sample size utilised in this report is within the range of suitable power, the absence of a power calculation specific for the MIDT should be considered as a limitation. While differences in task performance (accuracy and reaction time) were detected, brain activation differences between psychosis patients under placebo and healthy controls were not detected. Although group differences in antipsychotic exposure and cannabis use may also explain our inability to detect differences in this comparison, we cannot rule out that limited power affected the results reported here. This underscores the need for future studies to use larger samples. Future studies may also consider investigation of the acute effects of CBD relative to placebo in healthy controls in parallel with the design employed in patients, to aid interpretation of the specificity of the effects of CBD in the psychosis patients.

Another limitation of this study was the confounding effects of dopamine antagonism that likely precluded our ability to detect a

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difference in insular activation in psychosis patients, relative to healthy control participants. Moreover, the healthy participants in this study had a lifetime cannabis use history of fewer than 10 instances. This is in contrast to the participants within the psychosis group, who were all lifetime cannabis users with 9 of them being current regular users. Although results remained unchanged following sensitivity analysis that attempted to control for the potential confounding effect of difference in cannabis exposure between the two groups, we cannot be certain that this did not affect our ability to detect significant differences in brain activation between the healthy and psychosis group. Nevertheless, we were able to detect an attenuating effect of CBD on insular activation that was over and above any potential effect of antipsychotic medications on insular activation using a within-subject design. While the use of a healthy control group as a comparator with placebo-treated psychosis patients was intended to help examine whether the CBD effects in psychosis patients were observed in the same regions that were differentially affected in psychosis patients under placebo, compared to healthy controls, and to contextualise the direction of any CBD-related change in activation in patients, group differences in cannabis and antipsychotic exposure may have precluded our ability to detect disease-related change as originally intended. Therefore, the results presented here indicate that future studies may also need to consider strategies to better match participant groups in terms of potential confounding factors such as cannabis exposure and antipsychotic exposure.

It is also important to consider that the MIDT recruits cognitive processes other than motivational salience, as evident from meta-analyses examining the anticipation phase of the MIDT in healthy participants. These studies have highlighted the engagement of a number of brain regions outside of the salience network that may serve a range of processes including executive function, psychomotor control and impulsivity (Jauhar et al., 2021; Oldham et al., 2018; Wilson et al., 2018). Further, the insula is known to be engaged in a range of cognitive processes other than salience processing (Uddin et al., 2017). Therefore, we cannot be completely certain that engagement of some of these processes may have influenced the results presented here, although, lack of group differences in brain activation outside of the insula indicate that this may be less likely.

Finally, although the primary aim of this study was to complement clinical investigations of CBD in people with established psychosis by investigating potential mechanisms which may underlie its putative antipsychotic action, it remains to be seen whether similar effects on brain substrates, as those reported here, would be observed following sustained dosing. In particular, it would be important to demonstrate longitudinal changes in brain activation following sustained CBD dosing that occurs in parallel with the improvement in the severity of psychotic symptoms.

Conclusion

This study highlighted an attenuating effect of CBD on insular activation, in participants with an established psychotic disorder during salience processing that is consistent with independent evidence. Whether these effects of CBD on insular activation persist following sustained treatment and whether they are related to any symptomatic benefits remains to be seen in larger studies.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722001672.

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Conflict of interest. The authors report no conflicts of interest.

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